Comparative efficacy and safety of tirbanibulin for actinic keratosis of the face and scalp in Europe: A systematic review and network meta-analysis of randomised controlled trials

Supplementary file

1 Methods

1.1 Systematic review methods

Supplementary Figure S1: Search strategies

Source: MEDLINE(R) ALL
Interface / URL: OvidSP
Database coverage dates: 1946 to June 22, 2020
Search date: 24/06/20
Retrieved records: 1210
Search strategy:

1 Keratosis, Actinic / (2048)
2 (actinic$ adj6 (keratos$ or keratoma$ or keratotic$ or keratopath$)).ti,ab,kf. (3649)
3 (actinic$ adj6 (cheilit$ or cheilos$)).ti,ab,kf. (339)
4 ((solar$ or senil$) adj6 (keratos$ or keratoma$ or keratotic$ or keratopath$)).ti,ab,kf. (647)
5 ((solar$ or senil$) adj6 (cheilit$ or cheilos$)).ti,ab,kf. (16)
6 (hyperkeratos$ or hyperkeratoma$ or hyperkeratotic$ or hyperkeratopath$).ti,ab,kf. (6790)
7 (keratinocytic intraepidermal neoplasia$ or keratinocytic intra-epidermal neoplasia$).ti,ab,kf. (13)
8 ((sailor$ or farmer$) adj (lip or lips)).ti,ab,kf. (3)
9 (ak or aks).ti,ab,kf. (7668)
10 (hak or haks).ti,ab,kf. (241)
11 (kin or kins).ti,ab,kf. (6501)
12 or / 1-11 (24881)
13 tirbanibulin$.ti,ab,kf,rn,nm. (2)
14 (alm-14789$2 or alm14789$2 or kx01$2 or kx-01$2 or kx2391$2 or kx2-391$2 or kx-2391$2 or kx-2-391$2).ti,ab,kf,rn,nm. (28)
15 (1080645-95-9 or 4v9848rs5g or 84ac3796wj or 897016-82-9).ti,ab,kf,rn,nm. (0)
16 Diclofenac / (7820)
17 diclofenac$.ti,ab,kf,rn,nm. (13203)
18 (abitren$2 or aceclofenac$2 or benfofen$2 or dealgic$2 or deflamat$2 or delphinac$2 or dichlofenal$2 or dicloflex$2 or diclomax$2 or diclonate$ or diclophenac$2 or diclophlogont$2 or dicloreum$2 or dicrofenac$2 or duravolten$2 or dyloject$2 or ecofenac$2 or effekton$2 or feloran$2 or gp45840$2 or gp-45840$2 or las41007$2 or las-41007$2 or lexobene$2 or neriodin$2 or novapirina$2 or orthofen$2 or orthophen$2 or ortofen$2 or pennsaid$2 or primofenac$2 or prophenatin$2 or rewodina$2 or rhumalgan$2 or solacutan$2 or solaraze$2 or sr-38$2 or sr38$2 or voldal$2 or voltaren$2 or voltarol$2 or xenid$2).ti,ab,kf,rn,nm. (1080)
19 (cataflam$2 or d11ax18 or m01ab05 or m02aa15 or s01bc03).ti,ab,kf,rn,nm. (18)
20 (15307-79-6 or 239-346-4 or qtg126297q or 144o8ql0l1 or 15307-86-5 or 239-348-5 or 15307-81-0 or l4d5ua6cb4).ti,ab,kf,rn,nm. (7831)
21 Fluorouracil / (41350)
22 (fluorouracil$ or fluoro-uracil$).ti,ab,kf,rn,nm. (54203)
23 (5fluoropyrimidin$2 or 5-fluoropyrimidin$2 or 5fluoropyrimidine$2 or 5-fluoropyrimidine$2 or 5fluorouracil$2 or 5fluoro-uracil$2 or 5fluoruracil$2 or 5fu$2 or 5-fu$2 or 5hu hexal$2 or 5-hu hexal$2 or accusite$2 or actikerall$2 or actikerell$2 or actino-hermal$2 or adrucil$2 or agicil$2 or arac$2 or carac$2 or cinkef-u$2 or effluderm$2 or efudex$2 or efudix$2 or efurix$2 or emtricitabine impurity f$2 or eurofluor$2 or f6627$2 or f-6627$2 or fivoflu$2 or flucytosine impurity a$2 or fluoroblastin$2 or fluoroplex$2 or fluorouricil$2 or fluoruracil$2 or fluouracil$2 or fluoxan$2 or flurablastin$2 or

fluracedyl$2 or fluracil$2 or fluracilium$2 or fluril$2 or fluroblastin$2 or fluroblastine$2 or fluro-uracil$2 or flurodex$2 or haemato-fu$2 or ifacil$2 or l01bc02$2 or neofluor$2 or nsc-18913$2 or nsc-19893$2 or nsc18913$2 or nsc19893$2 or oncofu$2 or onkofluor$2 or phthoruracil$2 or queroplex$2 or ribofluor$2 or ro-2-9757$2 or ro2-9757$2 or ro-29757$2 or ro29757$2 or tolak$2 or uflahex$2 or utoral$2 or verrumal$2).ti,ab,kf,rn,nm. (24747)
24 (10318-20-4 or 200-085-6 or 51-21-8 or 57050-04-1 or 57172-36-8 or 68021-61-4 or u3p01618rt or 15fs54053u or 56177-80-1 or 260-029-1 or q0e5j9oq9o or 766-63-2 or pm476l7o8g or 14787-18-9).ti,ab,kf,rn,nm. (41353)
25 Imiquimod / (2485)
26 imiquimod$.ti,ab,kf,rn,nm. (3745)
27 (aldara$2 or d06bb10 or imunocare$2 or r-837$2 or r837$2 or s-26308$2 or s26308$2 or zartra$2 or zyclara$2).ti,ab,kf,rn,nm. (341)
28 (99011-02-6 or p1qw714r7m).ti,ab,kf,rn,nm. (2485)
29 ingenol$ mebutate$.ti,ab,kf,rn,nm. (314)
30 (agn-204332$2 or agn204332$2 or d06bx02 or ingenol-3-angelate$ or ingenol-3-mebutate$ or ingenol$ angelate$ or pep-005$2 or pep005$2 or picato$2).ti,ab,kf,rn,nm. (81)
31 (75567-37-2 or 7686s50jah).ti,ab,kf,rn,nm. (0)
32 or / 13-31 (77448)
33 Cryotherapy / (5083)
34 Cryosurgery / (12887)
35 (cryotherap$ or cryo-therap$ or cryotreat$ or cryo-treat$).ti,ab,kf. (7587)
36 (cryoablat$ or cryo-ablat$ or cryoapplication$ or cryo-application$ or cryoblat$ or cryo-blat$ or cryocoag$ or cryo-coag$ or cryodestr$ or cryo-destr$ or cryoenerg$ or cryo-energ$ or cryogen$ or cryo-gen$ or cryoisolat$ or cryo-isolat$ or cryosurg$ or cryo-surg$ or cryotherm$ or cryo-therm$).ti,ab,kf. (16768)
37 (freez$ or froz$).ti,ab,kf. (136808)
38 (liquid adj (nitrogen or n2)).ti,ab,kf. (8553)
39 ln2.ti,ab,kf. (662)
40 (cold adj (treatment$ or therap$)).ti,ab,kf. (1563)
41 or / 33-40 (169803)
42 phototherapy / or intense pulsed light therapy / or low-level light therapy / or exp photochemotherapy / (33672)
43 Photosensitizing Agents / (15934)
44 (photodynamic$ or photo-dynamic$).ti,ab,kf. (25233)
45 (photochemotherap$ or photo-chemotherap$ or photoradiat$ or photo-radiat$ or photosensiti$ or photo-sensiti$ or phototherap$ or photo-therap$).ti,ab,kf. (39838)
46 chemophototherap$.ti,ab,kf. (31)
47 (light adj (treatment$ or therap$)).ti,ab,kf. (4577)
48 pdt.ti,ab,kf. (13630)
49 or / 42-48 (74403)
50 12 and (32 or 41 or 49) (2289)
51 randomized controlled trial.pt. (508066)
52 controlled clinical trial.pt. (93724)
53 randomized.ab. (483747)
54 placebo.ab. (208801)
55 drug therapy.fs. (2213019)
56 randomly.ab. (335722)
57 trial.ab. (509998)
58 groups.ab. (2060491)
59 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 (4731122)
60 50 and 59 (1469)

61 exp Animals / not Humans / (4709505)
62 (news or case reports).pt. or case report.ti. (2350019)
63 60 not (61 or 62) (1213)
64 remove duplicates from 63 (1210)

Key to Ovid symbols and commands

$	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,rn,nm	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf), Registry Number / Name of Substance (rn) and Name of Substance Word (nm) fields
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or / 1-11	Combines sets 1 to 11 using OR
.fs.	Term is searched as a floating subheading

Source: Embase
Interface / URL: OvidSP
Database coverage dates: 1974 to 2020 June 24
Search date: 25/06/20
Retrieved records: 881
Search strategy:

1 Keratosis, Actinic/ (4505)
2 (actinic$ adj6 (keratos$ or keratoma$ or keratotic$ or keratopath$)).ti,ab,kw,dq. (5358)
3 (actinic$ adj6 (cheilit$ or cheilos$)).ti,ab,kw,dq. (444)
4 ((solar$ or senil$) adj6 (keratos$ or keratoma$ or keratotic$ or keratopath$)).ti,ab,kw,dq. (783)
5 ((solar$ or senil$) adj6 (cheilit$ or cheilos$)).ti,ab,kw,dq. (21)
6 (hyperkeratos$ or hyperkeratoma$ or hyperkeratotic$ or hyperkeratopath$).ti,ab,kw,dq. (9732)
7 (keratinocytic intraepidermal neoplasia$ or keratinocytic intra-epidermal neoplasia$).ti,ab,kw,dq. (14)
8 ((sailor$ or farmer$) adj (lip or lips)).ti,ab,kw,dq. (2)
9 (ak or aks).ti,ab,kw,dq. (7341)
10 (hak or haks).ti,ab,kw,dq. (249)
11 (kin or kins).ti,ab,kw,dq. (7821)
12 or/1-11 (30960)
13 tirbanibulin/ (7)
14 tirbanibulin$.ti,ab,kw,rn,tn,dq,dy. (7)
15 (alm-14789$2 or alm14789$2 or kx01$2 or kx-01$2 or kx2391$2 or kx2-391$2 or kx-2391$2 or kx-2-391$2).ti,ab,kw,rn,tn,dq,dy. (95)
16 (1080645-95-9 or 4v9848rs5g or 84ac3796wj or 897016-82-9).ti,ab,kw,rn,tn,dq,dy. (7)
17 diclofenac/ (39993)
18 diclofenac$.ti,ab,kw,rn,tn,dq,dy. (41834)
19 (abitren$2 or aceclofenac$2 or benfofen$2 or dealgic$2 or deflamat$2 or delphinac$2 or dichlofenal$2 or dicloflex$2 or diclomax$2 or diclonate$ or diclophenac$2 or diclophlogont$2 or

dicloreum$2 or dicrofenac$2 or duravolten$2 or dyloject$2 or ecofenac$2 or effekton$2 or feloran$2 or gp45840$2 or gp-45840$2 or las41007$2 or las-41007$2 or lexobene$2 or neriodin$2 or novapirina$2 or orthofen$2 or orthophen$2 or ortofen$2 or pennsaid$2 or primofenac$2 or prophenatin$2 or rewodina$2 or rhumalgan$2 or solacutan$2 or solaraze$2 or sr-38$2 or sr38$2 or voldal$2 or voltaren$2 or voltarol$2 or xenid$2).ti,ab,kw,rn,tn,dq,dy. (5551)
20 (cataflam$2 or d11ax18 or m01ab05 or m02aa15 or s01bc03).ti,ab,kw,rn,tn,dq,dy. (231)
21 (15307-79-6 or 239-346-4 or qtg126297q or 144o8ql0l1 or 15307-86-5 or 239-348-5 or 15307-81-0 or l4d5ua6cb4).ti,ab,kw,rn,tn,dq,dy. (38312)
22 fluorouracil/ (137520)
23 fluorouracil plus salicylic acid/ (17)
24 (fluorouracil$ or fluoro-uracil$).ti,ab,kw,rn,tn,dq,dy. (142589)
25 (5fluoropyrimidin$2 or 5-fluoropyrimidin$2 or 5fluoropyrimidine$2 or 5-fluoropyrimidine$2 or 5fluorouracil$2 or 5fluoro-uracil$2 or 5fluoruracil$2 or 5fu$2 or 5-fu$2 or 5hu hexal$2 or 5-hu hexal$2 or accusite$2 or actikerall$2 or actikerell$2 or actino-hermal$2 or adrucil$2 or agicil$2 or arac$2 or carac$2 or cinkef-u$2 or effluderm$2 or efudex$2 or efudix$2 or efurix$2 or emtricitabine impurity f$2 or eurofluor$2 or f6627$2 or f-6627$2 or fivoflu$2 or flucytosine impurity a$2 or fluoroblastin$2 or fluoroplex$2 or fluorouricil$2 or fluoruracil$2 or fluouracil$2 or fluoxan$2 or flurablastin$2 or fluracedyl$2 or fluracil$2 or fluracilium$2 or fluril$2 or fluroblastin$2 or fluroblastine$2 or fluro-uracil$2 or flurodex$2 or haemato-fu$2 or ifacil$2 or l01bc02$2 or neofluor$2 or nsc-18913$2 or nsc-19893$2 or nsc18913$2 or nsc19893$2 or oncofu$2 or onkofluor$2 or phthoruracil$2 or queroplex$2 or ribofluor$2 or ro-2-9757$2 or ro2-9757$2 or ro-29757$2 or ro29757$2 or tolak$2 or uflahex$2 or utoral$2 or verrumal$2).ti,ab,kw,rn,tn,dq,dy. (39041)
26 (10318-20-4 or 200-085-6 or 51-21-8 or 57050-04-1 or 57172-36-8 or 68021-61-4 or u3p01618rt or 15fs54053u or 56177-80-1 or 260-029-1 or q0e5j9oq9o or 766-63-2 or pm476l7o8g or 14787-18-9).ti,ab,kw,rn,tn,dq,dy. (128723)
27 imiquimod/ (8934)
28 imiquimod$.ti,ab,kw,rn,tn,dq,dy. (9445)
29 (aldara$2 or d06bb10 or imunocare$2 or r-837$2 or r837$2 or s-26308$2 or s26308$2 or zartra$2 or zyclara$2).ti,ab,kw,rn,tn,dq,dy. (1514)
30 (99011-02-6 or p1qw714r7m).ti,ab,kw,rn,tn,dq,dy. (7849)
31 ingenol mebutate/ (680)
32 ingenol$ mebutate$.ti,ab,kw,rn,tn,dq,dy. (734)
33 (agn-204332$2 or agn204332$2 or d06bx02 or ingenol-3-angelate$ or ingenol-3-mebutate$ or ingenol$ angelate$ or pep-005$2 or pep005$2 or picato$2).ti,ab,kw,rn,tn,dq,dy. (254)
34 (75567-37-2 or 7686s50jah).ti,ab,kw,rn,tn,dq,dy. (553)
35 or/13-34 (200585)
36 exp cryotherapy/ (32896)
37 cryotherapy device/ (51)
38 (cryotherap$ or cryo-therap$ or cryotreat$ or cryo-treat$).ti,ab,kw,dv,dq,my. (10941)
39 (cryoablat$ or cryo-ablat$ or cryoapplication$ or cryo-application$ or cryoblat$ or cryo-blat$ or cryocoag$ or cryo-coag$ or cryodestr$ or cryo-destr$ or cryoenerg$ or cryo-energ$ or cryogen$ or cryo-gen$ or cryoisolat$ or cryo-isolat$ or cryosurg$ or cryo-surg$ or cryotherm$ or cryo-therm$).ti,ab,kw,dv,dq,my. (19633)
40 (freez$ or froz$).ti,ab,kw,dv,dq,my. (176928)
41 liquid nitrogen/ (7227)
42 (liquid adj (nitrogen or n2)).ti,ab,kw,dv,dq,my. (11605)
43 ln2.ti,ab,kw,dv,dq,my. (937)
44 (cold adj (treatment$ or therap$)).ti,ab,kw,dv,dq,my. (1403)
45 or/36-44 (223483)
46 exp photochemotherapy/ or phototherapy/ or intense pulsed light therapy/ or low level laser therapy/ (85428)

47 photosensitizing agent/ (14828)
48 (photodynamic$ or photo-dynamic$).ti,ab,kw,dv,dq,my. (30228)
49 (photochemotherap$ or photo-chemotherap$ or photoradiat$ or photo-radiat$ or photosensiti$ or photo-sensiti$ or phototherap$ or photo-therap$).ti,ab,kw,dv,dq,my. (49018)
50 chemophototherap$.ti,ab,kw,dv,dq,my. (34)
51 (light adj (treatment$ or therap$)).ti,ab,kw,dv,dq,my. (5591)
52 pdt.ti,ab,kw,dv,dq,my. (17017)
53 or/46-52 (120852)
54 12 and (35 or 45 or 53) (4561)
55 Randomized controlled trial/ (607969)
56 Controlled clinical study/ (463992)
57 Random$.ti,ab. (1544012)
58 randomization/ (87071)
59 intermethod comparison/ (260580)
60 placebo.ti,ab. (307111)
61 (compare or compared or comparison).ti. (510393)
62 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2121426)
63 (open adj label).ti,ab. (79627)
64 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (232697)
65 double blind procedure/ (173401)
66 parallel group$1.ti,ab. (25605)
67 (crossover or cross over).ti,ab. (105255)
68 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (330911)
69 (assigned or allocated).ti,ab. (389265)
70 (controlled adj7 (study or design or trial)).ti,ab. (349827)
71 (volunteer or volunteers).ti,ab. (246980)
72 human experiment/ (500451)
73 trial.ti. (301581)
74 or/55-73 (5029155)
75 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8079)
76 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (237333)
77 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (17276)
78 (Systematic review not (trial or study)).ti. (144841)
79 (nonrandom$ not random$).ti,ab. (16145)
80 "Random field$".ti,ab. (2310)
81 (random cluster adj3 sampl$).ti,ab. (1278)
82 (review.ab. and review.pt.) not trial.ti. (803210)
83 "we searched".ab. and (review.ti. or review.pt.) (32091)
84 "update review".ab. (104)
85 (databases adj4 searched).ab. (35906)
86 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1064694)
87 Animal experiment/ not (human experiment/ or human/) (2246558)
88 or/75-87 (3474234)
89 74 not 88 (4477050)

90 54 and 89 (913)
91 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6019117)
92 case report.ti. (292163)
93 90 not (91 or 92) (900)
94 remove duplicates from 93 (881)

Source: Cochrane Central Register of Controlled Trials
Interface / URL: Cochrane Library / Wiley
Database coverage dates: Information not found. Issue searched: Issue 6 of 12, June 2020
Search date: 25/06/20
Retrieved records: 822
Search strategy:

#1 [mh ^"Keratosis, Actinic"] 389
#2 (actinic* near/6 (keratos* or keratoma* or keratotic* or keratopath*)) 1006
#3 (actinic* near/6 (cheilit* or cheilos*)) 20
#4 ((solar* or senil*) near/6 (keratos* or keratoma* or keratotic* or keratopath*)) 55
#5 ((solar* or senil*) near/6 (cheilit* or cheilos*)) 2
#6 (hyperkeratos* or hyperkeratoma* or hyperkeratotic* or hyperkeratopath*) 293
#7 (keratinocytic next intraepidermal next neoplasia* or keratinocytic next intra next epidermal next neoplasia*) 1
#8 ((sailor* or farmer*) next (lip or lips)) 1
#9 (ak or aks) not (ak or aks):au 1267
#10 (hak or haks) 149
#11 (kin or kins) 550
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 2664
#13 tirbanibulin* 0
#14 ("alm-14789" or "alm-14789r" or "alm-14789tm" or alm14789* or kx01* or "kx-01" or "kx-01r" or "kx-01tm" or kx2391* or "kx2-391" or "kx2-391r" or "kx2-391tm" or "kx-2391" or "kx-2391r" or "kx-2391tm" or "kx-2-391" or "kx-2-391r" or "kx-2-391tm") 1
#15 ("1080645-95-9" or 4v9848rs5g or 84ac3796wj or "897016-82-9") 0
#16 [mh ^Diclofenac] 1916
#17 diclofenac* 5300
#18 (abitren* or aceclofenac* or benfofen* or dealgic* or deflamat* or delphinac* or dichlofenal* or dicloflex* or diclomax* or diclonate* or diclophenac* or diclophlogont* or dicloreum* or dicrofenac* or duravolten* or dyloject* or ecofenac* or effekton* or feloran* or gp45840* or "gp-45840" or "gp-45840r" or "gp-45840tm" or las41007* or "las-41007" or "las-41007r" or "las-41007tm" or lexobene* or neriodin* or novapirina* or orthofen* or orthophen* or ortofen* or pennsaid* or primofenac* or prophenatin* or rewodina* or rhumalgan* or solacutan* or solaraze* or "sr-38" or "sr-38r" or "sr-38tm" or sr38* or voldal* or voltaren* or voltarol* or xenid*) 686
#19 (cataflam* or d11ax18 or m01ab05 or m02aa15 or s01bc03) 25
#20 ("15307-79-6" or "239-346-4" or qtg126297q or 144o8ql0l1 or "15307-86-5" or "239-348-5" or "15307-81-0" or l4d5ua6cb4) 0
#21 [mh ^Fluorouracil] 4881
#22 (fluorouracil* or fluoro next uracil*) 10464
#23 (5fluoropyrimidin* or 5 next fluoropyrimidin* or 5fluoropyrimidine* or 5 next fluoropyrimidine* or 5fluorouracil* or 5fluoro next uracil* or 5fluoruracil* or 5fu* or 5 next fu* or 5hu next hexal* or 5 next hu next hexal* or accusite* or actikerall* or actikerell* or actino next hermal* or adrucil* or agicil* or arac* or carac* or cinkef or effluderm* or efudex* or efudix* or efurix* or emtricitabine next impurity or eurofluor* or f6627* or "f-6627" or "f-6627r" or "f-6627tm" or fivoflu* or flucytosine next impurity or

fluoroblastin* or fluoroplex* or fluorouricil* or fluoruracil* or fluouracil* or fluoxan* or flurablastin* or fluracedyl* or fluracil* or fluracilium* or fluril* or fluroblastin* or fluroblastine* or fluro next uracil* or flurodex* or "haemato fu" or "haemato fur" or "haemato futm" or ifacil* or l01bc02* or neofluor* or "nsc-18913" or "nsc-18913r" or "nsc-18913tm" or "nsc-19893" or "nsc-19893r" or "nsc-19893tm" or nsc18913* or nsc19893* or oncofu* or onkofluor* or phthoruracil* or queroplex* or ribofluor* or "ro-2-9757" or "ro-2-9757r" or "ro-2-9757tm" or "ro2-9757" or "ro2-9757r" or "ro2-9757tm" or "ro-29757" or "ro-29757r" or "ro-29757tm" or ro29757* or tolak* or uflahex* or utoral* or verrumal*) 14274
#24 ("10318-20-4" or "200-085-6" or "51-21-8" or "57050-04-1" or "57172-36-8" or "68021-61-4" or u3p01618rt or 15fs54053u or "56177-80-1" or "260-029-1" or q0e5j9oq9o or "766-63-2" or pm476l7o8g or "14787-18-9") 0
#25 [mh ^Imiquimod] 244
#26 imiquimod* 550
#27 (aldara* or d06bb10 or imunocare* or "r-837" or "r-837r" or "r-837tm" or r837* or "s-26308" or "s-26308r" or "s-26308tm" or s26308* or zartra* or zyclara*) 97
#28 ("99011-02-6" or p1qw714r7m) 0
#29 ingenol* next mebutate* 124
#30 ("agn-204332" or "agn-204332r" or "agn-204332tm" or agn204332* or d06bx02 or ingenol next 3 next angelate* or ingenol next 3 next mebutate* or ingenol* next angelate* or "pep-005" or "pep-005r" or "pep-005tm" or pep005* or picato*) 35
#31 ("75567-37-2" or 7686s50jah) 0
#32 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 27245
#33 [mh ^Cryotherapy] 661
#34 [mh "Cryosurgery"] 337
#35 (cryotherap* or cryo next therap* or cryotreat* or cryo next treat*) 2210
#36 (cryoablat* or cryo next ablat* or cryoapplication* or cryo next application* or cryoblat* or cryo next blat* or cryocoag* or cryo next coag* or cryodestr* or cryo next destr* or cryoenerg* or cryo next energ* or cryogen* or cryo next gen* or cryoisolat* or cryo next isolat* or cryosurg* or cryo next surg* or cryotherm* or cryo next therm*) 970
#37 (freez* or froz*) 6662
#38 (liquid next (nitrogen or n2)) 351
#39 ln2 22
#40 (cold next (treatment* or therap*)) 255
#41 #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 9604
#42 [mh ^phototherapy] or [mh ^"intense pulsed light therapy"] or [mh ^"low level light therapy"] or [mh photochemotherapy] 2552
#43 [mh ^"Photosensitizing Agents"]677
#44 (photodynamic* or photo next dynamic*) 2330
#45 (photochemotherap* or photo next chemotherap* or photoradiat* or photo next radiat* or photosensiti* or photo next sensiti* or phototherap* or photo next therap*) 5171
#46 chemophototherap* 6
#47 (light next (treatment* or therap*)) 2242
#48 pdt 1734
#49 #42 or #43 or #44 or #45 or #46 or #47 or #48 8254
#50 #12 and (#32 or #41 or #49) 1014
#51 #50 in Trials 822

Source: Cochrane Database of Systematic Reviews
Interface / URL: Cochrane Library / Wiley
Database coverage dates: Information not found. Issue 6 of 12, June 2020
Search date: 25/06/20

Retrieved records: 11
Search strategy:

#1 [mh ^"Keratosis, Actinic"] 389
#2 (actinic* near/6 (keratos* or keratoma* or keratotic* or keratopath*)):ti,ab,kw 980
#3 (actinic* near/6 (cheilit* or cheilos*)):ti,ab,kw 18
#4 ((solar* or senil*) near/6 (keratos* or keratoma* or keratotic* or keratopath*)):ti,ab,kw 45
#5 ((solar* or senil*) near/6 (cheilit* or cheilos*)):ti,ab,kw 0
#6 (hyperkeratos* or hyperkeratoma* or hyperkeratotic* or hyperkeratopath*):ti,ab,kw 260
#7 (keratinocytic next intraepidermal next neoplasia* or keratinocytic next intra next epidermal next neoplasia*):ti,ab,kw 0
#8 ((sailor* or farmer*) next (lip or lips)):ti,ab,kw 0
#9 (ak or aks):ti,ab,kw 803
#10 (hak or haks):ti,ab,kw 6
#11 (kin or kins):ti,ab,kw 397
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 1878
#13 tirbanibulin*:ti,ab,kw 0
#14 ("alm-14789" or "alm-14789r" or "alm-14789tm" or alm14789* or kx01* or "kx-01" or "kx-01r" or "kx-01tm" or kx2391* or "kx2-391" or "kx2-391r" or "kx2-391tm" or "kx-2391" or "kx-2391r" or "kx-2391tm" or "kx-2-391" or "kx-2-391r" or "kx-2-391tm"):ti,ab,kw 1
#15 ("1080645-95-9" or 4v9848rs5g or 84ac3796wj or "897016-82-9"):ti,ab,kw 0
#16 [mh ^Diclofenac] 1916
#17 diclofenac*:ti,ab,kw 5099
#18 (abitren* or aceclofenac* or benfofen* or dealgic* or deflamat* or delphinac* or dichlofenal* or dicloflex* or diclomax* or diclonate* or diclophenac* or diclophlogont* or dicloreum* or dicrofenac* or duravolten* or dyloject* or ecofenac* or effekton* or feloran* or gp45840* or "gp-45840" or "gp-45840r" or "gp-45840tm" or las41007* or "las-41007" or "las-41007r" or "las-41007tm" or lexobene* or neriodin* or novapirina* or orthofen* or orthophen* or ortofen* or pennsaid* or primofenac* or prophenatin* or rewodina* or rhumalgan* or solacutan* or solaraze* or "sr-38" or "sr-38r" or "sr-38tm" or sr38* or voldal* or voltaren* or voltarol* or xenid*):ti,ab,kw 639
#19 (cataflam* or d11ax18 or m01ab05 or m02aa15 or s01bc03):ti,ab,kw 22
#20 ("15307-79-6" or "239-346-4" or qtg126297q or 144o8ql0l1 or "15307-86-5" or "239-348-5" or "15307-81-0" or l4d5ua6cb4):ti,ab,kw 0
#21 [mh ^Fluorouracil] 4881
#22 (fluorouracil* or fluoro next uracil*):ti,ab,kw 10276
#23 (5fluoropyrimidin* or 5 next fluoropyrimidin* or 5fluoropyrimidine* or 5 next fluoropyrimidine* or 5fluorouracil* or 5fluoro next uracil* or 5fluoruracil* or 5fu* or 5 next fu* or 5hu next hexal* or 5 next hu next hexal* or accusite* or actikerall* or actikerell* or actino next hermal* or adrucil* or agicil* or arac* or carac* or cinkef or effluderm* or efudex* or efudix* or efurix* or emtricitabine next impurity or eurofluor* or f6627* or "f-6627" or "f-6627r" or "f-6627tm" or fivoflu* or flucytosine next impurity or fluoroblastin* or fluoroplex* or fluorouricil* or fluoruracil* or fluouracil* or fluoxan* or flurablastin* or fluracedyl* or fluracil* or fluracilium* or fluril* or fluroblastin* or fluroblastine* or fluro next uracil* or flurodex* or "haemato fu" or "haemato fur" or "haemato futm" or ifacil* or l01bc02* or neofluor* or "nsc-18913" or "nsc-18913r" or "nsc-18913tm" or "nsc-19893" or "nsc-19893r" or "nsc-19893tm" or nsc18913* or nsc19893* or oncofu* or onkofluor* or phthoruracil* or queroplex* or ribofluor* or "ro-2-9757" or "ro-2-9757r" or "ro-2-9757tm" or "ro2-9757" or "ro2-9757r" or "ro2-9757tm" or "ro-29757" or "ro-29757r" or "ro-29757tm" or ro29757* or tolak* or uflahex* or utoral* or verrumal*):ti,ab,kw 12230
#24 ("10318-20-4" or "200-085-6" or "51-21-8" or "57050-04-1" or "57172-36-8" or "68021-61-4" or u3p01618rt or 15fs54053u or "56177-80-1" or "260-029-1" or q0e5j9oq9o or "766-63-2" or pm476l7o8g or "14787-18-9"):ti,ab,kw 0
#25 [mh ^Imiquimod] 244

#26 imiquimod*:ti,ab,kw 523
#27 (aldara* or d06bb10 or imunocare* or "r-837" or "r-837r" or "r-837tm" or r837* or "s-26308" or "s-26308r" or "s-26308tm" or s26308* or zartra* or zyclara*):ti,ab,kw 82
#28 ("99011-02-6" or p1qw714r7m):ti,ab,kw 0
#29 (ingenol* next mebutate*):ti,ab,kw 114
#30 ("agn-204332" or "agn-204332r" or "agn-204332tm" or agn204332* or d06bx02 or ingenol next 3 next angelate* or ingenol next 3 next mebutate* or ingenol* next angelate* or "pep-005" or "pep-005r" or "pep-005tm" or pep005* or picato*):ti,ab,kw 35
#31 ("75567-37-2" or 7686s50jah):ti,ab,kw 0
#32 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 25062
#33 [mh ^Cryotherapy] 661
#34 [mh "Cryosurgery"] 337
#35 (cryotherap* or cryo next therap* or cryotreat* or cryo next treat*):ti,ab,kw 2074
#36 (cryoablat* or cryo next ablat* or cryoapplication* or cryo next application* or cryoblat* or cryo next blat* or cryocoag* or cryo next coag* or cryodestr* or cryo next destr* or cryoenerg* or cryo next energ* or cryogen* or cryo next gen* or cryoisolat* or cryo next isolat* or cryosurg* or cryo next surg* or cryotherm* or cryo next therm*):ti,ab,kw909
#37 (freez* or froz*):ti,ab,kw 6273
#38 (liquid next (nitrogen or n2)):ti,ab,kw 328
#39 ln2:ti,ab,kw 20
#40 (cold next (treatment* or therap*)):ti,ab,kw 254
#41 #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 9084
#42 [mh ^phototherapy] or [mh ^"intense pulsed light therapy"] or [mh ^"low level light therapy"] or [mh photochemotherapy] 2552
#43 [mh ^"Photosensitizing Agents"]677
#44 (photodynamic* or photo next dynamic*):ti,ab,kw 2203
#45 (photochemotherap* or photo next chemotherap* or photoradiat* or photo next radiat* or photosensiti* or photo next sensiti* or phototherap* or photo next therap*):ti,ab,kw 4985
#46 chemophototherap*:ti,ab,kw 6
#47 (light next (treatment* or therap*)):ti,ab,kw 2165
#48 pdt:ti,ab,kw 1671
#49 #42 or #43 or #44 or #45 or #46 or #47 or #48 7947
#50 #12 and (#32 or #41 or #49) 822
#51 #50 in Cochrane Reviews, Cochrane Protocols 11

Source: Health Technology Assessment Database (HTA Database)
Interface / URL: https://www.crd.york.ac.uk/CRDWeb
Database coverage dates: Information not found. From 31 March 2018, the HTA database remains available, but CRD are no longer adding new records to it.
Search date: 25/06/20
Retrieved records: 18
Search strategy:

1 MeSH DESCRIPTOR Keratosis, Actinic 20
2 (actinic*) 35
3 (((solar* OR senil*) NEAR6 (keratos* OR keratoma* OR keratotic* OR keratopath*))) 4
4 (((keratos* OR keratoma* OR keratotic* OR keratopath*) NEAR6 (solar* OR senil*))) 1
5 (((solar* OR senil*) NEAR6 (cheilit* OR cheilos*))) 0
6 (((cheilit* OR cheilos*) NEAR6 (solar* OR senil*))) 0
7 ((hyperkeratos* OR hyperkeratoma* OR hyperkeratotic* OR hyperkeratopath*)) 8

8	((keratinocytic intraepidermal neoplasia* OR keratinocytic intra-epidermal neoplasia*))	0
9	(((sailor* OR farmer*) NEAR0 (lip OR lips)))	0
10	((ak OR aks)) NOT ((ak OR aks)):AU	47
11	((hak OR haks)) NOT ((hak OR haks)):AU	0
12	((kin OR kins))	7
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	86
14	(#13) IN DARE	27
15	(#13) IN HTA	18

Source: Database of Abstracts of Reviews of Effects (DARE)
Interface / URL: https://www.crd.york.ac.uk/CRDWeb
Database coverage dates: Information not found. Bibliographic records were published on DARE until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.
Search date: 25/06/20
Retrieved records: 27
Search strategy:

1	MeSH DESCRIPTOR Keratosis, Actinic	20
2	(actinic*)	35
3	(((solar* OR senil*) NEAR6 (keratos* OR keratoma* OR keratotic* OR keratopath*)))	4
4	(((keratos* OR keratoma* OR keratotic* OR keratopath*) NEAR6 (solar* OR senil*)))	1
5	(((solar* OR senil*) NEAR6 (cheilit* OR cheilos*)))	0
6	(((cheilit* OR cheilos*) NEAR6 (solar* OR senil*)))	0
7	((hyperkeratos* OR hyperkeratoma* OR hyperkeratotic* OR hyperkeratopath*))	8
8	((keratinocytic intraepidermal neoplasia* OR keratinocytic intra-epidermal neoplasia*))	0
9	(((sailor* OR farmer*) NEAR0 (lip OR lips)))	0
10	((ak OR aks)) NOT ((ak OR aks)):AU	47
11	((hak OR haks)) NOT ((hak OR haks)):AU	0
12	((kin OR kins))	7
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	86
14	(#13) IN DARE	27

Source: PubMed
Interface / URL: https://pubmed.ncbi.nlm.nih.gov/
Database coverage dates: Information not found
Search date: 26/06/20
Retrieved records: 60
Search strategy:

65	#63 NOT #64	60
64	medline[sb]	26,901,869
63	#60 NOT (#61 OR #62)	1,207
62	("news"[pt:noexp] OR "case reports"[pt:noexp]) OR case report[ti]	2,348,994
61	"animals"[mh] NOT "humans"[mh:noexp]	4,711,847
60	#50 AND #59	1,469
59	#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58	4,793,879
58	groups [tiab]	2,085,731
57	trial [tiab]	600,325
56	randomly [tiab]	335,764
55	drug therapy [sh]	2,214,815

54 placebo [tiab] 214,265
53 randomized [tiab] 523,207
52 controlled clinical trial [pt] 598,209
51 randomized controlled trial [pt] 509,336
50 #12 AND (#32 OR #41 OR #49) 2,312
49 #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 74,295
48 pdt[tiab] 13,626
47 (light treatment*[tiab] OR light therap*[tiab]) 4,553
46 chemophototherap*[tiab] 81
45 (photochemotherap*[tiab] OR photo-chemotherap*[tiab] OR photoradiat*[tiab] OR photo-radiat*[tiab] OR photosensiti*[tiab] OR photo-sensiti*[tiab] OR phototherap*[tiab] OR photo-therap*[tiab]) 39,757
44 (photodynamic*[tiab] OR photo-dynamic*[tiab]) 25,159
43 "Photosensitizing Agents"[mesh:noexp] 15,945
42 "phototherapy"[mesh:noexp] OR "intense pulsed light therapy"[mesh:noexp] OR "low-level light therapy"[mesh:noexp] OR "photochemotherapy"[mesh] 33,699
41 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 169,615
40 (cold treatment*[tiab] OR cold therap*[tiab]) 1,561
39 ln2[tiab] 804
38 (liquid nitrogen[tiab] OR liquid n2[tiab]) 8,523
37 (freez*[tiab] OR froz*[tiab]) 136,624
36 (cryoablat*[tiab] OR cryo-ablat*[tiab] OR cryoapplication*[tiab] OR cryo-application*[tiab] OR cryoblat*[tiab] OR cryo-blat*[tiab] OR cryocoag*[tiab] OR cryo-coag*[tiab] OR cryodestr*[tiab] OR cryo-destr*[tiab] OR cryoenerg*[tiab] OR cryo-energ*[tiab] OR cryogen*[tiab] OR cryo-gen*[tiab] OR cryoisolat*[tiab] OR cryo-isolat*[tiab] OR cryosurg*[tiab] OR cryo-surg*[tiab] OR cryotherm*[tiab] OR cryo-therm*[tiab]) 16,727
35 (cryotherap*[tiab] OR cryo-therap*[tiab] OR cryotreat*[tiab] OR cryo-treat*[tiab]) 7,565
34 "Cryosurgery"[mesh:noexp] 12,896
33 "Cryotherapy"[mesh:noexp] 5,085
32 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 154,978
31 ((75567-37-2[tiab] OR 75567-37-2[rn] OR 75567-37-2[nm]) OR (7686s50jah[tiab] OR 7686s50jah[rn] OR 7686s50jah[nm])) 0
30 ((agn-204332*[tiab] OR agn-204332*[rn] OR agn-204332*[nm]) OR (agn204332*[tiab] OR agn204332*[rn] OR agn204332*[nm]) OR (d06bx02[tiab] OR d06bx02[rn] OR d06bx02[nm]) OR ((ingenol*[tiab] OR ingenol*[rn] OR ingenol*[nm]) AND (angelate*[tiab] OR angelate*[rn] OR angelate*[nm])) OR (pep-005[tiab] OR pep-005[rn] OR pep-005[nm]) OR (pep-005r[tiab] OR pep-005r[rn] OR pep-005r[nm]) OR (pep-005tm[tiab] OR pep-005tm[rn] OR pep-005tm[nm]) OR (pep005*[tiab] OR pep005*[rn] OR pep005*[nm]) OR (picato*[tiab] OR picato*[rn] OR picato*[nm])) 258
29 ((ingenol*[tiab] OR ingenol*[rn] OR ingenol*[nm]) AND (mebutate*[tiab] OR mebutate*[rn] OR mebutate*[nm])) 316
28 ((99011-02-6[tiab] OR 99011-02-6[rn] OR 99011-02-6[nm]) OR (p1qw714r7m[tiab] OR p1qw714r7m[rn] OR p1qw714r7m[nm])) 2,486
27 ((aldara*[tiab] OR aldara*[rn] OR aldara*[nm]) OR (d06bb10[tiab] OR d06bb10[rn] OR d06bb10[nm]) OR (imunocare*[tiab] OR imunocare*[rn] OR imunocare*[nm]) OR (r-837[tiab] OR r-837[rn] OR r-837[nm]) OR (r-837r[tiab] OR r-837r[rn] OR r-837r[nm]) OR (r-837tm[tiab] OR r-837tm[rn] OR r-837tm[nm]) OR (r837*[tiab] OR r837*[rn] OR r837*[nm]) OR (s-26308*[tiab] OR s-26308*[rn] OR s-26308*[nm]) OR (s26308*[tiab] OR s26308*[rn] OR s26308*[nm]) OR (zartra*[tiab] OR zartra*[rn] OR zartra*[nm]) OR (zyclara*[tiab] OR zyclara*[rn] OR zyclara*[nm])) 349
26 (imiquimod*[tiab] OR imiquimod*[rn] OR imiquimod*[nm]) 3,741
25 "Imiquimod"[mesh:noexp] 2,486

24	((10318-20-4[tiab] OR 10318-20-4[rn] OR 10318-20-4[nm]) OR (200-085-6[tiab] OR 200-085-6[rn] OR 200-085-6[nm]) OR (51-21-8[tiab] OR 51-21-8[rn] OR 51-21-8[nm]) OR (57050-04-1[tiab] OR 57050-04-1[rn] OR 57050-04-1[nm]) OR (57172-36-8[tiab] OR 57172-36-8[rn] OR 57172-36-8[nm]) OR (68021-61-4[tiab] OR 68021-61-4[rn] OR 68021-61-4[nm]) OR (u3p01618rt[tiab] OR u3p01618rt[rn] OR u3p01618rt[nm]) OR (15fs54053u[tiab] OR 15fs54053u[rn] OR 15fs54053u[nm]) OR (56177-80-1[tiab] OR 56177-80-1[rn] OR 56177-80-1[nm]) OR (260-029-1[tiab] OR 260-029-1[rn] OR 260-029-1[nm]) OR (q0e5j9oq9o[tiab] OR q0e5j9oq9o[rn] OR q0e5j9oq9o[nm]) OR (766-63-2[tiab] OR 766-63-2[rn] OR 766-63-2[nm]) OR (pm476l7o8g[tiab] OR pm476l7o8g[rn] OR pm476l7o8g[nm]) OR (14787-18-9[tiab] OR 14787-18-9[rn] OR 14787-18-9[nm]))	41,367
23	((5fluoropyrimidin*[tiab] OR 5fluoropyrimidin*[rn] OR 5fluoropyrimidin*[nm]) OR (5-fluoropyrimidin*[tiab] OR 5-fluoropyrimidin*[rn] OR 5-fluoropyrimidin*[nm]) OR (5fluoropyrimidine*[tiab] OR 5fluoropyrimidine*[rn] OR 5fluoropyrimidine*[nm]) OR (5-fluoropyrimidine*[tiab] OR 5-fluoropyrimidine*[rn] OR 5-fluoropyrimidine*[nm]) OR (5fluorouracil*[tiab] OR 5fluorouracil*[rn] OR 5fluorouracil*[nm]) OR (5fluoro-uracil*[tiab] OR 5fluoro-uracil*[rn] OR 5fluoro-uracil*[nm]) OR (5fluoruracil*[tiab] OR 5fluoruracil*[rn] OR 5fluoruracil*[nm]) OR (5fu[tiab] OR 5fu[rn] OR 5fu[nm]) OR (5fur[tiab] OR 5fur[rn] OR 5fur[nm]) OR (5futm[tiab] OR 5futm[rn] OR 5futm[nm]) OR (5-fu[tiab] OR 5-fu[rn] OR 5-fu[nm]) OR (5-fur[tiab] OR 5-fur[rn] OR 5-fur[nm]) OR (5-futm[tiab] OR 5-futm[rn] OR 5-futm[nm]) OR (5hu[tiab] OR 5hu[rn] OR 5hu[nm]) OR (5-hu[tiab] OR 5-hu[rn] OR 5-hu[nm]) OR (accusite*[tiab] OR accusite*[rn] OR accusite*[nm]) OR (actikerall*[tiab] OR actikerall*[rn] OR actikerall*[nm]) OR (actikerell*[tiab] OR actikerell*[rn] OR actikerell*[nm]) OR (actino-hermal*[tiab] OR actino-hermal*[rn] OR actino-hermal*[nm]) OR (adrucil*[tiab] OR adrucil*[rn] OR adrucil*[nm]) OR (agicil*[tiab] OR agicil*[rn] OR agicil*[nm]) OR (arac*[tiab] OR arac*[rn] OR arac*[nm]) OR (carac*[tiab] OR carac*[rn] OR carac*[nm]) OR (cinkef[tiab] OR cinkef[rn] OR cinkef[nm]) OR (effluderm*[tiab] OR effluderm*[rn] OR effluderm*[nm]) OR (efudex*[tiab] OR efudex*[rn] OR efudex*[nm]) OR (efudix*[tiab] OR efudix*[rn] OR efudix*[nm]) OR (efurix*[tiab] OR efurix*[rn] OR efurix*[nm]) OR ((emtricitabine[tiab] OR emtricitabine[rn] OR emtricitabine[nm]) AND (impurity[tiab] OR impurity[rn] OR impurity[nm])) OR (eurofluor*[tiab] OR eurofluor*[rn] OR eurofluor*[nm]) OR (f6627*[tiab] OR f6627*[rn] OR f6627*[nm]) OR (f-6627*[tiab] OR f-6627*[rn] OR f-6627*[nm]) OR (fivoflu*[tiab] OR fivoflu*[rn] OR fivoflu*[nm]) OR ((flucytosine[tiab] OR flucytosine[rn] OR flucytosine[nm]) AND (impurity[tiab] OR impurity[rn] OR impurity[nm])) OR (fluoroblastin*[tiab] OR fluoroblastin*[rn] OR fluoroblastin*[nm]) OR (fluoroplex*[tiab] OR fluoroplex*[rn] OR fluoroplex*[nm]) OR (fluorouricil*[tiab] OR fluorouricil*[rn] OR fluorouricil*[nm]) OR (fluoruracil*[tiab] OR fluoruracil*[rn] OR fluoruracil*[nm]) OR (fluouracil*[tiab] OR fluouracil*[rn] OR fluouracil*[nm]) OR (fluoxan*[tiab] OR fluoxan*[rn] OR fluoxan*[nm]) OR (flurablastin*[tiab] OR flurablastin*[rn] OR flurablastin*[nm]) OR (fluracedyl*[tiab] OR fluracedyl*[rn] OR fluracedyl*[nm]) OR (fluracil*[tiab] OR fluracil*[rn] OR fluracil*[nm]) OR (fluracilium*[tiab] OR fluracilium*[rn] OR fluracilium*[nm]) OR (fluril*[tiab] OR fluril*[rn] OR fluril*[nm]) OR (fluroblastin*[tiab] OR fluroblastin*[rn] OR fluroblastin*[nm]) OR (fluroblastine*[tiab] OR fluroblastine*[rn] OR fluroblastine*[nm]) OR (fluro-uracil*[tiab] OR fluro-uracil*[rn] OR fluro-uracil*[nm]) OR (flurodex*[tiab] OR flurodex*[rn] OR flurodex*[nm]) OR (haemato-fu[tiab] OR haemato-fu[rn] OR haemato-fu[nm]) OR (haemato-fur[tiab] OR haemato-fur[rn] OR haemato-fur[nm]) OR (haemato-futm[tiab] OR haemato-futm[rn] OR haemato-futm[nm]) OR (ifacil*[tiab] OR ifacil*[rn] OR ifacil*[nm]) OR (l01bc02*[tiab] OR l01bc02*[rn] OR l01bc02*[nm]) OR (neofluor*[tiab] OR neofluor*[rn] OR neofluor*[nm]) OR (nsc-18913*[tiab] OR nsc-18913*[rn] OR nsc-18913*[nm]) OR (nsc-19893*[tiab] OR nsc-19893*[rn] OR nsc-19893*[nm]) OR (nsc18913*[tiab] OR nsc18913*[rn] OR nsc18913*[nm]) OR (nsc19893*[tiab] OR nsc19893*[rn] OR nsc19893*[nm]) OR (oncofu*[tiab] OR oncofu*[rn] OR oncofu*[nm]) OR (onkofluor*[tiab] OR onkofluor*[rn] OR onkofluor*[nm]) OR (phthoruracil*[tiab] OR phthoruracil*[rn] OR phthoruracil*[nm]) OR (queroplex*[tiab] OR queroplex*[rn] OR queroplex*[nm]) OR (ribofluor*[tiab] OR ribofluor*[rn] OR ribofluor*[nm]) OR (ro-2-9757*[tiab] OR ro-2-9757*[rn] OR ro-2-9757*[nm]) OR (ro2-9757*[tiab] OR ro2-9757*[rn] OR ro2-9757*[nm]) OR (ro-29757*[tiab] OR ro-29757*[rn] OR ro-29757*[nm]) OR (ro29757*[tiab] OR ro29757*[rn] OR ro29757*[nm]) OR (tolak*[tiab] OR tolak*[rn] OR	

tolak*[nm]) OR (uflahex*[tiab] OR uflahex*[rn] OR uflahex*[nm]) OR (utoral*[tiab] OR utoral*[rn] OR utoral*[nm]) OR (verrumal*[tiab] OR verrumal*[rn] OR verrumal*[nm])) 119,134
22 ((fluorouracil*[tiab] OR fluorouracil*[rn] OR fluorouracil*[nm]) OR (fluoro-uracil*[tiab] OR fluoro-uracil*[rn] OR fluoro-uracil*[nm])) 54,144
21 "Fluorouracil"[mesh:noexp] 41,364
20 ((15307-79-6[tiab] OR 15307-79-6[rn] OR 15307-79-6[nm]) OR (239-346-4[tiab] OR 239-346-4[rn] OR 239-346-4[nm]) OR (qtg126297q[tiab] OR qtg126297q[rn] OR qtg126297q[nm]) OR (144o8ql0l1[tiab] OR 144o8ql0l1[rn] OR 144o8ql0l1[nm]) OR (15307-86-5[tiab] OR 15307-86-5[rn] OR 15307-86-5[nm]) OR (239-348-5[tiab] OR 239-348-5[rn] OR 239-348-5[nm]) OR (15307-81-0[tiab] OR 15307-81-0[rn] OR 15307-81-0[nm]) OR (l4d5ua6cb4[tiab] OR l4d5ua6cb4[rn] OR l4d5ua6cb4[nm])) 7,831
19 ((cataflam*[tiab] OR cataflam*[rn] OR cataflam*[nm]) OR (d11ax18[tiab] OR d11ax18[rn] OR d11ax18[nm]) OR (m01ab05[tiab] OR m01ab05[rn] OR m01ab05[nm]) OR (m02aa15[tiab] OR m02aa15[rn] OR m02aa15[nm]) OR (s01bc03[tiab] OR s01bc03[rn] OR s01bc03[nm])) 17
18 ((abitren*[tiab] OR abitren*[rn] OR abitren*[nm]) OR (aceclofenac*[tiab] OR aceclofenac*[rn] OR aceclofenac*[nm]) OR (benfofen*[tiab] OR benfofen*[rn] OR benfofen*[nm]) OR (dealgic*[tiab] OR dealgic*[rn] OR dealgic*[nm]) OR (deflamat*[tiab] OR deflamat*[rn] OR deflamat*[nm]) OR (delphinac*[tiab] OR delphinac*[rn] OR delphinac*[nm]) OR (dichlofenal*[tiab] OR dichlofenal*[rn] OR dichlofenal*[nm]) OR (dicloflex*[tiab] OR dicloflex*[rn] OR dicloflex*[nm]) OR (diclomax*[tiab] OR diclomax*[rn] OR diclomax*[nm]) OR (diclonate*[tiab] OR diclonate*[rn] OR diclonate*[nm]) OR (diclophenac*[tiab] OR diclophenac*[rn] OR diclophenac*[nm]) OR (diclophlogont*[tiab] OR diclophlogont*[rn] OR diclophlogont*[nm]) OR (dicloreum*[tiab] OR dicloreum*[rn] OR dicloreum*[nm]) OR (dicrofenac*[tiab] OR dicrofenac*[rn] OR dicrofenac*[nm]) OR (duravolten*[tiab] OR duravolten*[rn] OR duravolten*[nm]) OR (dyloject*[tiab] OR dyloject*[rn] OR dyloject*[nm]) OR (ecofenac*[tiab] OR ecofenac*[rn] OR ecofenac*[nm]) OR (effekton*[tiab] OR effekton*[rn] OR effekton*[nm]) OR (feloran*[tiab] OR feloran*[rn] OR feloran*[nm]) OR (gp45840*[tiab] OR gp45840*[rn] OR gp45840*[nm]) OR (gp-45840*[tiab] OR gp-45840*[rn] OR gp-45840*[nm]) OR (las41007*[tiab] OR las41007*[rn] OR las41007*[nm]) OR (las-41007*[tiab] OR las-41007*[rn] OR las-41007*[nm]) OR (lexobene*[tiab] OR lexobene*[rn] OR lexobene*[nm]) OR (neriodin*[tiab] OR neriodin*[rn] OR neriodin*[nm]) OR (novapirina*[tiab] OR novapirina*[rn] OR novapirina*[nm]) OR (orthofen*[tiab] OR orthofen*[rn] OR orthofen*[nm]) OR (orthophen*[tiab] OR orthophen*[rn] OR orthophen*[nm]) OR (ortofen*[tiab] OR ortofen*[rn] OR ortofen*[nm]) OR (pennsaid*[tiab] OR pennsaid*[rn] OR pennsaid*[nm]) OR (primofenac*[tiab] OR primofenac*[rn] OR primofenac*[nm]) OR (prophenatin*[tiab] OR prophenatin*[rn] OR prophenatin*[nm]) OR (rewodina*[tiab] OR rewodina*[rn] OR rewodina*[nm]) OR (rhumalgan*[tiab] OR rhumalgan*[rn] OR rhumalgan*[nm]) OR (solacutan*[tiab] OR solacutan*[rn] OR solacutan*[nm]) OR (solaraze*[tiab] OR solaraze*[rn] OR solaraze*[nm]) OR (sr-38[tiab] OR sr-38[rn] OR sr-38[nm]) OR (sr-38r[tiab] OR sr-38r[rn] OR sr-38r[nm]) OR (sr-38tm[tiab] OR sr-38tm[rn] OR sr-38tm[nm]) OR (sr38*[tiab] OR sr38*[rn] OR sr38*[nm]) OR (voldal*[tiab] OR voldal*[rn] OR voldal*[nm]) OR (voltaren*[tiab] OR voltaren*[rn] OR voltaren*[nm]) OR (voltarol*[tiab] OR voltarol*[rn] OR voltarol*[nm]) OR (xenid*[tiab] OR xenid*[rn] OR xenid*[nm])) 1,572
17 (diclofenac*[tiab] OR diclofenac*[rn] OR diclofenac*[nm]) 13,155
16 "Diclofenac"[mesh:noexp] 7,820
15 ((1080645-95-9[tiab] OR 1080645-95-9[rn] OR 1080645-95-9[nm]) OR (4v9848rs5g[tiab] OR 4v9848rs5g[rn] OR 4v9848rs5g[nm]) OR (84ac3796wj[tiab] OR 84ac3796wj[rn] OR 84ac3796wj[nm]) OR (897016-82-9[tiab] OR 897016-82-9[rn] OR 897016-82-9[nm])) 0
14 ((alm-14789*[tiab] OR alm-14789*[rn] OR alm-14789*[nm]) OR (alm14789*[tiab] OR alm14789*[rn] OR alm14789*[nm]) OR (kx01*[tiab] OR kx01*[rn] OR kx01*[nm]) OR (kx-01[tiab] OR kx-01[rn] OR kx-01[nm]) OR (kx-01r[tiab] OR kx-01r[rn] OR kx-01r[nm]) OR (kx-01tm[tiab] OR kx-01tm[rn] OR kx-01tm[nm]) OR (kx2391*[tiab] OR kx2391*[rn] OR kx2391*[nm]) OR (kx2-391[tiab] OR kx2-391[rn] OR kx2-391[nm]) OR (kx2-391r[tiab] OR kx2-391r[rn] OR kx2-391r[nm]) OR (kx2-391tm[tiab] OR kx2-391tm[rn] OR kx2-391tm[nm]) OR (kx-2391*[tiab] OR kx-2391*[rn] OR kx-2391*[nm]) OR (kx-2-391[tiab]

OR kx-2-391[rn] OR kx-2-391[nm]) OR (kx-2-391r[tiab] OR kx-2-391r[rn] OR kx-2-391r[nm]) OR (kx-2-391tm[tiab] OR kx-2-391tm[rn] OR kx-2-391tm[nm])) 32
13 (tirbanibulin*[tiab] OR tirbanibulin*[rn] OR tirbanibulin*[nm]) 2
12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 23,379
11 (kin[tiab] or kins[tiab]) 6,658
10 (hak[tiab] or haks[tiab]) 206
9 (ak[tiab] OR aks[tiab]) 5,852
8 ((sailor*[tiab] OR farmer*[tiab]) AND (lip[tiab] OR lips[tiab])) 79
7 (keratinocytic[tiab] AND neoplasia*[tiab]) 27
6 (hyperkeratos*[tiab] OR hyperkeratoma*[tiab] OR hyperkeratotic*[tiab] OR hyperkeratopath*[tiab]) 6,778
5 ((solar*[tiab] OR senil*[tiab]) AND (cheilit*[tiab] OR cheilos*[tiab])) 42
4 ((solar*[tiab] OR senil*[tiab]) AND (keratos*[tiab] OR keratoma*[tiab] OR keratotic*[tiab] OR keratopath*[tiab])) 847
3 (actinic*[tiab] AND (cheilit*[tiab] OR cheilos*[tiab])) 353
2 (actinic*[tiab] AND (keratos*[tiab] OR keratoma*[tiab] OR keratotic*[tiab] OR keratopath*[tiab])) 3,714
1 "Keratosis, Actinic"[mesh:noexp] 2,050

Source: Epistemonikos
Interface / URL: https://www.epistemonikos.org/
Database coverage dates: Information not found.
Search date: 26/06/20
Retrieved records: 181
Search strategy:

The following two searches were entered into the search box at: https://www.epistemonikos.org/en/advanced_search. Search 1 was not limited by field

The searches were restricted by category to systematic reviews.

All results were imported into an empty EndNote Library (212 records in total). Records were then de-duplicated using EndNote default deduplication settings. 31 records were identified as duplicates and removed. The remaining 181 records were retrieved.

1. ((actinic* OR solar* OR senil*) AND (keratos* OR keratoma* OR keratotic* OR keratopath* OR cheilit* OR cheilos*)) OR (hyperkeratos* OR hyperkeratoma* OR hyperkeratotic* OR hyperkeratopath* OR keratinocytic) OR ((sailor* OR farmer*) AND (lip OR lips)) = 122

2. (title:(ak OR aks OR hak OR haks OR kin OR kins) OR abstract:(ak OR aks OR hak OR haks OR kin OR kins)) = 90

Source: ClinicalTrials.gov
Interface / URL: https://clinicaltrials.gov/ct2/home
Database coverage dates: Information not found. ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). The site was made available to the public in February 2000.
Search date: 06/07/20
Retrieved records: 418
Search strategy:

The following three searches were conducted separately. All search terms were entered using the Expert search interface.

The three sets of results were imported into an empty EndNote library (470 records) and deduplicated using EndNote default de-duplication settings. 52 records were identified as duplicates and removed from the EndNote library. The remaining 418 records were retrieved for assessment.

1. (actinic OR solar OR senile) AND (keratosis OR keratoses OR keratoma OR keratomas OR keratotic OR keratopathy OR keratopathies OR keratopathic OR cheilitis OR cheilosis OR cheiloses OR hyperkeratosis OR hyperkeratoses OR hyperkeratoma OR hyperkeratomas OR hyperkeratotic OR hyperkeratopathy OR hyperkeratopathies OR hyperkeratopathic OR "keratinocytic intraepidermal neoplasia" OR "keratinocytic intraepidermal neoplasias" OR "keratinocytic intra-epidermal neoplasia" OR "keratinocytic intra-epidermal neoplasias") = 336

2. ("sailor lip" OR "sailors lip" OR "sailor lips" OR "sailors lips" OR "farmer lip" OR "farmers lip" OR "farmer lips" OR "farmers lips") = 0

3. AREA[ConditionSearch] (ak OR aks OR hak OR haks OR kin OR kins) = 134

Search note:

- in clinicaltrials.gov, a search on "keratinocytic intraepidermal neoplasias" also searches on the term keratosis (the latter is identified by the interface as a synonym). This search for this term (and variants) was therefore restricted to records which also explicitly referred to the actinic, solar or senile context.

- in clinicaltrials.gov, a search on hyperkeratosis also searches on the term keratosis (the latter is identified by the interface as a synonym). This search for this term was therefore restricted to records which also explicitly referred to the actinic, solar or senile context.

- Abbreviation such as 'AK' are frequently found in non-relevant contexts in clinicaltrials.gov records. The search for the following terms was therefore restricted to the 'Condition or disease' field: ak OR aks OR hak OR haks OR kin OR kins

Source: EU Clinical Trials Register
Interface / URL: https://www.clinicaltrialsregister.eu/
Database coverage dates: The EU Clinical Trials Register contains information on interventional clinical trials on medicines conducted in the European Union (EU), or the European Economic Area (EEA) which started after 1 May 2004.
Search date: 08/07/20
Retrieved records: 448 (246 trials were identified and downloaded in 'Full Trial Details' format. Files in this format contain full details on each clinical trial selected for download. Where multi-state trials have been downloaded full information for each of the member states/countries involved in the trial are included separately. When imported into EndNote, records are created for each multi-state trial. When details for the 246 trials were imported into EndNote, 448 records were created. The figure has been used for the 'number of retrieved records' figure, and for informing PRISMA)
Search strategy:

The following terms were entered using the search interface at https://www.clinicaltrialsregister.eu/ctr-search/search:

((actinic OR solar OR senile) AND (keratosis OR keratoses OR keratoma OR keratomas OR keratotic OR keratopathy OR keratopathies OR keratopathic OR cheilitis OR cheilosis OR cheiloses)) OR (hyperkeratosis OR hyperkeratoses OR hyperkeratoma OR hyperkeratomas OR hyperkeratotic OR hyperkeratopathy OR hyperkeratopathies OR hyperkeratopathic OR "keratinocytic intraepidermal neoplasia" OR "keratinocytic intraepidermal neoplasias" OR "keratinocytic intra-epidermal neoplasia" OR "keratinocytic intra-epidermal neoplasias" OR "sailor lip" OR "sailors lip" OR "sailor lips" OR "sailors lips" OR "farmer lip" OR "farmers lip" OR "farmer lips" OR "farmers lips" OR ak OR aks OR hak OR haks OR kin OR kins) = 246 trials found (246 trials with a EudraCT protocol found. 0 paediatric studies in scope of Art45 of the Paediatric Regulation found).

Source: Drugs@FDA
Interface / URL: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
Database coverage dates: 1938 to present
Search date: 08/07/20
Retrieved records: 32
Search strategy:

Note: Drugs@FDA does not allow searching by indication.

The following documents were sought for the drugs of interest in AK: Medical Reviews, Statistical Reviews, Other Reviews.

The drugs of interest are:

- Tirbanibulin 1%
- Diclofenac 3%
- Imiquimod 3.75% or 5%
- Ingenol mebutate 0.015%
- Salicylic acid + 5-fluorouracil 0.5%
- 5-fluorouracil 5%
- 5-fluorouracil 4%
- aminolevulinic acid (as used in photodynamic therapy (PDT))
- methyl aminolevulinate (as used in PDT)

The search interface at the following URL was used:
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Separate searches were conducted on each drug name shown below.

For each search:
- Each returned drug name was selected to expand the result
- Each of the drugs shown on expansion was selected to display details
- The link to 'Approval Date(s) and History, Letters, Labels, Reviews' was selected (if available) to view documents
- Documents were checked to ensure the results was in the correct indication and contained at least one of the relevant reviews listed above
- PDFs for Medical reviews, Statistical Reviews or Other Reviews on the correct indication were retrieved for further assessment

Injectable and oral treatments were excluded.

1. tirbanibulin = 0 results returned
2. diclofenac = 5 documents retrieved
3. imiquimod = 7 documents downloaded
4. ingenol mebutate = 4 documents downloaded
5. salicylic acid = 0 documents retrieved
6. fluorouracil = 8 documents downloaded
7. 5-fu = 0 results returned
8. 5fu = 0 results returned
9. aminolevulinate = 2 documents downloaded
10. aminolaevulinate = 0 results returned
11. aminolaevulinic = 0 results returned
12. aminolevulinic = 6 documents downloaded

32 documents were retrieved

Source: European Medicines Agency (EMA) medicines webpages
Interface / URL: https://www.ema.europa.eu/en
Database coverage dates: n/a
Search date: 14/07/20
Retrieved records: 8
Search strategy:

The following document was sought for the interventions of interest in AK: 'EPAR - Public Assessment Report'. 'Assessment Report' documents with variant titles were also retrieved (e.g. 'EPAR - Assessment Report', 'EPAR - Assessment Report – Variation', 'EPAR – Refusal Assessment Report' and 'EPAR - Assessment Report – Article [#]', 'EPAR - Assessment Report – Extension' etc.)
Documents found under both 'Initial marketing-authorisation documents' and ' Changes since initial authorisation of medicine' were retrieved.

The search interface at the following URL was used: https://www.ema.europa.eu/en/medicines. The following searches were conducted separately:

actinic* AND kerato* = 21 results returned
actinic* AND cheil* = 1 result returned
solar* AND kerato* = 7 results returned
solar* AND cheil* = 3 results returned
senil* AND kerato* = 1 result returned
senil* AND cheil* = 0 results returned
hyperkerato* = 58 results returned
"keratinocytic intraepidermal neoplasia" = 0 results returned
"keratinocytic intraepidermal neoplasias" = 0 results returned
"keratinocytic intra-epidermal neoplasia" = 0 results returned
"keratinocytic intra-epidermal neoplasias" = 0 results returned

Results were restricted by applying the following filters (where available):
Categories: Human
Medicine: European public assessment reports (EPAR).

Each result was assessed for correct drug and correct indication.

For relevant results, documents under 'Assessment history' were checked to identify 'EPAR - Public Assessment Report' documents. PDFs for relevant EPARs were retrieved for further assessment. Duplicate documents were not retrieved.

8 documents were retrieved

Source: National Institute for Health and Care Excellence (NICE) webpages
Interface / URL: https://www.nice.org.uk/
Database coverage dates: n/a
Search date: 14/07/20
Retrieved records: 0
Search strategy:

The following documents were sought for the interventions of interest in AK: Company Submissions, Final Appraisal Determination Documents and Assessment Reports (the latter only if the NICE technology appraisal was a MTA - multiple technology appraisal).

The site-wide search interface was used at: https://www.nice.org.uk/. Separate searches were conducted on the terms below.

Results were filtered by 'Document Type' to 'Guidance', then by 'Guidance Category' to 'Technology appraisal guidance', 'Interventional procedures guidance' or 'Medical technologies guidance'.

Results were scanned to identify technology appraisals, interventional procedures guidance or medical technologies guidance for the correct interventions in the correct indication. Associated documents under the 'History' tab were viewed to check for Company Submissions, Final Appraisal Determination Documents and Assessment Reports.

PDFs for relevant documents were retrieved for further assessment. Duplicate documents were not retrieved.

1. keratosis OR keratoses OR keratoma OR keratomas = 2 results returned
2. keratotic OR keratopathy OR keratopathies OR keratopathic = 0 results returned
3. cheilitis OR cheilosis OR cheiloses = 0 results returned
4. hyperkeratosis OR hyperkeratoses OR hyperkeratoma OR hyperkeratomas = 2 results returned
5. hyperkeratotic OR hyperkeratopathy OR hyperkeratopathies OR hyperkeratopathic = 1 result returned
6. keratinocytic = 0 results returned

0 documents were retrieved

Source: Canadian Agency for Drugs and Technologies in Health (CADTH) webpages
Interface / URL: https://www.cadth.ca/
Database coverage dates: n/a
Search date: 15/07/20
Retrieved records: 4
Search strategy:

The following documents were sought for the drugs of interest in AK: CADTH clinical guidance and CADTH final recommendations.

The site-wide search interface was used at: https://www.cadth.ca/. Separate searches were conducted on the search terms shown below.

Results were assessed for correct intervention and correct indication. Relevant results were checked for document types of interest.

PDFs of relevant documents were retrieved for further assessment. Duplicate documents were not retrieved.

1. keratosis = 20 results returned
2. keratoses = 11 results returned
3. keratoma = 0 results returned
4. keratomas = 0 results returned
5. keratotic = 1 result returned
6. keratopathy = 6 results returned
7. keratopathies = 1 result returned
8. keratopathic = 0 results returned
9. cheilitis = 4 results returned
10. cheilosis = 0 results returned
11. cheiloses = 0 results returned
12. hyperkeratosis = 8 results returned
13. hyperkeratoses = 0 results returned
14. hyperkeratoma = 0 results returned
15. hyperkeratomas = 0 results returned
16. hyperkeratotic = 0 results returned
17. hyperkeratopathy = 0 results returned
18. hyperkeratopathies = 0 results returned
19. hyperkeratopathic = 0 results returned
20. keratinocytic = 0 results returned

4 documents were retrieved

Source: Institute for Clinical and Economic Review webpages
Interface / URL: https://icer-review.org/
Database coverage dates: n/a
Search date: 15/07/20
Retrieved records: 0
Search strategy:

The following were sought for the drugs of interest in weight loss: Final Evidence Report (or Draft Evidence Report if Final was not available) and the Evidence Presentation (if available).

'Past topics' were located at the following URL: https://icer-review.org/topics/. The "Filter by Topic" drop down was used to identify reviews in AK. No relevant reviews were identified

0 documents were retrieved

Source: European Association of Dermato-Oncology (EADO) Congress 2018
Interface / URL: n/a
Database coverage dates: n/a
Search date: 17/07/20

Retrieved records: 0
Search strategy:

A link to the 2018 14th EADO Congress was identified at: https://www.eado.org/activities/eado-congress/8. The link was: http://www.congresseado-melanomacenters2018.com/. The link led to a blank page.

Abstracts could not be identified freely available online.

EADO were contacted (info@eado.org) to enquire if abstracts were available to be freely viewed online anywhere or, if not, whether a PDF of the abstracts could be sent. EADO confirmed that the abstracts are available only to congress participants.

Almirall were asked if they could provide access to the abstracts. Almirall investigated, but were unable to access the EADO 2018 abstracts.

The decision was made by research team that the EADO 2018 abstracts were unobtainable

Source: European Association of Dermato-Oncology (EADO) Congress 2019
Interface / URL: n/a
Database coverage dates: n/a
Search date: 02/09/20
Retrieved records: 0
Search strategy:

Abstracts could not be identified freely available online.

EADO were contacted (info@eado.org) to enquire if abstracts were available to be freely viewed online anywhere or, if not, whether a PDF of the abstracts could be sent. EADO confirmed that the abstracts are available only to congress participants.

Almirall were asked if they could provide access to the abstracts. Almirall investigated and a PDF of the abstract book for EADO 2019 was provided.

Ctrl+F was used to search on the following terms across the 15th EADO Congress Abstract Book. Each term was searched on individually. Abstracts including the term were assessed by the Information Specialist for relevance. Potentially relevant abstracts were retrieved for further consideration:

actinic = 0 abstracts retrieved
solar = 0 abstracts retrieved
senil = 0 abstracts retrieved
hyperkerato = 0 abstracts retrieved
keratinocytic = 0 abstracts retrieved
sailor = 0 abstracts retrieved
farmer = 0 abstracts retrieved
ak = 0 abstracts retrieved
kin = 0 abstracts retrieved

0 abstracts were retrieved for further consideration

Source: European Academy of Dermatology and Venereology (EADV) Congress 2017
Interface / URL: n/a
Database coverage dates: n/a
Search date: 05/08/20
Retrieved records: 6
Search strategy:

The list of EADV Congresses was identified at: https://www.eadv.org/congress/show-congress. No link was given for a 2017 Congress webpage, and no link could be found elsewhere on the website. Abstracts could not be identified freely available online.

The conference organisers were contacted (congress@eadv.org) to enquire if abstracts were available to be freely viewed online anywhere or, if not, whether a PDF of the abstracts could be sent. EADV confirmed that abstracts submitted for previous EADV events are freely accessible only to EADV members.

Almirall were asked if they could provide access to the abstracts. Almirall investigated, and abstracts were sent.

Two routes of access were provided:

1. EADV Abstracts.exe application. This route only facilitated search by topic browsing, or by title, author or abstract id search – no abstract search was available. The topic browsing and title-only search options were not considered to be robust enough search approaches, so this application was not used.

2. A 'data' folder containing 2493 individual abstracts as PDF files

The following process was used to search across the PDF files contained in the 'data' folder:

1. The first PDF file in the 'data' folder was opened in Acrobat Reader
2. Shift+Ctrl+F was used to to open the Search panel
3. The option to search 'All PDF documents in' was selected.
4. The dropdown option was used to select 'Browse for Location'
5. Navigated to the 'data folder' containing the conference abstract PDFs and clicked OK
6. The following terms were entered into 'What word or phrase would you like to search for?' box: actinic solar senil keratinocytic sailor farmer
7. 'Show more options' was selected
8. From the dropdown options, 'Match Any of the words' was selected
9. Clicked on 'Search'.
10. 112 PDFs were found containing the terms
11. Each displayed PDF result was clicked on to open the PDF. The PDF was assessed for relevance by the Information Specialist. PDFs for RCTs or systematic reviews on treatment of AK with the interventions of interest were retrieved for further consideration.
12. Following assessment, 6 / 112 PDFs were retrieved for further consideration
13. 'New search' was selected
14. The following terms were entered into 'What word or phrase would you like to search for?' box: ak aks hak haks kin kins
15. 'Whole words only' was selected
16. Clicked on 'Search'
17. 25 PDFs were found containing the terms

18. Each displayed PDF result was clicked on to open the PDF. The PDF was assessed for relevance by the Information Specialist. PDFs for RCTs or systematic reviews on treatment of AK with the interventions of interest were retrieved for further consideration. Duplicates were not retrieved.
19. Following assessment, 0 / 25 PDFs were retrieved for further consideration

Search note on hyperkeratosis terms:

Search functionality was very limited and did not facilitate efficient search and assessment methods. In this context, and given that the population of interest was AK rather than non-specific hyperkeratosis, in relation to hyperkeratosis terms the search approach used was designed to only retrieve records containing hyperkeratosis terms (and variants including hyperkeratoma, hyperkeratotic, hyperkeratopathy) if the terms were found in the context of 'actinic', 'solar' or 'senile'.

Source: European Academy of Dermatology and Venereology (EADV) Congress 2018
Interface / URL: n/a
Database coverage dates: n/a
Search date: 06/08/20
Retrieved records: 2
Search strategy:

The list of EADV Congresses was identified at: https://www.eadv.org/congress/show-congress

A link was found for a 2018 Congress webpage (https://eadvparis2018.org/) but the link did not lead to any congress information. No link could be found elsewhere on the website. Abstracts could not be identified freely available online.

The conference organisers were contacted (congress@eadv.org) to enquire if abstracts were available to be freely viewed online anywhere or, if not, whether a PDF of the abstracts could be sent. EADV confirmed that abstracts submitted for previous EADV events are freely accessible only to EADV members.

Almirall were asked if they could provide access to the abstracts. Almirall investigated, and abstracts were sent.

Two routes of access were provided:

1. EADV Abstracts.exe application. This route only facilitated search by topic browsing, or by title, author or abstract id search – no abstract search was available. The topic browsing and title-only search options were not considered to be robust enough search approaches, so this application was not used.

2. A 'data' folder containing 2543 individual abstracts as PDF files

The following process was used to search across the PDF files contained in the 'data' folder:

1. The first PDF file in the 'data' folder was opened in Acrobat Reader
2. Shift+Ctrl+F was used to to open the Search panel
3. The option to search 'All PDF documents in' was selected.
4. The dropdown option was used to select 'Browse for Location'
5. Navigated to the 'data folder' containing the conference abstract PDFs and clicked OK
6. The following terms were entered into 'What word or phrase would you like to search for?' box: actinic solar senil keratinocytic sailor farmer

7. 'Show more options' was selected
8. From the dropdown options, 'Match Any of the words' was selected
9. Clicked on 'Search'.
10. 117 PDFs were found containing the terms
11. Each displayed PDF result was clicked on to open the PDF. The PDF was assessed for relevance by the Information Specialist. PDFs for RCTs or systematic reviews on treatment of AK with the interventions of interest were retrieved for further consideration.
12. Following assessment, 2 / 117 PDFs were retrieved for further consideration
13. 'New search' was selected
14. The following terms were entered into 'What word or phrase would you like to search for?' box: ak aks hak haks kin kins
15. 'Whole words only' was selected
16. Clicked on 'Search'
17. 20 PDFs were found containing the terms
18. Each displayed PDF result was clicked on to open the PDF. The PDF was assessed for relevance by the Information Specialist. PDFs for RCTs or systematic reviews on treatment of AK with the interventions of interest were retrieved for further consideration. Duplicates were not retrieved.
19. Following assessment, 0 / 20 PDFs were retrieved for further consideration

Search note on hyperkeratosis terms:

Search functionality was very limited and did not facilitate efficient search and assessment methods. In this context, and given that the population of interest was AK rather than non-specific hyperkeratosis, in relation to hyperkeratosis terms the search approach used was designed to only retrieve records containing hyperkeratosis terms (and variants including hyperkeratoma, hyperkeratotic, hyperkeratopathy) if the terms were found in the context of 'actinic', 'solar' or 'senile'.

Source: European Academy of Dermatology and Venereology (EADV) Congress 2019
Interface / URL: n/a
Database coverage dates: n/a
Search date: 06/08/20
Retrieved records: 1
Search strategy:

The list of EADV Congresses was identified at: https://www.eadv.org/congress/show-congress

A link was found for a 2019 Congress webpage (https://eadvmadrid2019.org/). No full abstracts could be found at this site. Abstracts could not be identified freely available online.

The conference organisers were contacted (congress@eadv.org) to enquire if abstracts were available to be freely viewed online anywhere or, if not, whether a PDF of the abstracts could be sent. EADV confirmed that abstracts submitted for previous EADV events are freely accessible only to EADV members.

Almirall were asked if they could provide access to the abstracts. Almirall investigated, and abstracts were sent.

Two routes of access were provided:

1. EADV Abstracts.exe application. This route only facilitated search by topic browsing, or by title, author or abstract id search – no abstract search was available. The topic browsing and title-only search options were not considered to be robust enough search approaches, so this application was not used.

2. A 'data' folder containing 2302 individual abstracts as PDF files

The following process was used to search across the PDF files contained in the 'data' folder:

1. The first PDF file in the 'data' folder was opened in Acrobat Reader
2. Shift+Ctrl+F was used to to open the Search panel
3. The option to search 'All PDF documents in' was selected.
4. The dropdown option was used to select 'Browse for Location'
5. Navigated to the 'data folder' containing the conference abstract PDFs and clicked OK
6. The following terms were entered into 'What word or phrase would you like to search for?' box: actinic solar senil keratinocytic sailor farmer
7. 'Show more options' was selected
8. From the dropdown options, 'Match Any of the words' was selected
9. Clicked on 'Search'.
10. 78 PDFs were found containing the terms
11. Each displayed PDF result was clicked on to open the PDF. The PDF was assessed for relevance by the Information Specialist. PDFs for RCTs or systematic reviews on treatment of AK with the interventions of interest were retrieved for further consideration.
12. Following assessment, 1 / 78 PDFs were retrieved for further consideration
13. 'New search' was selected
14. The following terms were entered into 'What word or phrase would you like to search for?' box: ak aks hak haks kin kins
15. 'Whole words only' was selected
16. Clicked on 'Search'
17. 14 PDFs were found containing the terms
18. Each displayed PDF result was clicked on to open the PDF. The PDF was assessed for relevance by the Information Specialist. PDFs for RCTs or systematic reviews on treatment of AK with the interventions of interest were retrieved for further consideration. Duplicates were not retrieved.
19. Following assessment, 0 / 14 PDFs were retrieved for further consideration

Search note on hyperkeratosis terms:

Search functionality was very limited and did not facilitate efficient search and assessment methods. In this context, and given that the population of interest was AK rather than non-specific hyperkeratosis, in relation to hyperkeratosis terms the search approach used was designed to only retrieve records containing hyperkeratosis terms (and variants including hyperkeratoma, hyperkeratotic, hyperkeratopathy) if the terms were found in the context of 'actinic', 'solar' or 'senile'.

Supplementary Table S1: Databases and information sources searched for the review

Resource	Interface / URL
MEDLINE(R) ALL	Ovid SP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley
Database of Abstracts of Reviews of Effects (DARE)	https://www.crd.york.ac.uk/CRDWeb/
Health Technology Assessment Database (HTA Database)	https://www.crd.york.ac.uk/CRDWeb/
Epistemonikos	https://www.epistemonikos.org/
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/
ClinicalTrials.gov	https://www.clinicaltrials.gov/ct
Drugs@FDA	https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
European Medicines Agency (EMA) medicines webpages	https://www.ema.europa.eu/en
National Institute for Health and Care Excellence (NICE) webpages	https://www.nice.org.uk/
Canadian Agency for Drugs and Technologies in Health (CADTH) webpages	https://www.cadth.ca/
Institute for Clinical and Economic Review (ICER) webpages	https://icer-review.org/

Recent research published as conference abstracts was identified by searching Embase (which indexes a significant number of conference publications). The following three conferences were identified as highly relevant:

- European Association of Dermato-Oncology (EADO) Congress
- American Academy of Dermatology (AAD) Annual Meeting
- European Academy of Dermatology and Venereology (EADV) Congress

We ascertained if records for these conferences (above) were included in Embase for the last three years (2017 to 2020). Records were not found in Embase for the sub-set of conferences listed below. For the conferences listed below, we undertook hand-searching of proceedings via conference webpages or journal supplements, where they were available online free of charge.

- EADV Congress: 2017, 2018, 2019
- EADO Congress: 2018, 2019

All were hand-searched, except EADO 2018. Abstracts were unobtainable for EADO 2018 – the abstracts could not be identified via an online search, and EADO confirmed that the abstracts were only available to conference attendees. AAD Annual Meeting 2020 was cancelled, and while EADO Congress 2020 and EADV Congress 2020 were held virtually in October 2020,

both were held after the review and NMA were completed, and for this reason are not included in this manuscript.

Supplementary Table S2: Documents excluded from the review (145)

Reference	Exclusion Reason
Actavis Inc. A Study Comparing Diclofenac Sodium Gel 3% to Solaraze® (Diclofenac Sodium) Gel 3% in the Treatment of Actinic Keratosis. Identifier: NCT01962987. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://ClinicalTrials.gov/show/NCT01962987.	Completed trial (no results)
Actavis Inc. Bioequivalence of Generic Imiquimod Cream, 5% When Compared to Aldara™ (Imiquimod) Cream, 5% in the Treatment of Actinic Keratosis. Identifier: NCT00948428. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2008. Available from https://ClinicalTrials.gov/show/NCT00948428.	Completed trial (no results)
Actavis Mid-Atlantic LLC. A Bioequivalence Study With Clinical Endpoints Comparing Generic Imiquimod Cream, 3.75% and Zyclara™ (Imiquimod) Cream, 3.75% in Subjects With Actinic Keratoses. Identifier: NCT01502020. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://ClinicalTrials.gov/show/NCT01502020.	Completed trial (no results)
Almirall SA. Study on the Efficacy of LAS41005 in the Treatment of Actinic Keratosis. Identifier: NCT00987246. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2008. Available from https://ClinicalTrials.gov/show/NCT00987246.	Completed trial (no results)
Apotex Inc. A Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled Therapeutic Equivalence Study of Three Imiquimod Cream 5% Treatments for Patients With Actinic Keratosis. Identifier: NCT00859105. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2008. Available from https://ClinicalTrials.gov/show/NCT00859105.	Completed trial (no results)
Biofrontera Bioscience GmbH. A Clinical Trial of Topical Photodynamic Therapy With 5-aminolevulinic Acid for the Treatment of Actinic Keratosis. Identifier: NCT02799030. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2006. Available from https://ClinicalTrials.gov/show/NCT02799030.	Possible ongoing trial (no results)
Braathen L. Photodynamic therapy for oncologic indications: actinic keratosis (Abstract W20-3). 11th congress of the european academy of dermatology & venereology prague october 2nd-6th, 2002. 11th congress of the european academy of dermatology & venereology prague october 2nd-6th, 2002. 2002; 16: 57. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00478479/full	Abstract - cannot link to full text paper
Charité. A randomized study of topical 3% Diclofenac in a 2.5% Hyaluronate base (Solaraze® 3% Gel) versus topical 5% 5-Fluorouracil (Efudix® Cream) versus liquid nitrogen spray cryotherapy in immunosufficient patients with actinic keratoses – a single center study H2H Solaraze-5FU-Cryo. Identifier: EUCTR2006-000815-24. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2006. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-000815-24/DE/.	Completed trial (no results)
Dartmouth-Hitchcock Medical Center. Indoor Daylight Photo Dynamic Therapy for Actinic Keratosis. Identifier: NCT03805737. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2019. Available from https://ClinicalTrials.gov/show/NCT03805737.	Possible ongoing trial (no results)
Dermapharm AG. Double-blind, randomised clinical study comparing efficacy and safety of Imiquimod 5% Cream (Test) vs. Aldara® 5% Cream (Reference) vs.	Possible ongoing trial (no results)

Reference	Exclusion Reason
Vehicle in patients with actinic keratosis. Identifier: EUCTR2016-000712-15. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2016. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000712-15/DE/.	
DUSA Pharmaceuticals I. Microneedle Lesion Preparation Prior to Aminolevulinic Acid Photodynamic Therapy (ALA-PDT) for AK on Face. Identifier: NCT02632110. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2016. Available from https://ClinicalTrials.gov/show/NCT02632110.	Ineligible study design
DUSA Pharmaceuticals I. Phase 3 Study of Levulan With New Blue Light for AK on the Face or Scalp. Identifier: NCT03024060. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2017. Available from https://ClinicalTrials.gov/show/NCT03024060.	Possible ongoing trial (no results)
Encube Ethicals Pvt. Ltd. Therapeutic Equivalence of Diclofenac Sodium Gel 3% vs Solaraze ® in the Treatment of Actinic Keratosis. Identifier: NCT03826550. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2018. Available from https://ClinicalTrials.gov/show/NCT03826550.	Possible ongoing trial (no results)
Foley K, Gupta A, Martin G, Tweed J, Villanueva E, Carviel J. Topical treatments and photodynamic therapy for actinic keratosis of the face and scalp. Cochrane Database Syst Rev. 2019; (10): Available from: http://dx.doi.org/10.1002/14651858.CD013452	Ineligible publication type
Galderma R&D. A Study to Assess Recurrence of Actinic Keratosis in Participants Treated With Methyl Aminolevulinate Hydrochloride Cream or Vehicle Cream Who Achieved Complete Response to Treated Lesions in Earlier Study. Identifier: NCT04269395. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2020. Available from https://ClinicalTrials.gov/show/NCT04269395.	Possible ongoing trial (no results)
Galderma R&D. Multicenter Study to Assess the Efficacy and Safety of Methyl Aminolevulinate Hydrochloride (MAL) 16.8% Cream (CD06809-41) Versus Vehicle Cream for Actinic Keratosis of the Face. Identifier: NCT04085367. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2019. Available from https://ClinicalTrials.gov/show/NCT04085367.	Possible ongoing trial (no results)
Galderma. Metvix PDT Versus Vehicle PDT With Aktilite CL128 Lamp in Patients With Actinic Keratosis on the Face and Scalp. Identifier: NCT00304239. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2006. Available from https://ClinicalTrials.gov/show/NCT00304239.	Completed trial (no results)
Glynis Ablon1 AB, Suzanne Bruce3, Michael Bukhalo4, Seth Forman5, Abel Jarell6, Steven Kempers7,, Edward Lain8 RL, Jane Fang10, 1 The Ablon Skin Institute Research Center MB, United States, 2 Oregon Medical Research Center,, Portland US, 3 The Center For Skin Research, Suzanne Bruce And Associates, Pa, Houston, United States,, 4 Arlington Dermatology AH, United States, 5 Forward Clinical Trials, Tampa, United States, 6 Activmed, Practices & Research P, United States, 7 Associated Skin Care Specialists, Fridley, United States, 8 Austin, et al. Abstract N°: FC05.06. Title: KX2-391 ointment 1%, a novel Src phosphorylation and tubulin polymerisation inhibitor, for the treatment of actinic keratosis: Results from two pivotal Phase III studies. In: European Academy of Dermatology and Venereology (EADV) Congress 2019, 2019.	Abstract - cannot link to full text paper
Grönroos M. Daylight-PDT in the treatment of actinic keratosis: a pilot study comparing two different light sensitizers. Identifier: EUCTR2013-001389-40. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2013.	Possible ongoing trial (no results)

Reference	Exclusion Reason
Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001389-40/FI/.	
Grönroos M. Treating actinic keratoses with natural daylight PDT: comparing two light sensitizers (ALA vs. MAL). Identifier: EUCTR2013-002108-15. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2013. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002108-15/FI/.	Possible ongoing trial (no results)
Infectopharm Arzneimittel GmbH. Study on the treatment of actinic keratosis with the medical device Solcera in comparison with the drug Solaraze and placebo. Identifier: EUCTR2019-003678-16. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2019. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-003678-16/DE/.	Possible ongoing trial (no results)
Intas Pharmaceuticals Ltd. A Randomized, Double-Blind, Placebo-controlled, Three-arm, Parallel Assignment, Multi-Centre, Therapeutic Equivalence Study of Two Fluorouracil 5% Topical Cream Formulations in Adult Patients with Multiple Actinic Keratoses Lesions. Identifier: EUCTr2018-003436-74. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2018. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-003436-74/ES/.	Possible ongoing trial (no results)
Janne Räsänen. Daylight photodynamic therapy for actinic keratoses: a multicentre study comparing two photosensitizers (BF-200 ALA versus MAL) Identifier: EUCTR2015-000265-32. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2015. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000265-32/FI/.	Possible ongoing trial (no results)
LEO Pharma. Risk of Squamous Cell Carcinoma on Skin Areas Treated with Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%. Identifier: EUCTR2012-003112-31. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2020. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003112-31/GB/.	Possible ongoing trial (no results)
LEO Pharma. Risk of Squamous Cell Carcinoma on Skin Areas Treated With Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%. Identifier: NCT01926496. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://ClinicalTrials.gov/show/NCT01926496.	Possible ongoing trial (no results)
Maastricht Universitair Medisch Centrum. Topical Ingenol mebutate versus 5% 5-fluorouracil versus 5% Imiquimod versus photodynamic therapy in the treatment of actinic keratosis: a multi-center randomized efficacy and cost-effectiveness study. Identifier: EUCTR2014-003691-23. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2014. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-003691-23/NL/.	Possible ongoing trial (no results)
Medicis Global Service Corporation. Potential Effect of Topical Imiquimod on Atrial Ectopy in Patients With Actinic Keratosis. Identifier: NCT01413763. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://ClinicalTrials.gov/show/NCT01413763.	Completed trial (no results)
Novartis Pharmaceuticals. Safety, tolerability, and efficacy study of LFX453 in actinic keratosis patients. Identifier: NCT02404389. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://ClinicalTrials.gov/show/NCT02404389.	Insufficient information to include
Perrigo Company. To Compare Safety and Efficacy of Perrigo's Drug Compared to an FDA Approved Drug in the Treatment of Actinic Keratosis. Identifier:	Completed trial (no results)

Reference	Exclusion Reason
NCT02459795. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://ClinicalTrials.gov/show/NCT02459795.	
Perrigo Company. To Compare Safety and Efficacy of Perrigo's Drug Product Compared to an FDA Approved Drug Product in the Treatment of Actinic Keratosis. Identifier: NCT02385318. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://ClinicalTrials.gov/show/NCT02385318.	Possible ongoing trial (no results)
PhotoCure ASA. A multicenter, double blind, vehicle-controlled, randomized study of photodynamic therapy (PDT) with Metvix®160 mg/g cream and Aktilite CL128 LED light in patients with multiple actinic keratoses on the face and/or scalp. Identifier: EUCTR2005-005015-13. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2005. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-005015-13/DE/.	Completed trial (no results)
Photonamic GmbH & Co. KG. PD P 506 A-PDT Versus Placebo-PDT and Cryosurgery for the Treatment of AK. Identifier: NCT00308867. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2006. Available from https://ClinicalTrials.gov/show/NCT00308867.	Completed trial (no results)
Photonamic GmbH & Co. KG. Photodynamic Therapy With PD P 506 A Compared With Placebo-PDT for the Treatment of AK. Identifier: NCT00308854. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2006. Available from https://ClinicalTrials.gov/show/NCT00308854.	Completed trial (no results)
Photonamic GmbH & Co. KG. Photodynamic Therapy with PD P 506 A or its placebo compared with cryosurgery for the treatment of mild to moderate actinic keratosis. Identifier: EUCTR2005-003556-36. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2005. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-003556-36/DE/.	Completed trial (no results)
RWTH Aachen University Hospital. Prospektive randomisierte studie zur untersuchung der wirksamkeit der photodynamischen therapie bei aktinischen keratosen PDT in AK. Identifier: EUCTR2005-002983-27. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2005. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-002983-27/DE/.	Ineligible comparator
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Taro Pharmaceuticals USA. A Study Comparing Diclofenac Sodium Gel 3% to Solaraze® Gel 3% in the Treatment of Actinic Keratosis. Identifier: NCT01742663. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2012. Available from https://ClinicalTrials.gov/show/NCT01742663.	Completed trial (no results)

Reference	Exclusion Reason
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Teva Pharmaceuticals USA. A Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled, Multicenter Study Comparing Diclofenac Sodium Gel, 3% to Solaraze® Gel, 3% in the Treatment of Actinic Keratosis on the Face or Bald Scalp. Identifier: NCT02611804. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://ClinicalTrials.gov/show/NCT02611804.	Possible ongoing trial (no results)
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University Hospital Regensburg. Daylight-PDT With MAL for AK and Photodamaged Skin. Identifier: NCT02736760. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2016. Available from https://ClinicalTrials.gov/show/NCT02736760.	Possible ongoing trial (no results)
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Reference	Exclusion Reason
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Berman B, Marmur E, Melgaard A, Larsson T. Three-day topical treatment with ingenol mebutate gel, 0.015% for actinic keratoses on the face and scalp: analysis of data pooled from two trials. J Dtsch Dermatol Ges. 2013;11(S2):109.	Abstract - cannot link to full text paper
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Reference	Exclusion Reason
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Garbe C, Basset-Seguin N, Poulin Y, Larsson T, Osterdal ML, Venkata R, et al. Efficacy and safety of follow-up field treatment of actinic keratosis with ingenol mebutate 0.015% gel: a randomized, controlled 12-month study. Br J Dermatol. 2016;174(3):505-13.	Ineligible study design
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Gebauer K, Brown P, Varigos G. Topical diclofenac in hyaluronan gel for the treatment of solar keratoses. Australas J Dermatol. 2003;44(1):40-3.	Ineligible patient population
Gholam P, Bosselmann I, Enk A, Fink C. Impact of red versus blue light on tolerability and efficacy of PDT: a randomized controlled trial. J Dtsch Dermatol Ges. 2018;16(6):711-17.	Ineligible study design
Goldberg D, Ciocon D, Hussain M. Comparison of 5-ALA alone, PDT alone and a combination of sequential 5-ALA and PDT in the treatment of actinic keratoses and photorejuvenation. Lasers Surg Med. 2010;42(S22):92.	Ineligible outcomes
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Reference	Exclusion Reason
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Jansen MHE, Kessels J, Merks I, Nelemans PJ, Kelleners-Smeets NWJ, Mosterd K, et al. A trial-based cost-effectiveness analysis of topical 5-fluorouracil vs. imiquimod vs. ingenol mebutate vs. methyl aminolaevulinate conventional photodynamic therapy for the treatment of actinic keratosis in the head and neck area performed in the Netherlands. Br J Dermatol. 2020;21:21.	Ineligible outcomes
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Reference	Exclusion Reason
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McEwan LE, Smith JG. Topical diclofenac/hyaluronic acid gel in the treatment of solar keratoses. Australas J Dermatol. 1997;38(4):187-9.	Ineligible patient population
Mei X, Wang L, Zhang R, Zhong S. Daylight versus conventional photodynamic therapy for the treatment of actinic keratosis: a meta-analysis of randomized controlled trials. Photodiagnosis Photodyn Ther. 2019;25:23-28.	SR for reference checking
Neittaanmakiperttu N, Gronroos M, Karppinen TT, Snellman E, Rissanen P. Photodynamic therapy for actinic keratoses: a randomized prospective non-sponsored cost-effectiveness study of daylightmediated treatment compared with light-emitting diode treatment. Acta Derm Venereol. 2016;96(2):241-44.	Ineligible comparator
Neittaanmaki-Perttu N, Gronroos M, Tani T, Snellman E. Long-term outcome of daylight photodynamic therapy with amino-5-laevulinate nanoemulsion vs. methyl-5-aminolaevulinate for actinic keratoses. Acta Derm Venereol. 2016;96(5):712-3.	Ineligible study design
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Nistico S, Torchia V, Gliozzi M, Bottoni U, Del Duca E, Muscoli C. Pharmacoeconomy of drugs used in the treatment of actinic keratoses. Int. 2016;29(4):796-804.	Ineligible study design
Peris K, Stockfleth E, Gupta G, Aractingi S, Dakovic R, Dirschka T, et al. Efficacy of imiquimod 3.75% from Lmax according to the number of actinic keratosis lesions. J Eur Acad Dermatol Venereol. 2015;29(12):2470-3.	Ineligible subgroup analysis
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Reference	Exclusion Reason
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Sachar M, Siegel JA, Walker JL, Chen SC, Swetter SM, Dellavalle R, et al. 5-fluorouracil decreases rates of persistent actinic keratoses. J Invest Dermatol. 2016;136(5 S1):S45.	Ineligible patient population
Samorano LP, Torezan LA, Sanches JA. Evaluation of the tolerability and safety of 0.015% ingenol mebutate gel compared to 5% 5-fluorouracil cream for the treatment of facial actinic keratosis: a prospective randomized trial. J Am Acad Dermatol. 2015;72(5 S1):AB184.	Duplicate
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Segatto MM, Dornelles SI, Silveira VB, Frantz Gde O. Comparative study of actinic keratosis treatment with 3% diclofenac sodium and 5% 5-fluorouracil. An Bras Dermatol. 2013;88(5):732-8.	Ineligible patient population
Serra-Guillen C, Nagore E, Hueso L, Llombart B, Requena C, Sanmartin O, et al. A randomized comparative study of tolerance and satisfaction in the treatment of actinic keratosis of the face and scalp between 5% imiquimod cream and photodynamic therapy with methyl aminolaevulinate. Br J Dermatol. 2011;164(2):429-33.	Ineligible outcomes
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Smith S, Piacquadio D, Morhenn V, Atkin D, Fitzpatrick R. Short incubation PDT versus 5-FU in treating actinic keratoses. J Drugs Dermatol. 2003;2(6):629-35.	Ineligible intervention
Steeb T, Heppt MV, Becker L, Kohl C, French LE, Berking C. Long-term efficacy of interventions for actinic keratosis: protocol for a systematic review and network meta-analysis. Syst Rev. 2019;8(1):237.	Ineligible publication type
Steeb T, Schlager JG, Kohl C, Ruzicka T, Heppt MV, Berking C. Laser-assisted photodynamic therapy for actinic keratosis: a systematic review and meta-analysis. J Am Acad Dermatol. 2019;80(4):947-56.	Ineligible intervention
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Stockfleth E, Gupta G, Peris K, Aractingi S, Dakovic R, Alomar A. 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(1):23-7.	Ineligible outcomes
Stockfleth E, Harwood CA, Serra-Guillen C, Larsson T, Osterdal ML, Skov T. Response to 'Phase IV head-to-head randomized controlled trial comparing ingenol mebutate 0.015% gel with diclofenac sodium 3% gel for the treatment of	Ineligible publication type

Reference	Exclusion Reason
actinic keratosis on the face or scalp': reply from the authors. Br J Dermatol. 2018;178(3):813-14.	
Stockfleth E, Meyer T, Benninghoff B, Salasche S, Papadopoulos L, Ulrich C, et al. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. Arch Dermatol. 2002;138(11):1498-502.	Ineligible patient population
Stockfleth E, Sibbring GC, Alarcon I. New topical treatment options for actinic keratosis: a systematic review. Acta Derm Venereol. 2016;96(1):17-22.	SR for reference checking
Stockfleth E, Ulrich M, Kerl H, Willers C. Long-term sustained efficacy of low dose 5-fluorouracil combined with 10% salicylic acid as a lesion directed treatment for actinic keratoses. Melanoma Res. 2011;21(S1):e53.	Ineligible outcomes
Swanson N, Smith CC, Kaur M, Goldenberg G. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: two phase 3 multicenter, randomized, double-blind, placebo-controlled studies. J Drugs Dermatol. 2013;12(11):1278-82.	Ineligible patient population
Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol. 2002;47(2):258-62.	Ineligible patient population
Szeimies RM, Matheson RT, Davis SA, Bhatia AC, Frambach Y, Klovekorn W, et al. Topical methyl aminolevulinate photodynamic therapy using red light-emitting diode light for multiple actinic keratoses: a randomized study. Dermatol Surg. 2009;35(4):586-92.	Ineligible patient population
Szeimies RM, Reinhold U, Dirschka T, Hauschild A, Novak B, Schmitz B, et al. Photodynamic therapy for actinic keratosis and basal cell carcinoma using BF-200 ALA: results of pivotal phase III trials and follow-up. J Eur Acad Dermatol Venereol. 2017;31(S3):89.	Ineligible patient population
Szeimies R-M, Reinhold U, Dirschka T, Hauschild A, Novak B, Schmitz B, et al. Photodynamic therapy for actinic keratosis and basal cell carcinoma using BF-200 ALA: results of pivotal phase III trials and follow-up. Journal of the european academy of dermatology and venereology : JEADV. 2017; 31: 89-. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01400060/full	Does not report comparative results
Szeimies RM, Stockfleth E, Popp G, Borrosch F, Bruning H, Dominicus R, et al. Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. Br J Dermatol. 2010;162(2):410-4.	Ineligible study design
Szeimies RM. A network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe. J Eur Acad Dermatol Venereol. 2016;30(9):1619-20.	Ineligible study design
Tanghetti E, Tanghetti M. Pre-treatment with topical 5 fluorouracil (5-FU) enhances the efficacy of ALA_PDT for the treatment of actinic keratoses; results of a randomized, controlled clinical trial with post-treatment 5-FU challenge. Lasers Surg Med. 2014;46(S25):46.	Ineligible outcomes
Tanghetti EA, Hamann C, Tanghetti M. A controlled comparison study of topical fluourouracil 5% cream pre-treatment of aminolevulinic acid/photodynamic therapy for actinic keratosis. J Drugs Dermatol. 2015;14(11):1241-4.	Ineligible outcomes
Tanghetti EA. Comparison of 5-fluorouracil 5% and imiquimod 5% for actinic keratoses. Cosmetic Dermatology. 2004;17(11 S3):16-20.	Ineligible study design
Tomas-Velazquez A, Redondo P. Switching from conventional photodynamic therapy to daylight photodynamic therapy for actinic keratoses: systematic review and meta-analysis. Actas Dermosifiliogr. 2017;108(4):282-92.	SR for reference checking

Reference	Exclusion Reason
Universidad de Antioquia. Trial of Methyl Aminolevulinate Plus Aktilite in Facial Photodamage. Identifier: NCT00629317. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2008. Available from https://clinicaltrials.gov/ct2/show/NCT00629317.	Completed trial (no results)
von Felbert V, Hoffmann G, Hoff-Lesch S, Abuzahra F, Renn CN, Braathen LR, et al. Photodynamic therapy of multiple actinic keratoses: reduced pain through use of visible light plus water-filtered infrared a compared with light from light-emitting diodes. Br J Dermatol. 2010;163(3):607-15.	Ineligible comparator
Walker JL, Siegel JA, Sachar M, Pomerantz H, Chen SC, Swetter SM, et al. 5-fluorouracil for actinic keratosis treatment and chemoprevention: a randomized controlled trial. J Invest Dermatol. 2017;137(6):1367-70.	Ineligible patient population
Walker JL, Siegel JA, Sachar M, Qureshi AA, Chen SC, Swetter SM, et al. Single course of 5-fluorouracil treatment prevents new actinic keratoses for 6 to 12 months. J Invest Dermatol. 2016;136(5 S1):S45.	Ineligible patient population
Wolf JE, Jr., Taylor JR, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. Int J Dermatol. 2001;40(11):709-13.	Ineligible patient population
Wu Y, Tang N, Cai L, Li Q. Relative efficacy of 5-fluorouracil compared with other treatments among patients with actinic keratosis: a network meta-analysis. Dermatol Ther. 2019;32(3):e12822.	SR for reference checking
Zhao W, Guan M, Nong X, Li Q, Chen Z. The safety and efficacy of daylight photodynamic therapy in the treatment of actinic keratoses: a systematic review and meta-analysis. Int J Dermatol. 2019;58(2):159-66.	SR for reference checking
Zhu L, Wang P, Zhang G, Zhang L, Liu X, Hu C, et al. Conventional versus daylight photodynamic therapy for actinic keratosis: a randomized and prospective study in China. Photodiagnosis Photodyn Ther. 2018;24:366-71.	Ineligible comparator

Supplementary Table S3: List of the 46 trials included in the review (reported in 86 documents)

Note that blue indicates a paper appearing twice in the table as it reports separate results (i.e. not pooled) for two different studies. This table also includes abstracts that are related to one of the included studies but do not contribute any additional data. These abstracts were not eligible for data extraction.

Study Identifier *(bold text indicates identifier used in this review)*	**Record**
Alomar 2007	Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. Br J Dermatol. 2007;157(1):133-41.
Athenex 2019a (NCT03285477; KX01-AK-003)	Athenex. Clinical Study Report: [KX01-AK-003] A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp. New Jersey, USA: Athenex Inc.; 09 August 2019a. 1-619.
	Athenex I. A Multi-Center Study to Evaluate the Efficacy and Safety of KX2-391 Ointment 1% on AK on Face or Scalp. Identifier: NCT03285477. In: ClinicalTrials.gov [internet]. Bethesda: 2017. Available from https://ClinicalTrials.gov/show/NCT03285477.
Athenex 2019b (NCT03285490; KX01-AK-004)	Athenex. Clinical Study Report: [KX01-AK-004] A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp. New Jersey, USA: Athenex Inc.; 09 September 2019b. 1-620.
	Athenex I. A Multi-Center Study to Evaluate the Efficacy and Safety of KX2-391 Ointment 1% on AK on Face or Scalp (AK004). Identifier: NCT03285490. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2017. Available from https://ClinicalTrials.gov/show/NCT03285490.
Arisi 2020	Arisi M, Zane C, Polonioli M, Tomasi C, Moggio E, Cozzi C, et al. Effects of MAL-PDT, ingenol mebutate and diclofenac plus hyaluronate gel monitored by high-frequency ultrasound and digital dermoscopy in actinic keratosis- a randomized trial. J Eur Acad Dermatol Venereol. 2020;34(6):1225-32.
Berman 2014	Berman B, Nestor MS, Newburger J, Park H, Swenson N. Treatment of facial actinic keratoses with aminolevulinic acid photodynamic therapy (ALA-PDT) or ingenol mebutate 0.015% gel with and without prior treatment with ALA-PDT. J Drugs Dermatol. 2014;13(11):1353-6.
Chen 2003	Chen K, Yap LM, Marks R, Shumack S. Short-course therapy with imiquimod 5% cream for solar keratoses: a randomized controlled trial. Australas J Dermatol. 2003;44(4):250-5

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
Dirschka 2012 NCT02799069 EUCTR- 2007-006854-24 ALA-AK-CT002	Biofrontera Bioscience GmbH. Evaluation of safety and efficacy of BF-200 ALA for the treatment of actinic keratosis with photodynamic therapy. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2008. Available from https://ClinicalTrials.gov/show/NCT02799069. Identifier: NCT02799069
	Biofrontera Bioscience GmbH. A randomized, observer blind, multinational phase III study to evaluate the safety and efficacy of a nanoemulsion gel formulation BF-200 ALA, in comparison with Metvix® and placebo, for the treatment of actinic keratosis with photodynamic therapy. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2009. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000486-72/results. Identifier: EUCTR2007-006854-24-DE
	Dirschka T, Radny P, Dominicus R, Mensing H, Bruning H, Jenne L, et al. Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolaevulinate for the treatment of actinic keratosis. Br J Dermatol. 2013;168(4):825-36.
	Dirschka T, Radny P, Dominicus R, Mensing H, Bruning H, Jenne L, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. Br J Dermatol. 2012;166(1):137-46.
	Dirschka T, Radny P, Dominicus R, Mensing H, Bruning H, Jenne L, et al. Efficacy and safety comparison of photodynamic therapy with BF-200 ALA versus Metvix for the treatment of actinic keratosis: a prospective, randomized, placebo-controlled multinational, phase III study. J Dtsch Dermatol Ges. 2011;9(S1):196-97. (Abstract; adds no additional information to study)
Dohil 2016: Study 2	Dohil MA. Efficacy, safety, and tolerability of 4% 5-fluorouracil cream in a novel patented aqueous cream containing peanut oil once daily compared with 5% 5-fluorouracil cream twice daily: meeting the challenge in the treatment of actinic keratosis. J Drugs Dermatol. 2016;15(10):1218-24.
	Swedish Medical Products Agency. Tolak 40 mg/g kräm: Produktresumé. Uppsala: Swedish Medical Products Agency; 2020. [cited 4 April 2021]. Available from: https://docetp.mpa.se/LMF/Tolak%20cream%20ENG%20SmPC_09001bee809dbaa1.pdf.
Dermapharm AG, 2011: EUCTR- 2011-003317-41 11-02 / Diclo-G	Dermapharm AG. Double-blind, randomized, clinical trial to compare the efficacy and safety of diclofenc 3% gel vs. solaraze 3% gel vs. vehicle for the treatment of patients with actinic keratosis. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2011. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-003317-41/DE/. Identifier: EUCTR2011-003317-41-DE/
Dermapharm AG, 2014: EUCTR- 2014-001621-33 14-01 / AK-Diclo	Dermapharm AG. Multicenter, randomised, double-blind clinical trial on the efficacy and safety of medicinal products containing diclofenac in patients with actinic keratosis. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2014. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001621-33/DE/. Identifier: EUCTR2014-001621-33-DE
Biofrontera Bioscience GmbH, 2006: EUCTR-2006-000314-20 ALA-AK-CT001	Biofrontera Bioscience GmbH. A randomized placebo-controlled clinical trial of topical photodynamic therapy with a nanoemulsion formulation of 5-aminolevulinic acid for the treatment of actinic keratosis. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2006. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-000314-20/DE/. Identifier: EUCTR2006-000314-20-DE

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
Almirall Hermal GmbH, 2007: EUCTR-2007-003889-18 H 1005 6002-0702	Almirall Hermal GmbH. Study on the efficacy of Verrumal(R) compared to placebo and Solaraze(R) in the treatment of actinic keratosis grade I to II. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2007. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-003889-18/DE/. Identifier: EUCTR2007-003889-18-DE
NCT01453179; MEDA Pharma GmbH & Co. KG, 2010: EUCTR-2010-022054-16 LEIDA 2 (X-03016-3284)	MEDA Pharma GmbH & Co. KG. Long-term Effects of Imiquimod and Diclofenac in Actinic Keratoses (LEIDA 2). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2011. Available from https://ClinicalTrials.gov/show/NCT01453179. Identifier: NCT01453179
	MEDA Pharma GmbH & Co. KG. Long-term effects of Aldara® 5% cream and Solaraze® 3% gel in the treatment of actinic keratoses on the face or scalp with respect to the risk of progression to in-situ and invasive squamous cell carcinoma (LEIDA 2). In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2010. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022054-16/DE/. Identifier: EUCTR2010-022054-16-DE
Almirall S.A., 2010: EUCTR-2010-022244-20 H 569 000 – 1004	Almirall S.A. Double-blind, randomized, vehicle- and comparator-controlled, multicenter trial to evaluate the efficacy and safety of LAS41007 in the treatment of actinic keratosis. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2010. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022244-20/DE/. Identifier: EUCTR2010-022244-20-DE
Foley 2011	Foley P, Merlin K, Cumming S, Campbell J, Crouch R, Harrison S, et al. A comparison of cryotherapy and imiquimod for treatment of actinic keratoses: lesion clearance, safety, and skin quality outcomes. J Drugs Dermatol. 2011;10(12):1432-8.
Freeman 2003	Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat. 2003;14(2):99-106.
	Foley P. A comparison of photodynamic therapy using methyl aminolaevulinate with cryotherapy in actinic keratosis. British Association of Dermatologists 83rd Annual Meeting. Abstract P-67. Br J Dermatol. 2003; 149(S64): P67. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1046/j.1365-2133.149.s64.8. (Abstract; adds no additional information to study)
	Foley P, Freeman M, Vinciullo C, Spelman L, Murrell D, Weightman W, et al. Photodynamic therapy using methyl aminolaevulinate with cryotherapy in actinic keratosis: an Australian study. abstract P-31 The 85th BAD Annual Meeting 5-8th July 2005, Glasgow, UK. Br J Dermatol. 2005; 153(S1): 29. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00527201/full. (Abstract; adds no additional information to study)
Hanke 2010 NCT00603798	Graceway Pharmaceuticals. Safety and effectiveness study of imiquimod creams for the treatment of actinic keratoses (AKs). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2008. Available from https://ClinicalTrials.gov/show/NCT00603798. Identifier: NCT00603798

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
GW01-0703 / 0705	Hanke CW, Beer KR, Stockfleth E, Wu J, Rosen T, Levy S. 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 3-week cycles. J Am Acad Dermatol. 2010;62(4):573-81.
Hauschild 2009 AK03 and **Hauschild 2009 AK04**	Hauschild A, Stockfleth E, Popp G, Borrosch F, Bruning H, Dominicus R, et al. 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;160(5):1066-74.
	Szeimies RM, Stockfleth E, Moor ACE, Stocker M, Ortland C, Hauschild A. A new 5-ALA-patch for the photodynamic therapy of actinic keratoses. Photodiagn Photodyn Ther. 2011;8(2):200. (Abstract; adds no additional information to study)
Jansen 2019 NCT02281682 EUCTR- 2014-003691-23 NL50621.068.14	Maastricht University Medical Center. IM Versus 5-FU Versus IMI Versus MAL-PDT in Treatment of Actinic Keratosis. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2014. Available from https://ClinicalTrials.gov/show/NCT02281682. Identifier: NCT02281682
	Jansen MHE, Kessels J, Nelemans PJ, Kouloubis N, Arits A, van Pelt HPA, et al. Randomized trial of four treatment approaches for actinic keratosis. N Engl J Med. 2019;380(10):935-46
	Jansen MHE. Topical treatment of actinic keratosis. Nederlands Tijdschrift voor Dermatologie en Venereologie. 2019;29(3):68. (Abstract; adds no additional information to study)
	Jansen MHE, Kessels JPHM, Nelemans PJ, Essers BA, Kelleners-Smeets NWJ, Mosterd K. Ingenolmebutaat bij actinische keratosen. Nederlands Tijdschrift voor Dermatologie en Venereologie. 2018;28(3):24. (Abstract; adds no additional information to study)
Jorizzo 2007	Jorizzo J, Dinehart S, Matheson R, Moore JK, Ling M, Fox TL, et al. Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratoses on the head. J Am Acad Dermatol. 2007;57(2):265-8.
Korman 2005	Korman N, Moy R, Ling M, Matheson R, Smith S, McKane S, et al. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. Arch Dermatol. 2005;141(4):467-73.
Kose 2008	Kose O, Koc E, Erbil AH, Caliskan E, Kurumlu Z. Comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% imiquimod cream in the treatment of actinic keratosis. J Dermatolog Treat. 2008;19(3):159-63.
Lebwohl 2004	Lebwohl M, Dinehart S, Whiting D, Lee PK, Tawfik N, Jorizzo J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol. 2004;50(5):714-21.
Peplin, 2008: NCT00700063 PEP005-015	Peplin. A multicenter study to evaluate the safety and efficacy of PEP005 topical gel when used to treat actinic keratoses on the head (face or scalp). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2008. Available from https://ClinicalTrials.gov/show/NCT00700063

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
MEDA Pharma GmbH & Co. KG, 2015: NCT00777127 EUCTR-2007-004884-24 LEIDA (X-03016-3271)	MEDA Pharma GmbH & Co. KG. Long-term Effects of Imiquimod and Diclofenac in Actinic Keratoses. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2008. Available from https://ClinicalTrials.gov/show/NCT00777127. Identifier: NCT00777127
	MEDA Pharma GmbH & Co. KG. Long-term effects of Aldara® 5% cream and Solaraze® 3% gel in the treatment of actinic keratoses on the face or scalp (LEIDA). In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2015. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-004884-24/DE. Identifier: EUCTR2007-004884-24-DE
Taro Pharmaceuticals USA, 2008: NCT00828568 MIQ-0403	Taro Pharmaceuticals USA. Bioequivalence study of two imiquimod cream 5%. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2008. Available from https://ClinicalTrials.gov/show/NCT00828568. Identifier: NCT00828568
Peplin, 2009a: NCT00915551 PEP005-025	Peplin. A multi-center study to evaluate the efficacy and safety of pep005 (ingenol mebutate) gel, when used to treat actinic keratoses on the head (face or scalp). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2009a. Available from https://ClinicalTrials.gov/show/NCT00915551. Identifier: NCT00915551
Peplin, 2009b: NCT00916006 PEP005-016	Peplin. A multi-center study to evaluate the efficacy and safety of pep005 (ingenol mebutate) gel, when used to treat actinic keratoses on the head (face or scalp). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2009b. Available from https://ClinicalTrials.gov/show/NCT00916006. Identifier: NCT00916006
Gage Development Company, 2016: NCT02952898 GDC-695-001	Gage Development Company. Study comparing GDC 695 and diclofenac sodium gel, 3% in subjects with actinic keratoses. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2016. Available from https://ClinicalTrials.gov/show/NCT02952898. Identifier: NCT02952898
Actavis Inc, 2016: NCT03200912 094-8152-301	Actavis Inc. An equivalence study of generic ingenol mebutate gel 0.015% and picato gel 0.015% in subjects with actinic keratosis. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2016. Available from https://ClinicalTrials.gov/show/NCT03200912. Identifier: NCT03200912
Pariser 2003 NCT00306800 PC T404 / 05	Galderma. Metvix PDT Versus Vehicle PDT With Aktilite CL128 Lamp in Patients With Actinic Keratosis on the Face and Scalp. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2007. Available from https://ClinicalTrials.gov/show/NCT00306800. Identifier: NCT00306800
	Pariser DM, Lowe NJ, Stewart DM, Jarratt MT, Lucky AW, Pariser RJ, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. J Am Acad Dermatol. 2003;48(2):227-32.
Pariser 2008	Pariser D, Loss R, Jarratt M, Abramovits W, Spencer J, Geronemus R, et al. Topical methyl-aminolevulinate photodynamic therapy using red light-emitting diode light for treatment of multiple actinic keratoses: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 2008;59(4):569-76.

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
Pariser 2016 NCT01475955 CP0105	DUSA Pharmaceuticals. Short-incubation levulan photodynamic therapy versus vehicle for face/scalp actinic keratosis (AK). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2011. Available from https://ClinicalTrials.gov/show/NCT01475955. Identifier: NCT01475955
	Pariser DM, Houlihan A, Ferdon MB, Berg JE, Group P-AI. Randomized vehicle-controlled study of short drug incubation aminolevulinic acid photodynamic therapy for actinic keratoses of the face or scalp. Dermatol Surg. 2016;42(3):296-304.
	Pariser D, McConnehey D, Bukhalo M, Matheson R, Guenthner S, Kempers S. A phase II study of photodynamic therapy (PDT) with aminolevulinic acid HCl (ALA) 20% topical solution + blue light vs ALA topical solution vehicle + blue light using spot and broad area application and incubation times of 1, 2 and 3 hours for the treatment. J Am Acad Dermatol. 2013;68(4 S1):AB156 (Abstract; adds no additional information to study)
Piacquadio 2004	Fowler Jr JF, Zax RH. Aminolevulinic acid hydrochloride with photodynamic therapy: efficacy outcomes and recurrence 4 years after treatment. Cutis. 2002;69(S6):2-7.
	Piacquadio DJ, Chen DM, Farber HF, Fowler JF, Jr., Glazer SD, Goodman JJ, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. Arch Dermatol. 2004;140(1):41-6.
Reinhold 2016 NCT01966120 EUCTR- 2013-002510-12 ALA-AK-CT007	Biofrontera Bioscience GmbH. Safety and efficacy study for the field-directed treatment of actinic keratosis (AK) with photodynamic therapy (PDT). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2013. Available from https://ClinicalTrials.gov/show/NCT01966120. Identifier: NCT01966120
	Biofrontera Bioscience GmbH. A randomized, double-blind, phase III multi-center study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) versus placebo in the field-directed treatment of mild to moderate actinic keratosis with photodynamic therapy (PDT) when using BF-RhodoLED®. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2013. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002510-12/DE/. Identifier: EUCTR2013-002510-12-DE
	Reinhold U, Dirschka T, Ostendorf R, Aschoff R, Berking C, Philipp-Dormston WG, et al. A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz(R)) vs. placebo in the field-directed treatment of mild-to-moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED(R) lamp. Br J Dermatol. 2016;175(4):696-705.
Samorano 2015 NCT02242747 11334	University of Sao Paulo. Safety and Tolerability Study of Ingenol Mebutate Compared to 5-FU to Treat Facial Actinic Keratosis. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2014. Available from https://ClinicalTrials.gov/show/NCT02242747. Identifier: NCT02242747
	Samorano LP, Torezan LA, Sanches JA. Evaluation of the tolerability and safety of a 0.015% ingenol mebutate gel compared to 5% 5-fluorouracil cream for the treatment of facial actinic keratosis: a prospective randomized trial. J Eur Acad Dermatol Venereol. 2015;29(9):1822-7.

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
Serra-Guillen 2012	Serra-Guillen C, Nagore E, Hueso L, Traves V, Messeguer F, Sanmartin O, et al. A randomized pilot comparative study of topical methyl aminolevulinate photodynamic therapy versus imiquimod 5% versus sequential application of both therapies in immunocompetent patients with actinic keratosis: clinical and histologic outcomes. J Am Acad Dermatol. 2012;66(4):e131-7.
Simon 2015 NCT01358851 EUCTR-2010-022980-37 H 1005 6002 1007	Almirall SA. LAS41005 in Hyperkeratotic Actinic Keratosis. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2011. Available from https://ClinicalTrials.gov/show/NCT01358851. Identifier: NCT01358851
	Simon JC, Dominicus R, Karl L, Rodriguez R, Willers C, Dirschka T. A prospective randomized exploratory study comparing the efficacy of once-daily topical 0.5% 5-fluorouracil in combination with 10.0% salicylic acid (5-FU/SA) vs. cryosurgery for the treatment of hyperkeratotic actinic keratosis. J Eur Acad Dermatol Venereol. 2015;29(5):881-9.
	Almirall Hermal GmbH. A prospective comparator controlled randomized exploratory study on the efficacy of LAS 41005 compared to cryotherapy in subjects with hyperkeratotic actinic keratosis. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2010. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022980-37/DE/. Identifier: EUCTR2010-022980-37-DE
Stockfleth 2017 NCT02289768 EUCTR- 2014-001171-31 98605101-1401	Almirall SA. Study To Evaluate The Efficacy And Safety Of Actikerall® Solution In Patients With Grade I-II Actinic Keratoses. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2014. Available from https://ClinicalTrials.gov/show/NCT02289768. Identifier: NCT02289768
	Ulrich M, Reinhold U, Falques M, Rodriguez Azeredo R, Stockfleth E. Use of reflectance confocal microscopy to evaluate 5-fluorouracil 0.5%/salicylic acid 10% in the field-directed treatment of subclinical lesions of actinic keratosis: subanalysis of a phase III, randomized, double-blind, vehicle-controlled trial. J Eur Acad Dermatol Venereol. 2018;32(3):390-6.
	Stockfleth E, von Kiedrowski R, Dominicus R, Ryan J, Ellery A, Falques M, 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. 2017;7(1):81-96.
	Stockfleth E, von Kiedrowski R, Dominicus R, Ryan J, Ellery A, Falques M, et al. Erratum to: 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. 2017;7(2):263.
	Stockfleth E, Von Kiedrowski R, Dominicus R, Ryan J, Ellery A, Falques M, et al. Evaluation of 5-fluorouracil 0.5%/salicylic acid 10% in the field-directed treatment of actinic keratosis: a phase III, randomised, vehicle-controlled trial. Melanoma Res. 2016;26(S1):e10.
	Almirall Hermal GmbH. Multicentre, randomized, parallel, double-blind, vehicle controlled study to evaluate the efficacy and safety of Actikerall® solution in the field-directed treatment of actinic keratoses grade I to II (field cancerization). In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2014. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001171-31/DE/. Identifier: EUCTR2014-001171-31-DE

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
	Stockfleth E, Ryan J, Falques M, Ivanoff N, Azeredo RR, Vilardell D. Predictors of response to 5-fluorouracil 0.5%/salicylic acid 10% in the field-directed treatment of actinic keratosis: a post hoc analysis of a phase III, randomized, vehicle-controlled trial. J Am Acad Dermatol. 2017;76(6 S1):AB202. (Abstract; adds no additional information to study)
Stockfleth 2018 NCT02406014 EUCTR- 2014-003218-98 LP0041-1120	LEO Pharma. Efficacy and Safety of Ingenol Mebutate Gel 0.015% Compared to Diclofenac Sodium Gel 3% in Subjects With Actinic Keratoses on the Face or Scalp. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2015. Available from https://ClinicalTrials.gov/show/NCT02406014. Identifier: NCT02406014
	Stockfleth E, Harwood CA, Serra-Guillen C, Larsson T, Osterdal ML, Skov T. 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):433-42.
	Stockfleth E, Harwood C, Serra-Guillen C, Larsson T, Osterdal ML, Skov T. Safety of ingenol mebutate compared to diclofenac for patients with actinic keratosis on the face or scalp. J Eur Acad Dermatol Venereol. 2017;31(S3):44.
	Stockfleth E, Harwood C, Serra-Guillen C, Larsson T, Osterdal ML, Skov T. Efficacy of ingenol mebutate compared to diclofenac for patients with actinic keratosis on the face or scalp. J Eur Acad Dermatol Venereol. 2017;31(S3):43-44.
	LEO Pharma. Efficacy and safety of ingenol mebutate gel 0.015% compared to diclofenac sodium gel 3% in subjects with actinic keratoses on the face or scalp In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2016. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-003218-98/results. Identifier: EUCTR2014-003218-98-DE
Swanson 2010 NCT00605176 GW01-0702 / 0704	Graceway Pharmaceuticals. Safety and effectiveness study of imiquimod creams for treatment of actinic keratoses (AKs). In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2008. Available from https://ClinicalTrials.gov/show/NCT00605176. Identifier: NCT00605176
	Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. 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(4):582-90.
	Swanson N, Smith CC, Kaur M, Goldenberg G. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: two phase 3, multicenter, randomized, double-blind, placebo-controlled studies. J Drugs Dermatol. 2014;13(2):166-9.
	Swanson N, Jorizzo J, Kaur M. Imiquimod 2.5% and 3.75% for the treatment of actinic keratosis: assessment of efficacy in 479 randomized patients. J Am Acad Dermatol. 2014;70(5 S1):AB127.
Szeimies 2004	Szeimies RM, Gerritsen MJ, Gupta G, Ortonne JP, Serresi S, Bichel J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. J Am Acad Dermatol. 2004;51(4):547-55.
Szeimies 2010 NCT02799082	Biofrontera Bioscience GmbH. Evaluation of efficacy and safety of BF-200 ala used with photodynamic therapy in patients with actinic keratosis. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2007. Available from https://ClinicalTrials.gov/show/NCT02799082. Identifier: NCT02799082

Study Identifier ***(bold text indicates identifier used in this review)***	**Record**
EUCTR- 2007-003371-39 ALA-AK-CT003	Dirschka T, Radny P, Dominicus R, Mensing H, Bruning H, Jenne L, et al. Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolaevulinate for the treatment of actinic keratosis. Br J Dermatol. 2013;168(4):825-36.
	Szeimies RM, Radny P, Sebastian M, Borrosch F, Dirschka T, Krahn-Senftleben G, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. Br J Dermatol. 2010;163(2):386-94.
	Biofrontera Bioscience GmbH. A randomized, double-blind, phase III multicenter study evaluating the safety and efficacy of BF-200 ALA versus placebo in the treatment of actinic keratosis when using PDT. In: EU Clinical Trials Register [internet]. London. European Medicines Agency. 2007. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-003371-39/DE/. Identifier: EUCTR2007-003371-39-DE
	Szeimies RM, Borrosch F, Dirschka T, KrahnSenftleben G, Radny P, Reich K, et al. Two prospective, randomized, placebo-controlled, double-blinded clinical studies with BF-200 ALA for photodynamic therapy of actinic keratosis. J Dtsch Dermatol Ges. 2011;9(S1):197. (Abstract; adds no additional information to study)
Tanghetti 2007	Tanghetti E, Werschler P. Comparison of 5% 5-fluorouracil cream and 5% imiquimod cream in the management of actinic keratoses on the face and scalp. J Drugs Dermatol. 2007;6(2):144-7.
Zane 2014	Zane C, Facchinetti E, Rossi MT, Specchia C, Calzavara-Pinton PG. A randomized clinical trial of photodynamic therapy with methyl aminolaevulinate vs. diclofenac 3% plus hyaluronic acid gel for the treatment of multiple actinic keratoses of the face and scalp. Br J Dermatol. 2014;170(5):1143-50.

Supplementary Table S4: 6 papers listed for information (not data extracted)

Record	Study identifiers	Notes
Almirall. Post-hoc statistical analyses of studies KX01-AK-003 and KX01-AK-004 to support the dossier of Tirbanibulin (KX2-391) ointment 1% in actinic keratosis on face or scalp. Barcelona: Almirall SA; 26 November 2019. 1-84.	NCT03285477 and NCT03285490	Document reports pooled data from the two Athenex trials
Del Rosso J, Swanson N, Berman B, Martin GM, Lin T, Rosen T. Imiquimod 2.5% and 3.75% cream for the treatment of photodamage: a meta-analysis of efficacy and tolerability in 969 randomized patients. J Clin Aesthet Dermatol. 2018;11(9):28-31.	NCT00605176 / GW01-0702 / 0704 (two trials reported together) *and* NCT00603798 / GW01-0703 / 0705 (two trials reported together)	Paper reports pooled outcomes for four trials. We already have full papers reporting these trials in pooled pairs, rather than as a group of four. We will use the data reported for pairs of trials rather than the group of four.
Del Rosso J, Swanson N, Berman B, Rosen T. Imiquimod 2.5% and 3.75% for the treatment of photodamage: meta-analysis of efficacy and tolerability in 969 randomized patients. J Clin Aesthet Dermatol. 2017;10(5 S1):S12. *(Abstract; adds no additional information to study)*		
Gollnick H, Dirschka T, Ostendorf R, Kerl H, Kunstfeld R. Long-term clinical outcomes of imiquimod 5% cream vs. diclofenac 3% gel for actinic keratosis on the face or scalp: a pooled analysis of two randomized controlled trials. JEADV. 2019: Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02053677/full	MEDA Pharma GmbH & Co. KG, 2015: NCT00777127 / 2007-004884-24 / LEIDA (X-03016-3271) *and* NCT01453179 / 2010-022054-16 / LEIDA 2 (X-03016-3284)	Paper reports pooled outcomes for two trials, both of which we have full papers and NCT records for. We will use the disaggregated data from the above sources rather than extracting the pooled data.
Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012;366(11):1010-9.	NCT00915551 / PEP005-025 *and* NCT00916006 / PEP005-016	Paper reports pooled outcomes for two trials, both of which we have full papers and NCT records for. We will use the disaggregated data from the above sources rather than extracting the pooled data.
Morales Toquero A, Ocampo Candiani J, Gomez Flores M, Gonzalez Gonzalez SE, Eguia Rodriguez R, Mendez Olvera NP, et al. Clinical and histological evaluation of 5% imiquimod cream vs 5% 5-fluorouracil ointment in patients with actinic keratosis on the face. Dermatol Rev Mex. 2010;54(6):326-31..	Paper not in English. Listed (as per protocol) but not eligible for data extraction.	

Supplementary Table S5: Details of the 46 trials included in the review

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
Alomar 2007 [61] 20 weeks 20 study centres (four in France, six in Germany, three in Italy, two in the Netherlands, three in Spain, and two in the UK)	259	Vehicle-controlled, randomised study Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** Partial clearance (75% reduction) and clearance of individual AK lesions (reduction in all AK lesions from all patients totalled together). Safety evaluations included physical examinations, clinical laboratory tests (haematology, blood chemistry and urinalysis), and urine pregnancy tests for women of childbearing potential. AEs and the use of concomitant medications were monitored at each study visit beginning with treatment initiation, as were LSRs	**IMQ5%:** One 4-week course, with the potential for a second course 4 weeks later	Age 70.3 (8.45); Range: 44 to 90 Gender (male) 115 (89.1) Lesion count NR
				PLAC_TOP: One 4-week course, with the potential for a second course 4 weeks later	Age 71.85 (7.25); Range: 53 to 94 Gender (male) 113 (86.9) Lesion count NR
Arisi 2020 [84] 13 weeks Dermatology Department of the University of Brescia, Italy	90	Randomised comparative noninferiority study Single-blind	**Primary outcome(s)** AKs cumulative area **Secondary outcome(s)** Number of patients attaining the clearance of all lesions (complete responders) in the 25 cm^2 treated area	**MAL_PDT:** One session, with potential for a second session 12 weeks later	Age Median: 80; Range: 71 to 89 Gender (male) 26 (100) Lesion count

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
					Median: 9; Range: 5 to 12
				IM0.015%: 3 days	Age Median: 76; Range: 49 to 89 Gender (male) 23 (76.7) Lesion count Median: 7; Range: 5 to 13
				DICLO3%: 90 days	Age Median: 77; Range: 54 to 91 Gender (male) 27 (96.4) Lesion count Median: 7; Range: 5 to 12
Athenex, Inc 2019a KX01-AK-003; NCT03285477 [53] 15 months	351	Multicenter, randomised, double-blind, vehicle-controlled,	**Primary outcome(s)** Complete and partial clearance **Secondary outcome(s)** • Recurrence	**TIRBA1%:** Once-daily self-administration for 5 consecutive days	Age 69.5 (8.5) Gender (male) 147 (84)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
31 study sites in the USA		parallel-group study	• AEs • Serious AEs (SAEs) • LSRs (erythema, flaking / scaling, crusting, swelling, vesiculation / pustulation, and erosion / ulceration) • Events of special interest (skin cancers, ocular exposure, overdose, and pregnancy) • Pigmentation and scarring • Vital signs, electrocardiograms (ECGs), physical examinations (PEs) including weight, and laboratory evaluation of haematology, biochemistry, and urinalyses at prespecified timepoints.		Lesion count Median 6; Range 4 to 8
				PLAC_TOP: Once-daily self-administration for 5 consecutive days	Age 70.2 (9.4) Gender (male) 154 (88) Lesion count Median 6; Range 4 to 8
Athenex, Inc 2019b KX01-AK-004; NCT03285490 [54] 15 months 31 study sites in the USA	351	Multicenter, randomised, double-blind, vehicle-controlled, parallel-group study	**Primary outcome(s)** Complete and partial clearance **Secondary outcome(s)** • Recurrence • AEs • Serious AEs (SAEs) • LSRs (erythema, flaking / scaling, crusting, swelling, vesiculation / pustulation, and erosion / ulceration) • Events of special interest (skin cancers, ocular exposure, overdose, and pregnancy) • Pigmentation and scarring • Vital signs, electrocardiograms (ECGs), physical examinations (PEs) including weight, and laboratory evaluation of haematology, biochemistry, and urinalyses at prespecified timepoints.	**TIRBA1%:** Once-daily self-administration for 5 consecutive days	Age 69.1 (8.7) Gender (male) 158 (89) Lesion count Median 6; Range 4 to 8
				PLAC_TOP: Once-daily self-administration for 5 consecutive days	Age 70.2 (8.9) Gender (male) 150 (87) Lesion count Median 6; Range 4 to 8

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
Berman 2014 [93] 10 weeks One centre in the USA	16	Randomised, three-group study Open-label	**Primary outcome(s)** Lesion clearance; LSRs; AEs **Secondary outcome(s)** NR	**ALA_PDT:** Two sessions two weeks apart	Age, gender and lesion count NR
				IM0.015%: 3 days	Age, gender and lesion count NR
Chen 2003 [51] 14 weeks Total number of sites unclear. Skin and Cancer Foundation Victoria, St Vincent's Hospital Melbourne, and private dermatology practices in Victoria and New South Wales, Australia	44	A randomised, vehicle-controlled study Double-blind	**Primary outcome(s)** The number of subjects achieving a clearance of 75% of baseline AK **Secondary outcome(s)** LSRs and AEs	**IMQ5%:** One 3-week course (i.e. 3 weeks' treatment, 4 weeks off) with the potential for a second course at the end of the first	Age 64.9 (10.2) Gender (male) 19 (65.5*) Lesion count 10.5 (2.8)
				PLAC_TOP: One 3-week course (i.e. 3 weeks' treatment, 4 weeks off) with the potential for a second course at the end of the first	Age 63.0 (12.1) Gender (male) 4* (40*) Lesion count 10.8 (3.7)
Dirschka 2012 [73] 12 to 24 weeks	571	Multicentre, placebo-controlled, interindividual RCT	**Primary outcome(s)** Complete clearance rate **Secondary outcome(s)** Rate of completely cleared lesions	**ALA_PDT:** 1 session, with potential for retreatment at 12 weeks	Age 70.2 (7.18) Gender (male) 214 (86.3)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
26 study centres in Germany, Austria and Switzerland		Single-blind			Lesion count 6.1 (1.6)
				MAL_PDT: 1 session, with potential for retreatment at 12 weeks	Age 71.0 (6.93) Gender (male) 205 (83.3) Lesion count 6.3 (1.5)
				PLAC_PDT: 1 session, with potential for retreatment at 12 weeks	Age 71.5 (6.68) Gender (male) 60 (78.9) Lesion count 6.4 (1.4)
Dohil 2016: Study 2 [63] 8 weeks 27 centres in the USA	841	Randomised, parallel-group study Double-blind	**Primary outcome(s)** 100% clearing of AK lesions **Secondary outcome(s)** • The proportion of subjects who had 75% clearing of AK lesions compared with baseline, in the ITT population.	**5FU4%:** 4 weeks (once daily)	Age Overall: Around 68 years Gender (male) Overall: Ratio of male to female was about 3:1
				5FU5%: 4 weeks (twice daily)	
				PLAC_TOP: 4 weeks (once daily)	
				PLAC_TOP: 4 weeks (twice daily)	

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
			• The percentage change from baseline in number of AK lesions, in the ITT population. • 100% clearing of AK lesions, in the PP population. • 75% clearing of AK lesions compared with baseline, in the PP population. • The percentage change from baseline in number of AK lesions, in the PP population.		Lesion count Overall: "Average" 15; Range: 5 to 90
Dermapharm AG, 2011: EUCTR- 2011-003317-41 [94] 17 weeks 12 centres in Germany	339	Randomised trial Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** • Course of the cumulative lesion number score (CLNS) between beginning of treatment (day 0) and final examination or early termination. • Evaluation of the global improvement by the investigator (IGII) and by the patient (PGII) during the whole study course. • Proportion of patients with the IGII rating "cured" at final examination. • Evaluation of the tolerability of the treatment by the investigator and the patient. • Safety (laboratory assessment) • AEs	**DICLO3%:** 90 days (13 weeks)	Age, gender and lesion count NR
				PLAC_TOP: 90 days (13 weeks)	Age, gender and lesion count NR
Dermapharm AG, 2014: EUCTR- 2014-001621-33 [70]	293	Multicenter, randomised, clinical trial	**Primary outcome(s)** Proportion of patients in the PP population with reduction of the Target Lesion Number Score (TLNS) of ≥75% at the final examination	**DICLO3%:** NR, but may be 13 weeks as previous trial (Dermapharm AG, 2011: EUCTR- 2011-003317-41)	Age Overall: Adults (18-64 years): 66

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
17 weeks Multiple sites in Germany (number not stated)		Double-blind	**Secondary outcome(s)** • Proportion of patients with a TLNS reduction of ≥75% at the end of treatment • Changes of the severity of the target lesions • Course of the cumulative lesion number score (CLNS) between beginning of treatment (day 0) and final examination or early termination • Evaluation of the global improvement by the investigator (IGII) and by the patient (PGII) during the whole study course • Proportion of patients with the IGII rating "cured" at final examination • 100% clearance of all AK lesions at the final examination (CLNS =0) and proportion of patients with 100% reduction of the TLNS	with same methods and investigators **PLAC_TOP:** NR, but may be 13 weeks as previous trial (Dermapharm AG, 2011: EUCTR- 2011-003317-41) with same methods and investigators	65 to 84 years: 355 85 years and over: 18 Gender (male) Overall: 371 (84.5*) Lesion count NR
Biofrontera Bioscience GmbH, 2006: EUCTR-2006-000314-20 [81] 12 months 11 study centres in Germany	55	Randomised placebo-controlled clinical trial Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** Safety and tolerability, cosmetic outcome, recurrence rates of AK lesions within the treated area	**ALA_PDT:** One session **PLAC_PDT:** One session	Age Overall mean age: 71.1 Range between the different treatment groups: 69.9 to 72.6 Gender NR Lesion count

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
					ALA_PDT: Face / forehead: 4.4; Bald scalp: 5.3 PLAC_PDT: NR
Almirall Hermal GmbH, 2007: EUCTR-2007-003889-18 [79] 20 weeks 38 sites in Germany	470	Randomised, active- and placebo-controlled trial Double-blind	**Primary outcome(s)** Histological status of (one) target lesion (cleared, not cleared) **Secondary outcome(s)** Lesion response, tolerability and safety	**5FU0.5%+SA:** 12 weeks **DICLO3%:** 12 weeks **PLAC_TOP:** 12 weeks	Age Overall: 71.8 (between 71.6 and 72.3 between treatment groups) across the FAS Gender (male) Overall: 398* (84.7) (between 84.4% and 85.9% between the treatment groups) across the safety set Lesion count 5FU0.5%+SA: 5.8 DICLO3%:5.9 PLAC_TOP: 5.6
MEDA Pharma GmbH & Co. KG, 2010: EUCTR-2010-022054-16 LEIDA 2	221	RCT Open-label	**Primary outcome(s)** To determine long-term risk of progression to squamous cell cancer (SCC). Histological finding of an in situ SCC or an invasive SCC after start of treatment will be considered as "histological progression", which is the primary endpoint.	**IMQ5%:** Each cycle could be either: 4 weeks' treatment, 4 weeks off, 4 weeks' treatment, OR 4 weeks' treatment, 8 weeks	Age 71.36 (8.1) Gender (male) 92 (83.6*)

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
[90] 36 months 14 sites in Germany and 3 in Austria			**Secondary outcome(s)** • Recurrence rates • Time to recurrence • Need of rescue treatment • Cosmetic outcome	off. Patients received between 1 and 6 cycles. **DICLO3%:** 12 weeks. Patients received between 1 and 6 cycles.	Lesion count NR Age 70.75 (8.4) Gender (male) 99 (89.2*) Lesion count NR
Almirall S.A., 2010: EUCTR-2010-022244-20 [71] 21 weeks (12 months post-treatment follow up was planned but study was discontinued before this) 40 sites in Germany, 5 in the UK, and 9 in Poland	508	Randomised, vehicle- and comparator-controlled, multicenter trial Double-blind	**Primary outcome(s)** Histological clearance of one pre-selected AK lesion as a marker of complete clearance **Secondary outcome(s)** Rate of clinical clearance (target lesions, or target + non-target lesions + new lesions) and rate of responders, reduction of total AK target lesion area per patient, improvement of target lesions. Safety determined by incidence of AEs, tolerability (overall and local), laboratory variables, vital signs, and the patient's compliance.	**DICLO3%:** 90 days (13 weeks) **PLAC_TOP:** 90 days (13 weeks)	Age Overall: 72.7; Range: 39 to 94 Gender (male) Overall: 791 (89) Lesion count DICLO3%: Median: 9 PLAC_TOP: Median: 9

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
Foley 2011 [86] 12 months Single site in Australia (Melbourne)	71	Single centre prospective RCT Open-label	**Primary outcome(s)** Lesion response rates **Secondary outcome(s)** Patient response rates, AEs	**IMQ5%:** One 3 to 4 week course with potential for a second course 4 weeks later	Age 71.3 (1.88) Gender (male) 28 (80) Lesion count Total across arm: 340 (35 patients)
				CRYO: 1 session, with potential for retreatment at 3, 6 and 9 months	Age 71.7 (1.63) Gender (male) 28 (77.8) Lesion count Total across arm: 360 (36 patients)
Freeman 2003 [77] 13 weeks 9 study centres in Australia	200	Randomised, reference- and placebo-controlled, parallel group multicentre study	**Primary outcome(s)** Lesion response rate, overall cosmetic outcome, cosmetic outcome in individual lesions, patient satisfaction, AEs **Secondary outcome(s)** NR	**MAL_PDT:** Two sessions of PDT one week apart	Age 64; Range: 33 to 86 Gender (male) 49 (56) Lesion count overall 1–2: 48 (55) 3–7: 27 (31)

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
		The study was open with regard to PDT versus cryosurgery and double-blind with regard to methyl aminolevulinate versus placebo PDT			8–28: 13 (15)
				PLAC_PDT: Two sessions of PDT one week apart	Age 66; Range: 49 to 89 Gender (male) 16 (70) Lesion count overall 1–2: 13 (57) 3–7: 8 (35) 8–28: 2 (9)
				CRYO: One session	Age 65; Range: 38 to 86 Gender (male) 54 (61) Lesion count overall 1–2: 39 (44) 3–7: 31 (35) 8–28: 19 (21)
Hanke 2010 [58] 17 weeks 26 USA study centres	326	Two randomised, multicenter, placebo-controlled studies	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** • 75% reduction in the number of AK lesions in the treatment area compared with baseline	**IMQ3.75%:** Two 3-week treatment cycles, i.e. 3 weeks' treatment, 3 weeks off, 3 weeks' treatment	Age 64.3 (10.2) Gender (male) 123 (75.9)

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
		Double-blind	• Percent change from baseline in AK lesion count • Local skin reactions		Lesion count 11.1 (4.9)
				PLAC_TOP: Two 3-week treatment cycles, i.e. 3 weeks' treatment, 3 weeks off, 3 weeks' treatment	Age 63.7 (10.9) Gender (male) 135 (82.3) Lesion count 10.3 (4.3)
Hauschild 2009 AK 03 [78] 12 weeks 29 centres in Germany	103	Two separate confirmatory randomised parallel-group studies Single-blind	**Primary outcome(s)** Lesion complete clearance, LSRs, AEs **Secondary outcome(s)** NR	**ALA_PDT Patch:** One session	Age 70.4 (8.32) Gender (male) 58 (84) Lesion count 5.8 (1.91)
				PLAC_PDT Patch: One session	Age 71.4 (6.77) Gender (male) 26 (76) Lesion count 5.5 (1.91)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
Hauschild 2009 AK 04 [78] 12 weeks 29 centres in Germany	346	Two separate confirmatory randomised parallel-group studies Open-label	**Primary outcome(s)** Lesion complete clearance, LSRs, AEs **Secondary outcome(s)** NR	**ALA_PDT Patch**: One session	Age 70.0 (8.32) Gender (male) 104 (70) Lesion count 5.8 (1.64)
				PLAC_PDT patch: One session	Age 71.6 (7.54) Gender (male) 40 (82) Lesion count 5.9 (1.76)
				CRYO: One session	Age 70.6 (8.73) Gender (male) 104 (70) Lesion count 5.4 (1.57)
Jansen 2019 [28] Up to 72 weeks	624	Multicenter, randomised trial	**Primary outcome(s)**	**5FU5%:** One 4-week treatment course, with	Age Median: 74; Range: 48 to 90

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
Four hospitals (Maastricht University Medical Centre, Catharina Hospital, VieCuri Medical Centre and Zuyderland Medical Centre) in the Netherlands		Single-blind	Proportion of patients who remained free from treatment failure during 12 months of follow-up after the last treatment[1]. **Secondary outcome(s)** Initial treatment success[2] at 3 months after the last treatment, AEs, adherence, patient satisfaction with treatment, health-related quality of life, and cosmetic results.	potential for retreatment 12 weeks later	Gender (male) 136 (87.7) Lesion count Median: 16; Range: 5 to 48
				IMQ5%: One 4-week treatment course, with potential for retreatment 4 weeks later	Age Median: 73; Range: 59 to 89 Gender (male) 143 (91.7) Lesion count Median: 16.5; Range: 5 to 37
				MAL_PDT: 1 session, with potential for retreatment at 12 weeks	Age Median: 73; Range: 55 to 90

[1] Treatment failure was defined as a reduction of less than 75% in the number of actinic keratosis lesions counted at baseline and could occur at 3 months after the last treatment (initial failure) or at 12 months after initial successful treatment.
[2] Treatment success was defined as ≥75% reduction from baseline in the number of actinic keratosis lesions

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
					Gender (male) 140 (89.7) Lesion count Median: 16; Range: 5 to 38
				IM0.015%: One 3-day course, with potential for retreatment 12 weeks later	Age Median: 72; Range: 51 to 94 Gender (male) 139 (88.5) Lesion count Median: 15; Range: 5 to 40
Jorizzo 2007 [60] 12 months (only 8 weeks outcomes eligible) 13 USA study centres	246	A randomised, vehicle-controlled study Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** • Partial clearance (75% reduction) • Individual AK lesion clearance rate • AEs and local skin reactions (LSRs) • Clinical laboratory tests (haematology and chemistry blood tests, and urinalysis), and the culture of suggested skin infections.	**IMQ5%:** One 4-week course, with the potential for a second course 4 weeks later **PLAC_TOP:** One 4-week course, with the potential for a second course 4 weeks later	Age and gender NR; lesion count overall median across arms: 6
Korman 2005 [57]	492		**Primary outcome(s)**	**IMQ5%:** 16 weeks	Age

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
24 weeks 26 USA study centres		Two independent, randomised, parallel-group, vehicle-controlled studies Double-blind	Complete clearance. **Secondary outcome(s)** • Partial clearance rate, (75% reduction) • AEs • Local skin reactions • Clinical laboratory tests • Skin quality assessment		66.7 (10.6); Range: 41 to 87 Gender (male) 210 (86.6) Lesion count NR
				PLAC_TOP: 16 weeks	Age 65.9 (9.9); Range: 41 to 93 Gender (male) 221 (88.4) Lesion count NR
Kose 2008 [88] 12 months Department of Dermatology, Gulhane School of Medicine, Ankara 06018, Turkey	49	Single center, randomised controlled study Open-label	**Primary outcome(s)** ≥75% AK clearance **Secondary outcome(s)** • Investigator and Patient Global Improvement Indices (IGII and PGII) • Baseline Severity Index • Tolerability • Safety • Routine laboratory tests (complete blood cell counts, urine analysis, and fasting chemistry)	**DICLO3%:** 12 weeks	Age 57.6 (10.6) Gender (male) 12 (50.0*) Lesion count NR
				IMQ5%: 12 weeks	Age 56.5 (9.8) Gender (male) 12 (48.0*)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
					Lesion count NR
Lebwohl 2004 [56] 24 weeks 24 centres in the USA and Canada	436	Two large, randomised, parallel group, vehicle-controlled trials Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** Partial clearance rate (75% reduction). Other outcomes were AEs; local skin reactions; clinical laboratory tests; skin quality assessment	**IMQ5%:** 16 weeks	Age 66.6 (10.6); Range: 39 to 88 Gender (male) 187 (87) Lesion count Median: 6; Range: 4 to 10
				PLAC_TOP: 16 weeks	Age 65.5 (9.8); Range: 37 to 88 Gender (male) 193 (87.3) Lesion count Median: 6; Range: 3 to 9
Peplin, 2008: NCT00700063 [65] 8 weeks	131	Multicenter, randomised, vehicle-controlled, dose-ranging study	**Primary outcome(s)** AEs, complete clearance **Secondary outcome(s)** Partial clearance	**IM0.015%:** Two days' treatment	Age 67.8 (7.0) Gender (male) 32 (97)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
25 centres in the USA and 3 centres in Australia		Double-blind			Lesion count NR
				IM0.015%: Three days' treatment	Age 65.2 (9.7) Gender (male) 29 (87.9) Lesion count NR
				PLAC_TOP: Two days' treatment	Age 67.2 (10.1) Gender (male) 28 (87.5) Lesion count NR
				PLAC_TOP: Three days' treatment	Age 69.3 (10.7) Gender (male) 28 (84.8) Lesion count NR
MEDA Pharma GmbH & Co. KG, 2015: NCT00777127	261	Randomised, active controlled, multicentre, multinational study	**Primary outcome(s)** Recurrence of AK **Secondary outcome(s)**	**IMQ5%:** Each course could be either: 4 weeks' treatment, 4 weeks off, 4 weeks' treatment, OR 4 weeks' treatment, 8 weeks	Age Overall: 70.88 (7.6) Gender (male) Overall: 227 (87.3)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
EUCTR-2007-004884-24 LEIDA (X-03016-3271) [76] 36 months 26 centres in Germany, Austria, and France		Open-label	Incidence of squamous cell carcinoma. Cosmetic outcome determined by patient and investigator. Complete and partial clinical clearance; AEs and LSRs	off. Patients received between 1 and 6 courses. **DICLO3%:** Each course contained 12 weeks' treatment. Patients received between 1 and 6 courses.	Lesion count Overall: Median 7.0
Taro Pharmaceuticals USA, 2008: NCT00828568 [80] 24 weeks 20 centres in the USA	246	Randomised, parallel-group, vehicle-controlled therapeutic equivalence study Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** AEs	**IMQ5%:** 16 weeks **PLAC_TOP:** 16 weeks	Age 68.0 (9.5) Gender (male) 149 (81.4) Lesion count NR Age 64.7 (9.7) Gender (male) 52 (86.7) Lesion count NR

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
Peplin, 2009a: NCT00915551 [66] 8 weeks 19 centres in the USA and 2 in Australia	278	Multicenter, randomised, parallel group, vehicle-controlled study Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** Partial clearance defined as ≥75% reduction in the number of AK lesions identified at baseline in the treatment area	**IM0.015%:** 3 days	Age Between 18 and 65 years: 73 (51.4) ≥65 years: 69 (48.6) Gender (male) 117 (82.4) Lesion count NR
				PLAC_TOP: 3 days	Age Between 18 and 65 years: 63 (46.3) ≥65 years: 73 (53.7) Gender (male) 112 (82.4) Lesion count NR
Peplin, 2009b: NCT00916006 [67] 8 weeks 19 centres in the USA and 2 in Australia	269	Multicenter, randomised, parallel group, vehicle-controlled study Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** Partial clearance defined as ≥75% reduction in the number of AK lesions identified at baseline in the treatment area	**IM0.015%:** 3 days	Age Between 18 and 65 years: 71 (52.6) ≥65 years: 64 (47.4) Gender (male) 116 (85.9) Lesion count NR

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
				PLAC_TOP: 3 days	Age Between 18 and 65 years: 77 (57.5) ≥65 years: 57 (42.5) Gender (male) 120 (89.6) Lesion count NR
Gage Development Company, 2016: NCT02952898 [68] 13 weeks 16 centres in the USA	445	Multicenter, randomised, placebo-controlled, parallel group comparison study Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** AEs	**DICLO3%:** 60 days	Age 69.6 (9.8) Gender (male) 175 (79.5) Lesion count NR
				PLAC_TOP: 60 days	Age 69.1 (9.3) Gender (male) 187 (83.9) Lesion count NR
Actavis Inc, 2016: NCT03200912 [69] 8 weeks	337	Multicenter, randomised, vehicle-controlled	**Primary outcome(s)** Complete clearance **Secondary outcome(s)**	**IM0.015%:** 3 days	Age 68.9 (8.6) Gender (male)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
23 centres in the USA		parallel comparison study Double-blind	NR		137 (81.1) Lesion count NR
				PLAC_TOP: 3 days	Age 70.2 (9.4) Gender (male) 133 (79.2) Lesion count NR
Pariser 2003: NCT00306800 [64] 13 weeks 5 centres in the USA	80	Multicenter, randomised Double-blind	**Primary outcome(s)** Patient complete response rate **Secondary outcome(s)** Cosmetic outcome, patient satisfaction, safety	**MAL_PDT:** Two treatments, one week apart	Age 64; Range: 31 to 84 Gender (male) 36 (85.7*) Lesion count Total: 260 Mean: 6.2 per patient
				PLAC_PDT: Two treatments, one week apart	Age 67; Range: 39 to 84 Gender (male) 34 (89.5*) Lesion count Total: 242

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
					Mean: 6.4 per patient
Pariser 2008 [72] 13 weeks 8 centres in the USA	96	Randomised, vehicle-controlled, Double-blind	**Primary outcome(s)** Lesion complete response (complete disappearance of the lesion); patient complete response; new lesions **Secondary outcome(s)** NR	**MAL_PDT:** Two sessions of PDT one week apart	Age 66.1; Range: 43 to 86 Gender (male) 42 (85.7*) Lesion count Median: 8; Range: 4 to 10
				PLAC_PDT: Two sessions of PDT one week apart	Age 66.7; Range: 48 to 89 Gender (male) 37 (78.7*) Lesion count Median: 8; Range: 4 to 10
Pariser 2016: NCT01475955 [74] 24 weeks 13 sites in the USA	93	Randomised vehicle-controlled study Single-blind	**Primary outcome(s)** Lesion clearance; patient complete (100%) clearance rate, partial (≥75%) clearance rate, and subject satisfaction and acceptability of treatment. Tolerability assessments **Secondary outcome(s)**	**ALA_PDT:** One session with potential for a second session 8 weeks later	Age 66.4 (10.6) Gender (male) 40 (85.1) Lesion count

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
			NR		Median: 13.0; Range: 6 to 20
				PLAC_PDT: One session with potential for a second session 8 weeks later	Age 68.4 (9.4) Gender (male) 40 (87.0) Lesion count Median: 14.0; Range: 7 to 20
Piacquadio 2004 [85] 12 weeks 16 sites in the USA	243	This was a multicentre, investigator-blinded, randomised, vehicle-controlled, uneven parallel-group study. The results from 2 independent, identical, phase 3 clinical trials are presented as a single research effort	**Primary outcome(s)** Safety was assessed by analyses of AEs, PDT response, pigmentary changes, and laboratory results. Efficacy was assessed using (1) the complete response rate or clearing of individual AK lesions, (2) the percentage of patients who experienced 75% or greater clearance of all target AKs treated (75% response rate), and (3) the percentage of patients who experienced 100% clearance of all target AKs treated (100% response rate). **Secondary outcome(s)** NR	**ALA_PDT:** One session with potential for a second session at 8 weeks	Age 67.1; Range: 34 to 89 Gender (male) 147 (81) Lesion count NR
				PLAC_PDT: One session with potential for a second session at 8 weeks	Age 64.5; Range: 35 to 85 Gender (male) 56 (90) Lesion count NR

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
		Single-blind			
Reinhold 2016 [52] 24 weeks 7 centres in Germany	87	Randomised, multicentre, placebo-controlled, parallel-group trial Double-blind	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** Cosmetic outcome, safety and tolerability	**ALA_PDT:** One session with the potential for a second session 12 weeks later	Age 71.9 (6.4) Gender (male) 50 (91) Lesion count 5.4 (1.0)
				PLAC_PDT: One session with the potential for a second session 12 weeks later	Age 71.0 (6.4) Gender (male) 29 (91) Lesion count 5.4 (1.2)
Samorano 2015: NCT02242747 [87] 7 weeks Hospital das Clínicas of the University of São	100	Prospective single-site RCT Open-label	**Primary outcome(s)** Total local skin reaction (LSR) grading scale values; adverse effects related to drug treatment **Secondary outcome(s)** To evaluate and compare the area under the curve for each component of the total local skin reaction score using generalised linear models	**IM0.015%:** 3 days **5FU5%:** 4 weeks	Age Overall mean: 74; Range: 38 to 95 Gender (male) Overall: 35 (35) Lesion count NR

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
Paulo Medical School, Brazil					
Serra-Guillen 2012 [92] 8 weeks Dermatology Service of the Instituto Valenciano de Oncología, Spain	NR	Randomised pilot study Open-label	**Primary outcome(s)** Complete clinical response **Secondary outcome(s)** Partial response (75% or more reduction in lesions); complete clinicopathologic response = lack of AK in the biopsy specimen	**MAL_PDT:** One session	Age 72.7 Gender (male) 37 (9.25*) Lesion count 9.0 (2.7)
				IMQ5%: 4 weeks	Age 74.3 Gender (male) 28 (84.8*) Lesion count 9.4 (3.1)
Simon 2015: NCT01358851 [89] 32 weeks 4 centres in Germany	67	An exploratory, open, randomised, prospective, two-armed study Open-label	**Primary outcome(s)** Percentage of patients with histological clearance of a predefined target lesion at 8 weeks **Secondary outcome(s)** Lesion counts, lesion response at each study visit, AK clearance rate (complete and partial (>75%)), determined by clinical evaluation, the physicians'	**5FU0.5%+SA:** 6 weeks	Age 70.6 (8.3); Range: 51 to 83 Gender (male) 29 (87.9) Lesion count 8.1 (1.2)

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
			global assessment, cosmetic outcome and patients' assessment of clinical improvement.	**CRYO:** 1 session, with potential for a second session within 3 weeks (88% of patients had a second session)	Age 71.3 (7.6); Range: 53 to 85 Gender (male) 29 (87.9) Lesion count 8.0 (1.1)
Stockfleth 2017: NCT02289768 [62] 20 weeks 14 sites in Germany and the UK	166	Multicentre, vehicle-controlled study Double-blind	**Primary outcome(s)** Complete clinical clearance **Secondary outcome(s)** • Partial clearance (≥75% reduction in clinically visible AK lesions) • Change from baseline in the total number of AK lesions • Number of lesions by AK grade severity • Proportional change from baseline in the total number of lesions • Global assessment of efficacy: Physician Global Assessment (PGA) • Patient-reported outcomes included patient satisfaction with treatment by recording individual domain scores of the Treatment Satisfaction Questionnaire for Medication (TSQM, version 1.4)	**5FU0.5%+SA:** 12 weeks	Age 71.8 (7.3) Gender (male) 92 (85.2) Lesion count 5.6 (1.4)
				PLAC_TOP: 12 weeks	Age 72.8 (6.9) Gender (male) 51 (92.7) Lesion count 5.6 (1.5)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
			• Quality-of-life assessment by recording the change from baseline in total and individual domain scores of the Dermatology Life Quality Index (DLQI) • AEs		
Stockfleth 2018 [75] 17 weeks 33 sites in Germany, Spain and the UK	502	Multicentre Open-label	**Primary outcome(s)** Complete clearance **Secondary outcome(s)** 75% clearance; AEs	**IM0.015%:** One 3-day course, with potential for retreatment at 8 weeks	Age Median: 75; Range: 49 to 95 Gender (male) 216 (84.7) Lesion count Median: 6; Range 4 to 8
				DICLO3%: 90 days	Age Median: 75; Range: 34 to 96 Gender (male) 212 (85.8) Lesion count Median: 6; Range: 4 to 9
Swanson 2010: NCT00605176 [59] 14 weeks	319	Two randomised, placebo-controlled studies	**Primary outcome(s)** Complete clearance **Secondary outcome(s)**	**IMQ3.75%**: Two 2-week treatment cycles; i.e. 2 weeks' treatment, 2 weeks off, 2 weeks' treatment	Age 64.5 (10.6) Gender (male) 132 (82.5)

Study identifier, duration of trial**, and location	Participants randomised	Trial design (as described by authors)	Primary and secondary outcomes and outcome measures	Duration of treatment	Patient characteristics Age *(mean (SD) in years)* Gender *(N (%) male)* Lesion count per patient at baseline *(mean (SD))*
25 study centres in the USA		Double-blind	• 75% reduction in the number of AK lesions in the treatment area compared with baseline • Percent change from baseline in AK lesion count • Local skin reactions • Investigator Global Integrated Photodamage (IGIP) score		Lesion count 11.0 (4.8)
				PLAC_TOP: Two 2-week treatment cycles; i.e. 2 weeks' treatment, 2 weeks off, 2 weeks' treatment	Age 64.3 (8.9) Gender (male) 130 (81.8) Lesion count 11.3 (4.7)
Szeimies 2004 [55] 24 weeks 18 European centres (3 in France, 5 in Germany, 3 in Italy, 1 in the Netherlands, 3 in Spain, and 3 in the UK)	286	Multicentre, parallel group, vehicle-controlled RCT Double-blind	**Primary outcome(s)** Complete clearance rate **Secondary outcome(s)** Partial clearance rate	**IMQ5%:** 16 weeks	Age 71.1 (7.9) Gender (male) 131 (89.1) Lesion count NR
				PLAC_TOP: 16 weeks	Age 70.9 (8.4) Gender (male) 117 (84.2) Lesion count NR
Szeimies 2010 [82]	122	Randomised, multicentre,	**Primary outcome(s)** Complete clearance	**ALA_PDT:** One session with the potential for a	Age 70.4 (5.1)

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
24 weeks 8 study centres in Germany		placebo-controlled, inter-individual, two-armed trial Double-blind	**Secondary outcome(s)** Safety and tolerability	second session 12 weeks later	Gender (male) 73 (90.1) Lesion count 5.7
				PLAC_PDT: One session with the potential for a second session 12 weeks later	Age 70.6 (6.6) Gender (male) 32 (78.0) Lesion count 5.5
Tanghetti 2007 [83] 24 weeks 2 centres; Centre for Dermatology and Laser Surgery, Sacramento, CA and Dermatology, University of Washington, Seattle, WA, USA	39	2-centre, physician-blinded randomised study Single-blind	**Primary outcome(s)** AK count, % change in AK count, complete clearance, physician's global assessment, patient perception of efficacy, physician's assessment of erythema, patient perception of discomfort **Secondary outcome(s)** NR	**5FU5%:** 2 to 4 weeks	Age, gender and lesion count NR
				IMQ5%: 16 weeks	Age, gender and lesion count NR
Zane 2014 [91]	200		**Primary outcome(s)**	**DICLO3%:** 90 days	Age

Study identifier, duration of trial, and location**	**Participants randomised**	**Trial design (as described by authors)**	**Primary and secondary outcomes and outcome measures**	**Duration of treatment**	**Patient characteristics** **Age** ***(mean (SD) in years)*** **Gender** ***(N (%) male)*** **Lesion count per patient at baseline** ***(mean (SD))***
12 months Dermatology Department of the University of Brescia, Italy		Single-centre, prospective, non sponsored, randomised controlled clinical trial Open-label	Complete clearance, partial clearance, AEs, cosmetic outcome, cost-effectiveness **Secondary outcome(s)** NR		72 (8) Gender (male) 76 (76) Lesion count 8.05
				MAL_PDT: One session, with potential for a second session 12 weeks later	Age 74 (9) Gender (male) 66 (66) Lesion count 8.69*

* Indicates value calculated by reviewers

** "Duration of trial" defined as treatment plus follow up, figures are standardised into weeks / months and are taken from the beginning of treatment

AE - Adverse event; AG – Aktiengesellschaft (joint-stock company); AK - Actinic keratosis; ALA - Aminolevulinic acid; CA - California; CLNS - Cumulative lesion number score; CRYO – cryosurgery; DHA - Diclofenac plus hyaluronate gel; DICLO - Diclofenac; DLQI - Dermatology Life Quality Index; EUCTR - EU Clinical Trials Register; FAS – full analysis set; 5FU - 5-Fluorouracil; HFUS - High-frequency ultrasound; IGII - Investigator Global Improvement Indices; IGIP - Investigator Global Integrated Photodamage; IM - Ingenol mebutate; IMQ - Imiquimod; ITT - Intent to Treat; KG – Kommanditgesellschaft (limited commercial partnership); LED – light-emiting diode; LEIDA - Long-term Effects of Imiquimod and Diclofenac in Actinic Keratoses; LLC – limited liability company; LSR - Local skin reaction; MAL - Methyl aminolevulinate; NR - Not reported; PDT - Photodynamic therapy; PGA - Physician Global Assessment; PGII - Patient Global Improvement Indices; PGT - Physician Global Assessment; PP – per protocol; RCT - Randomised controlled trial; SA - Salicylic acid; SCC - Squamous cell carcinoma; TIRBA1% – Tirbanibulin; TLNS - Target lesion number score; TOP – Topical; TSQM - Treatment Satisfaction Questionnaire for Medication; UK - United Kingdom; USA - United States of America; VEH - Vehicle; WA – Washington.

1.2 Data extraction elements

For each study, information was collected on:

- Trial details (bibliographic details)
- Trial characteristics:
  - Trial design
  - Trial objective
  - Number of participating centres
  - Country
  - Eligibility criteria
  - Number of patients randomised/analysed
  - Treatment duration
  - Follow up duration
  - Data collection time points
- Patient baseline characteristics:
  - Age
  - Gender
  - Time since diagnosis
  - Location and area of AK
  - Severity of AK
  - Lesion count at baseline
  - Number and details of prior treatments for AK
  - Fitzpatrick skin type
  - History of skin cancer
  - Details of any current immunosuppression
- Details of intervention and placebo
  - Treatment
  - Dose
  - Regimen
  - Duration of treatment
  - Concomitant medications, including sunscreen use
- Details of statistical analyses
- For each of the outcomes specified we will extract the following:
  - Outcome definition
  - The unit of measurement
  - The number of patients included in the analysis
  - The size of the effect:
    - For dichotomous outcomes; absolute and relative risks (or ORs) and risk (or rate) differences
    - For continuous outcomes; the mean change and measure of variance from baseline (or at both baseline and final visit), or mean difference between treatments
    - For time-to-event analysis; the number of events in each arm, median time to event and a hazard ratio and p-value
    - Where possible, absolute and relative data were extracted

- A measure of precision for each estimate of effect (95% confidence intervals, standard error or standard deviation)

1.3 Details of the PRISMA flow diagram

The following provides additional information on the reasons for exclusion of documents from the systematic review.

Abstract - cannot link to full text paper: Document is an abstract that appeared to be reporting an eligible study, but the study could not be linked (using details of patient N, interventions, location, and any reported clinical trial numbers or study names) to any study reported in an included full text paper. Studies only reported in abstract form did not offer sufficient information to include them in the review.

Completed trial (no results): Document is a clinical trial record reporting the methods of an apparently eligible clinical trial. Based on the dates supplied, the trial appears to be completed. However, no results were reported in the trial record and the trial could not be linked (using details of patient N, interventions, location, and any reported clinical trial numbers or study names) to any study reported in an included full text paper.

Does not report comparative results: Document is a paper reporting the conduct of eligible studies, but results are not presented for both arms of the study.

Duplicate record: Document is an exact duplicate of an already-included document, e.g. this may be the same record downloaded twice from different databases.

Ineligible publication type: Document does not report a clinical study, e.g. a letter to editor or report of a non-systematic review.

Ineligible subgroup analysis: Document reports an eligible study but the only results reported are for a subgroup analysis of a patient subgroup not of interest to this systematic review.

Insufficient information to include: Document does not report sufficient information to judge whether the study reported is eligible or not.

Possible ongoing trial (no results): Document is a clinical trial record reporting the methods of an apparently eligible clinical trial. Based on the dates supplied, the trial appears to be ongoing: no results are reported.

Review, non-systematic: Narrative (non-systematic) reviews of studies were not eligible for inclusion or reference checking.

SR for reference checking: Systematic reviews of treatments for actinic keratosis were excluded but the lists of included studies were checked to ensure all relevant studies had been identified.

Document unobtainable: Document was unavailable for purchase and subsequent screening.

Ineligible comparator: Document reports a study assessing an eligible intervention (i.e. one listed in the PICO for this systematic review) against a non-eligible comparator.

Ineligible intervention: Document reports a study assessing a non-eligible intervention (i.e. one other than those listed in the PICO for this systematic review).

Ineligible outcomes: Document reports a study that did not assess / report any outcomes of interest listed in the PICO for this systematic review.

Ineligible patient population: Document reports a study assessing treatments for AK in a population other than that detailed in the PICO for this systematic review, e.g. children or organ transplant patients.

Ineligible study design: Document reports a clinical study that is not an interindividual RCT, e.g. a retrospective study or an intraindividual RCT.

2 Selection of studies for NMA

2.1 Results of the feasibility assessment

Following a comparison of the populations, interventions, comparators and designs of the 46 trials included in the review, six studies were deemed to be unsuitable for inclusion in an NMA.

Dermapharm AG, 2011: EUCTR- 2011-003317-41 [94] was removed from the feasibility assessment as the lack of reporting of the number of patients per arm meant the study could not be used in a NMA.

Both MEDA Pharma studies [76, 90] were removed from consideration for the NMA as the number of courses of treatment assessed by both arms (DICLO3% and IMQ5%_EU) of these studies was not sufficiently similar to the rest of the studies included in the review to allow for pooling.

Berman 2014 [93] treated all patients with two sessions of MAL_PDT, four weeks apart, while the US label for Levulan Kerastick states that retreatment should be after eight weeks, and should only be for those patients for whom it is necessary. The study was therefore excluded from consideration for the NMA as the scheduling was not as per label.

The DICLO3% arm of Kose 2008 [88] was removed from consideration for the analyses, as it assessed one-daily treatment with DICLO3%. This is both off-label, and insufficiently comparable with the rest of the included studies of diclofenac, all of which assessed application

twice daily. The IMQ5%_USA arm of Kose 2008 was also removed from consideration for the analyses, as it assessed treatment for 12 weeks, rather than the 16 weeks both as suggested by the US label and as assessed by the other studies of the US scheduling of IMQ5%. As Kose 2008 is a two-armed trial it was therefore removed at this stage.

The IMQ3.75% arm of Hanke 2010 [58] was excluded from consideration for the analyses as it assesses a length of treatment other than that suggested by the relevant labelling for this intervention. As Hanke is a two-armed trial the whole trial was therefore removed from consideration for the NMA.

Placebo / vehicle arms were grouped into topical placebo (PLAC_TOP) or placebo PDT (PLAC_PDT). While this is an assumption around the equivalence of the included placebo / vehicle arms (for example, it does not take into consideration the fact that the hyaluronic acid vehicle for DICLO3% may have some efficacy of its own), this was necessary to form connected networks. The assumption of placebo equivalence is also consistent with the practices of previous NMA authors [21, 22, 47, 48], and by separating PLAC_TOP and PLAC_PDT into separate nodes, this NMA retains a greater degree of differentiation than prior NMAs which grouped PLAC_TOP and PLAC_PDT into one node [21, 22, 48].

2.2 Selection of studies for the European analyses

Of the 40 studies remaining for use in the analyses after the feasibility assessment [28, 51-57, 59-75, 77-87, 89, 91, 92], five studies were not relevant to a European perspective [55-57, 80, 83] as they assessed the US scheduling of imiquimod 5% against another intervention or placebo. Following the removal of these further five studies, 35 studies remained eligible for use in the European analyses [28, 51-54, 59-75, 77-79, 81, 82, 84-87, 89, 91, 92].

Supplementary Table S6 provides a summary of the studies informing the qualitative analyses and the NMA base case and sensitivity analyses, assessed for the European perspective.

Supplementary Table S6: Summary of studies contributing to the European perspective analyses

Study identifier	NMA of complete clearance					Qualitative analyses		
	Base case European analysis	Sensitivity analyses				Lesion count reduction	Discontinuations due to TRAEs / TEAEs / local AEs / LSRs	Number of severe LSRs
	Any number of courses	One treatment cycle	Treatment area limited to 25 cm^2	Single placebo node	Response assessment ≥8wks after treatment			
Actavis Inc, 2016: NCT03200912	x	x	x	x	x			
Almirall Hermal GmbH, 2007: EUCTR-2007-003889	x	x	x	x	x	x	x	
Almirall S.A., 2010: EUCTR-2010-022244-20	x	x		x	x			
Alomar 2007	x		x	x			x	x
Arisi 2020	x	x	x	x	x	x		
Athenex, Inc 2019a KX01-AK-003: NCT03285477	x	x	x	x	x	x	x	x
Athenex, Inc 2019b KX01-AK-004: NCT03285490	x	x	x	x	x	x	x	x
Biofrontera Bioscience GmbH, 2006: EUCTR-2006-000314-20	x	x		x			x	
Dirschka 2012	x			x	x		x	
Dohil 2016	x	x		x		x		
Foley 2011	x			x	x			
Gage Development Company, 2016: NCT02952898	x	x		x				
Hauschild 2009 AK 03	x	X (but does not link to main network)		x	x		x	
Hauschild 2009 AK 04	x	X (but does not link to main network)		x	x		x	
Jorizzo 2007	x		x	x				
Pariser 2003	x			x	x	x		
Pariser 2008	x			x	x			
Pariser 2016	x			x	x			x

Study identifier	NMA of complete clearance					Qualitative analyses		
	Base case European analysis	Sensitivity analyses				Lesion count reduction	Discontinuations due to TRAEs / TEAEs / local AEs / LSRs	Number of severe LSRs
	Any number of courses	One treatment cycle	Treatment area limited to 25 cm^2	Single placebo node	Response assessment ≥8wks after treatment			
Peplin, 2008: NCT00700063	x	x		x	x			
Peplin, 2009a: NCT00915551	x	x	x	x	x			
Peplin, 2009b: NCT00916006	x	x	x	x	x			
Piacquadio 2004	x			x			x	
Reinhold 2016	x		x (but does not link to main network)	x	x	x	x	
Serra-Guillen 2012	x	x	x	x				
Simon 2015	x		x	x	x		x	
Stockfleth 2017	x	x	x	x	x	x	x	
Stockfleth 2018	x		x	x		x	x	
Swanson 2010	x			x	x	x	x	x
Szeimies 2010	x			x	x			
Zane 2014	x			x	x	x		
Chen 2003							x	
Freeman 2003							x	
Jansen 2019							x	
Studies eligible for European perspective analyses but reporting safety outcomes other than those described in this report								
Dermapharm AG, 2014: EUCTR- 2014-001621-33	Reports overall serious adverse events, deaths, and LSRs (overall, not severe, so does not contribute to writeup)							
Samorano 2015	Reports serious adverse events, and LSRs (overall, not severe, so does not contribute to writeup)							
Studies assessing IMQ5%_USA excluded from the European perspective analyses								
Korman 2005								
Lebwohl 2004								
Szeimies 2004								
Tanghetti 2007								
Taro Pharmaceuticals USA, 2008: NCT00828568								
Studies excluded from all analyses following feasibility assessment								

Study identifier	NMA of complete clearance					Qualitative analyses		
	Base case European analysis	**Sensitivity analyses**				**Lesion count reduction**	**Discontinuations due to TRAEs / TEAEs / local AEs / LSRs**	**Number of severe LSRs**
	Any number of courses	One treatment cycle	Treatment area limited to 25 cm^2	Single placebo node	Response assessment ≥8wks after treatment			
Berman 2014	Scheduling off label							
Dermapharm AG, 2011: EUCTR- 2011-003317-41	Not enough data reported to use either arm; no N reported							
Hanke 2010	Scheduling off label							
Kose 2008	Both arms are off label, and one arm assesses IMQ5%_USA							
MEDA Pharma GmbH & Co. KG, 2015: NCT00777127, EUCTR-2007-004884-24, LEIDA (X-03016-3271)	Both arms offer more treatment than other studies of these interventions, so are not comparable							
MEDA Pharma GmbH & Co. KG, 2010: EUCTR-2010-022054-16 (LEIDA 2)	Both arms offer more treatment than other studies of these interventions, so are not comparable							

AE – adverse event; LSR – local skin reaction; TEAE – treatment emergent adverse event; TRAE – treatment related adverse event

3 Detailed results of the qualitative analyses: Europe

The following analyses are from the European perspective only.

3.1.1 Lesion count reduction

Eleven studies eligible for inclusion in this analysis [52-54, 59, 62-64, 75, 79, 84, 91] reported data on lesion count reduction. Nine of the studies [52, 59, 62-64, 75, 79, 91] reported change as a percentage and did not include any variance data. The remaining three studies [53, 54, 84] reported a mean or median change rather than a percentage change.

Lesion count reductions of between 51.8% (DICLO3% [91]) and 94.3% (ALA_PDT [52] were reported in the active arms of the six studies. Five of the eleven studies reported a percentage reduction in the placebo / vehicle arms, ranging from 25% [59] to 46.9% [62]. A further two studies [53, 54] reported the mean and SD change from baseline in the placebo / vehicle arms.

Summary of interventions:

- TIRBA1%: Both studies [53, 54] reported a mean and standard deviation (SD) at baseline and endpoint. In these studies, there was a significant reduction from around six lesions to one or two lesions in the intervention arm ($p<0.001$) compared with a reduction from around six lesions to around four lesions in the placebo / vehicle arm.
- ALA_PDT: One study [52] reported a reduction from baseline of 94.3% compared with reduction of 32.8% in placebo / vehicle arm.
- DICLO3%: One study [79] showed a 54.6% reduction from baseline in the intervention arm compared with a 36.5% reduction in the placebo arm. Two additional studies [75, 91] reported a reduction from baseline of 51.8% and 57.7%, respectively, but with no placebo / vehicle data for comparison. A final study [84] showed a reduction from a baseline median of seven (range: 5 to 12) to three (range 0 to 8) at endpoint. This last study did not contain a placebo / vehicle arm.
- IM0.015%: One study [84] reported a baseline median of seven (range: 5 to 13) which reduced to two (range: 0 to 6). The small overlap in the ranges indicates a substantial difference between baseline and endpoint. No placebo / vehicle for comparison. A second study [75] reported a reduction from baseline of 80.2%. No placebo / vehicle for comparison.
- IMQ3.75%: One study [59] reported a reduction from baseline of 81.8% compared with a reduction of 25% in the placebo / vehicle arm.
- MAL_PDT: Two studies [91] and [64] reported a reduction from baseline of 85.9% and 89%, respectively. One of these [64] included a placebo / vehicle arm which had reduction of 38%. A third study [84] reported a baseline median of nine (range: 5 to 12) which reduced to

two (range: 0 to 4) in the active arm. The lack of overlap in the ranges indicates a substantial difference between the baseline and endpoint data. No placebo / vehicle for comparison.

- 5FU0.5%+SA: Two studies [62] and [79] reported a reduction from baseline of 74.5% and 78% in the intervention arm and 36.5% and 46.9% in the placebo / vehicle arm, respectively.
- 5FU4%: One study [63] reported an 80.1% reduction from baseline in the intervention arm. The reduction in the placebo / vehicle arm was not reported.
- 5FU5%: One study [63] reported a reduction from baseline of 79%. The reduction in the placebo / vehicle arm was not reported.

In conclusion all interventions, including TIRBA1%, showed substantial reductions in lesion counts, including when compared to placebo / vehicle. The comparisons with placebo / vehicle were sparse.

3.1.2 Discontinuation due to Adverse Events / Local Skin Reactions

As described in the main manuscript, rather than looking at discontinuation due to any adverse events (AEs), we only assessed discontinuations due to treatment-emergent AEs (TEAEs), treatment-related AEs (TRAEs), local AEs or local skin reactions (LSRs). These were deemed to most likely to provide data on discontinuations related to the study treatment, rather than reflecting the study methods, baseline characteristics of the study population, or events that were independent from the intervention.

A total of 17 studies reported discontinuations due to TEAEs, TRAEs, serious TRAEs, local AEs or LSRs. Thirteen of the 17 studies reported discontinuation rates for a placebo / vehicle arm. A summary of the discontinuation rates in the interventions of interest is presented below:

In summary:

- TIRBA1%: Two studies [53, 54] reported discontinuation rates of 0% due to TRAEs in the intervention and placebo / vehicle arms.
- ALA_PDT: AK03 and AK04 [78] reported discontinuations of 1.4% due to TEAEs. No discontinuation data were reported for the placebo / vehicle arms of either AK03 or AK04. Two further studies [52, 85] reported discontinuations of 0% due to TRAEs in the intervention arm, and a fifth study [73] reported discontinuations of 0.8% due to serious TRAEs. These final three studies all reported discontinuations of 0% in the placebo / vehicle arms.
- CRYO: One study [89] reported discontinuations of 0% due to LSRs. No placebo / vehicle for comparison.
- DICLO3%: One study [79] reported discontinuations of 4.9% due to local TEAEs compared with 1% (as calculated by reviewers) in the placebo / vehicle arm. The second study [71] reported rates of 2.1% and 12.3% in the intervention arm compared with 3.9% and 2.4% in the placebo / vehicle arm due to local TEAEs and "cutaneous side effects", respectively. Data from this study was taken from an EU Clinical Trials Registry (EUCTR) clinical study

report synopsis, and the relationship between local TEAEs and cutaneous side effects is unclear (i.e. whether one is a subset of the other). A third [75] reported discontinuations of 6% due to TRAEs in the DICLO3% arm. No placebo / vehicle for comparison in this final study.

- IM0.015%: Two studies [28, 75] reported discontinuation rates of 0% and 2% due to serious TRAEs and any TRAEs, respectively. No placebo / vehicle for comparison.
- IMQ3.75%: One study [59] reported discontinuations of 0.6% in the active arm and 0.6% in placebo / vehicle arm due to TRAEs.
- IMQ5%_EU: Two studies [28, 51] reported discontinuation rates in the intervention arm of 0% due to serious TRAEs and LSRs. A third study [61] reported a discontinuation rate of 1.6% due to LSRs. Two studies [51, 61] reported placebo / vehicle arm discontinuation rates of 0%.
- MAL_PDT: Three studies reported discontinuations of 0.8% due to local AEs [73] 1.1% due to LSRs [77] and 0 discontinuations for reasons related to treatment [28]. Of the three trials, two had placebo / vehicle arms [73, 77], for which only one reported data [73], with zero discontinuations due to local AEs.
- 5FU0.5%+SA: Two studies [62, 79] reported discontinuations of 1.9% and 3.7% due to TEAEs. One study [62] reported zero discontinuations in placebo / vehicle arm, and the other study [79] reported one discontinuation (1%, as calculated by reviewers). A third study [89] reported discontinuations due to LSRs of 9.1% in the intervention arm compared with 0% in placebo / vehicle arm.
- 5FU5%: One study [28] reported discontinuations of 0% in the active arm due to serious TRAEs. No placebo / vehicle for comparison.

Rates for the active arms were generally low, ranging from 0% (TIRBA1%; two studies [53, 54]; CRYO, one study [89]; IM0.015%, one study [28]; IMQ5%_EU, two studies [28, 51] and MAL_PDT, one study [28]) to 12.3% (DICLO3% [71] with placebo / vehicle arms ranging between 0% and 3.9% [71]. Exact reasons for discontinuation varied across studies.

The two studies assessing TIRBA1% reported 0% discontinuations due to TEAEs, TRAEs, local AEs or LSRs (these studies reported rates of 0% for both the intervention and the placebo / vehicle arms).

In conclusion, while intervention arms generally reported low rates of 2% or below (with even lower rates presented for placebo / vehicle, between 0% and 0.6%), two of the interventions, 5FU0.5%+ SA and DICLO3% [75, 89], reported rates of 9% and up to 12.3% respectively, compared with 0% discontinuation rates for placebo / vehicle (placebo / vehicle rates available for 5FU0.5%+ SA only).

3.1.3 Incidence of severe LSRs

Analyses were planned to investigate the relative incidence of severe forms of LSRs. However, on closer investigation of the available data, only a maximum of five studies contributed to the analysis for any of these outcomes.

- Severe redness / erythema: Reported by five studies [53, 54, 59, 61, 74]
- Severe flaking / scaling / dryness: Reported by five studies [53, 54, 59, 61, 74]
- Severe scabbing / crusting: Reported by four studies [53, 54, 59, 61]
- Severe erosion / ulceration: Reported by four studies [53, 54, 59, 61]
- Severe vesicles: Reported by three studies [53, 54, 61].
- Severe swelling / oedema: Reported by five studies [53, 54, 59, 61, 74]
- Severe itching / pruritis: Reported by three studies [53, 54, 79]
- Severe weeping / exudate: Reported by two studies [59, 61]

The following provides a summary of severe LSRs by intervention, as reported by studies assessing one course or session of treatment only. All LSRs referred to in the following paragraphs are severe.

- TIRBA1%: Across both studies [53, 54] 3% and 10% of patients experienced a severe form of redness / erythema, 6% and 11% experienced flaking / scaling / dryness, no patients experienced erosion, 1% and 3% experienced scabbing / crusting, 0.6% experienced vesicles, 0.6% experienced swelling / oedema, 0% and 0.6% experienced pruritis, and no data were reported for weeping / exudation. In the placebo / vehicle arm, none of these LSRs were reported [53, 54].
- ALA_PDT: One study [74] reported that no patients in the intervention or placebo / vehicle arms experienced any LSR.
- DICLO3%: One study [79] reported that 7% of patients in the intervention arm experienced a severe form of itching / pruritis compared with 0% in the placebo / vehicle arm. No data on redness / erythema, flaking / scaling / dryness, erosion / ulceration, scabbing / crusting, vesicles, swelling / oedema, or weeping / exudation were presented in this study.
- IMQ5%_EU: One study [61] reported that 31% of patients in the intervention arm experienced redness / erythema (placebo / vehicle arm: 0%), 11.6% experienced flaking / scaling / dryness (placebo / vehicle arm: 0.8%), 10.9% experienced erosion / ulceration (placebo / vehicle arm: 0.8%), 24% experienced scabbing / crusting (placebo / vehicle arm: 1.5%), 1.6% experienced vesicles (placebo / vehicle arm: 0%), 7% experienced swelling / oedema (placebo / vehicle arm: 0%), and 4.7% experienced weeping / exudation (placebo / vehicle arm: 0.8%). No data were presented on itching / pruritis.
- IMQ3.75%: One study [59] reported that 25.2% of patients in the intervention arm experienced redness / erythema (placebo / vehicle arm: 0%), 8.2% experienced flaking / scaling / dryness (placebo / vehicle arm: 1.3%), 10.7% experienced erosion / ulceration (placebo / vehicle arm: 0%), 13.8% experienced scabbing / crusting (placebo / vehicle arm:

0%), 5.7% experienced swelling / oedema (placebo / vehicle arm: 0%), and 5.7% experienced weeping / exudation (placebo / vehicle arm: 0%). This study did not report data on vesicles or itching / pruritis.

- 5FU0.5%+SA: One study [79] reported that 4.8% of patients in the intervention arm experienced a severe form of itching / pruritis compared with 0% in the placebo / vehicle arm. This study did not report data on redness / erythema, flaking / scaling / dryness, erosion / ulceration, scabbing / crusting, vesicles, swelling / oedema, or weeping / exudation.

With incidence of severe LSRs only being reported for six of the interventions of interest, the lack of reporting makes a comparison between drugs difficult. Overall, IMQ5%_EU and IMQ3.75% showed relatively high rates of severe LSRs, whereas no severe LSRs were reported for ALA_PDT.

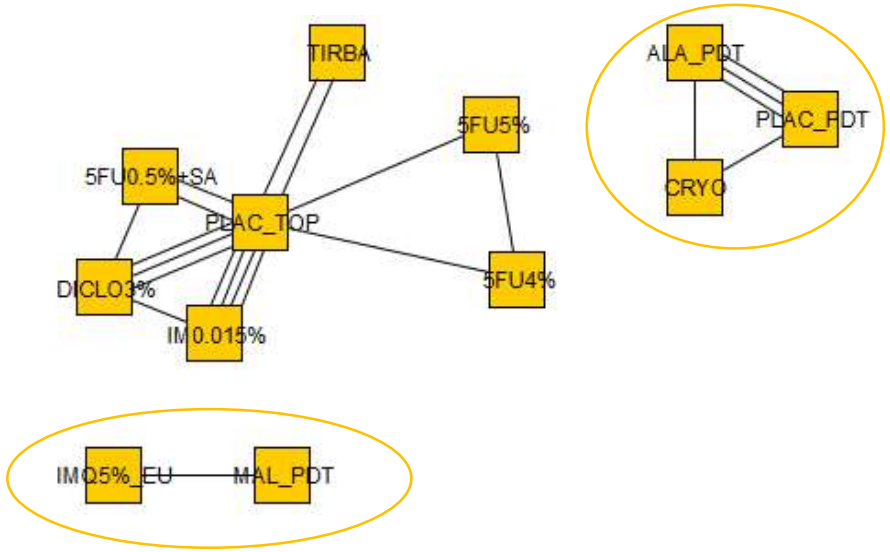
4 Supplementary results of the European NMA

4.1 Fixed or random effects models

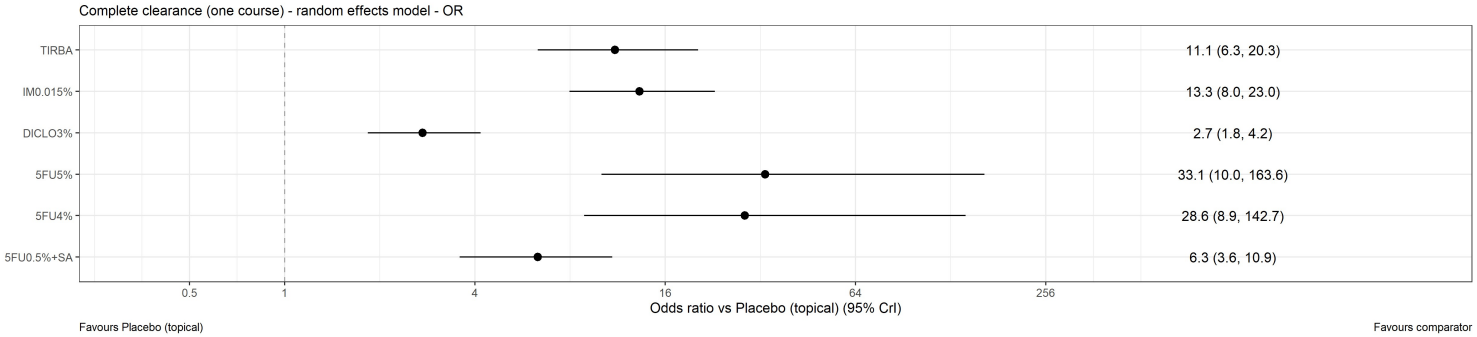
NMA can be based on either fixed or random effects models. With a fixed effects model, we assume that there is a true treatment effect that is the same across studies, and the differences between studies are due to chance alone. With random effects, we assume that the effects being estimated are not the same, but that they are related and follow a shared distribution. The mean of this distribution is the estimate of the treatment effect. Random effects models can be considered as both more plausible and more conservative, and for this reason this manuscript presents the results of the random rather than fixed effects models.

4.2 Sensitivity analyses: plots and networks

The following section presents networks and results plots for the four sensitivity analyses detailed in Section 2.5 of the main manuscript.



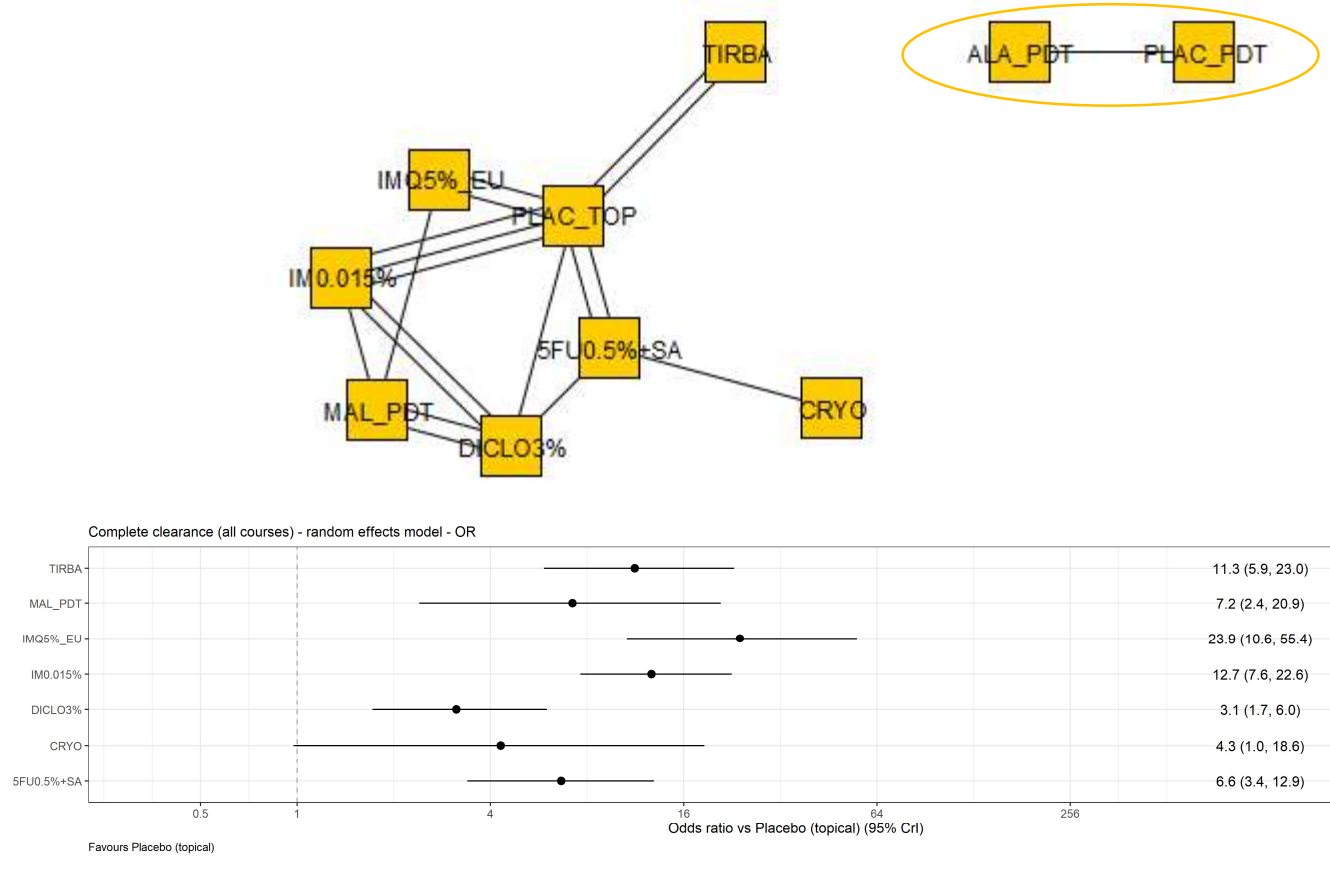
(a) Network diagram (circled nodes indicate non-linked subnetworks disconnected from the main network)



(b) Forest plot of the interventions from the main network showing odds ratios against placebo with 95% credible intervals

Supplementary Figure S2: Complete clearance, subgroup analysis, only studies assessing a single course or session of treatment – network diagram and forest plot

5FU0.5%+SA - 5 fluorouracil 0.5% + salicylic acid 10%; 5FU4% - 5 fluorouracil 4%; 5FU5% - 5 fluorouracil 5%; ALA_PDT - Photodynamic therapy with 5-Aminolevulinic acid sensitiser; CRYO - Cryotherapy; DICLO3% - Diclofenac 3%; IM0.015% - Ingenol mebutate 0.015%; IMQ5%_EU - Imiquimod 5% EU posology; MAL_PDT - Photodynamic therapy with methyl aminolevulinate sensitiser; PLAC_PDT - Photodynamic therapy with placebo sensitiser; PLAC_TOP - Topical placebo; TIRBA1% - Tirbanibulin 1%

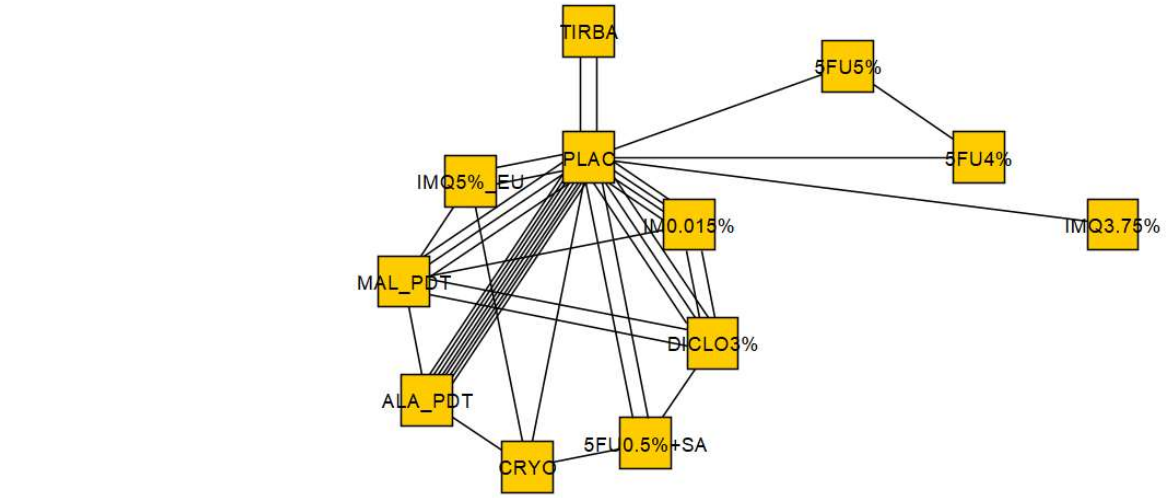


(a) Network diagram (circled nodes indicate non-linked subnetworks disconnected from the main network)

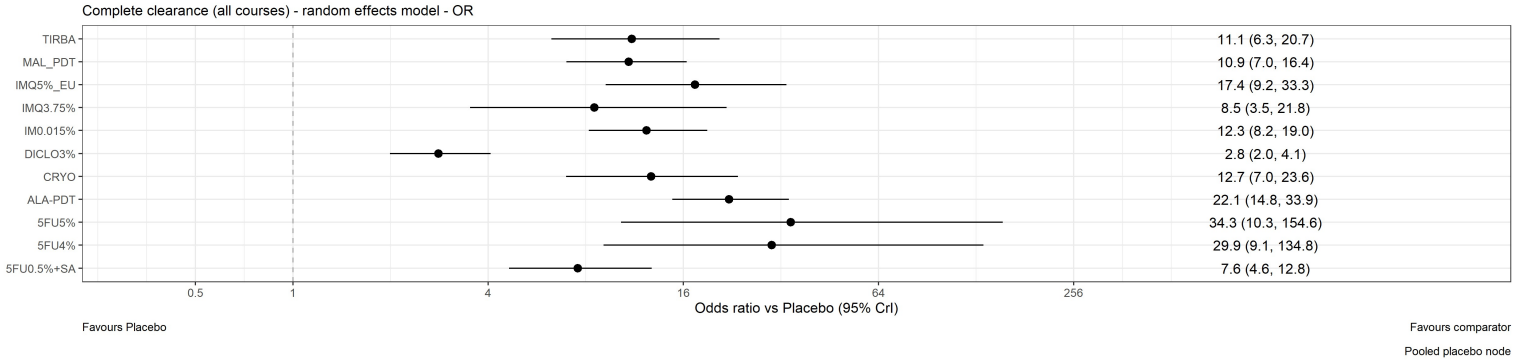
(b) Forest plot of the interventions from the main network showing odds ratios against placebo with 95% credible intervals

Supplementary Figure S3: Complete clearance, subgroup analysis, only studies assessing a treatment area of ≤25 cm^2 - network diagram and forest plot

5FU0.5%+SA - 5 fluorouracil 0.5% + salicylic acid 10%; ALA_PDT - Photodynamic therapy with 5-Aminolevulinic acid sensitiser; CRYO - Cryotherapy; DICLO3% - Diclofenac 3%; IM0.015% - Ingenol mebutate 0.015%; IMQ5%_EU - Imiquimod 5% EU posology; MAL_PDT - Photodynamic therapy with methyl aminolevulinate sensitiser; PLAC_PDT - Photodynamic therapy with placebo sensitiser; PLAC_TOP - Topical placebo; TIRBA1% - Tirbanibulin 1%



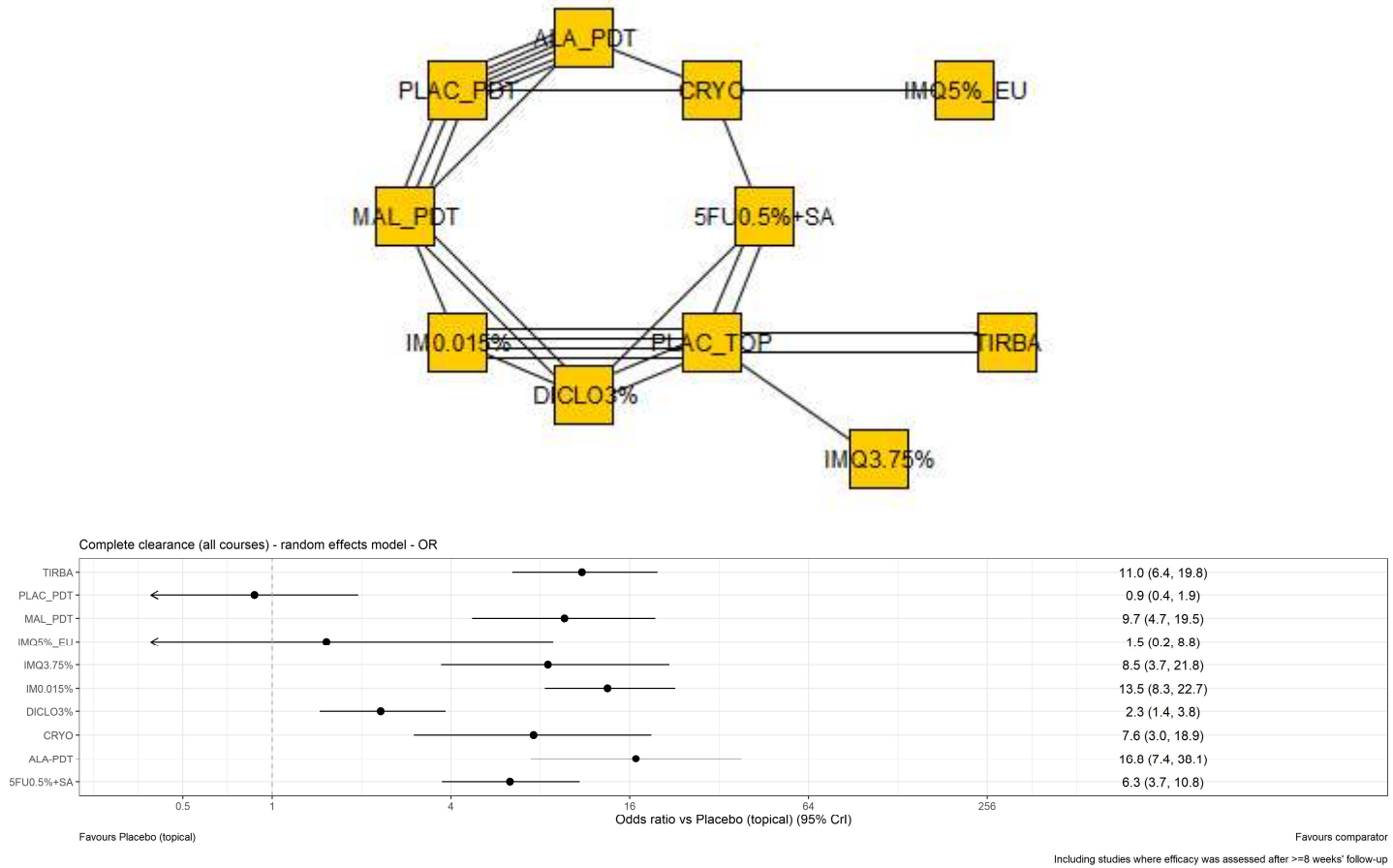
(a) Network diagram



(b) Forest plot of the interventions from the main network showing odds ratios against placebo with 95% credible intervals

Supplementary Figure S4: Complete clearance, sensitivity analysis, single placebo node

5FU0.5%+SA - 5 fluorouracil 0.5% + salicylic acid 10%; 5FU4% - 5 fluorouracil 4%; 5FU5% - 5 fluorouracil 5%; ALA_PDT - Photodynamic therapy with 5-Aminolevulinic acid sensitiser; CRYO - Cryotherapy; DICLO3% - Diclofenac 3%; IM0.015% - Ingenol mebutate 0.015%; IMQ3.75% - Imiquimod 3.75%; IMQ5%_EU - Imiquimod 5% EU posology; MAL_PDT - Photodynamic therapy with methyl aminolevulinate sensitiser; PLAC - Placebo, topical or placebo PDT; TIRBA1% - Tirbanibulin 1%



(a) Network diagram

(b) Forest plot of the interventions from the main network showing odds ratios against placebo with 95% credible intervals

Supplementary Figure S5. Complete clearance, sensitivity analysis, only studies assessing efficacy ≥8 weeks after treatment

5FU0.5%+SA - 5 fluorouracil 0.5% + salicylic acid 10%; ALA_PDT - Photodynamic therapy with 5-Aminolevulinic acid sensitiser; CRYO - Cryotherapy; DICLO3% - Diclofenac 3%; IM0.015% - Ingenol mebutate 0.015%; IMQ3.75% - Imiquimod 3.75%; IMQ5%_EU - Imiquimod 5% EU posology; MAL_PDT - Photodynamic therapy with methyl aminolevulinate sensitiser; PLAC_PDT - Photodynamic therapy with placebo sensitiser; PLAC_TOP - Topical placebo; TIRBA1% - Tirbanibulin 1%

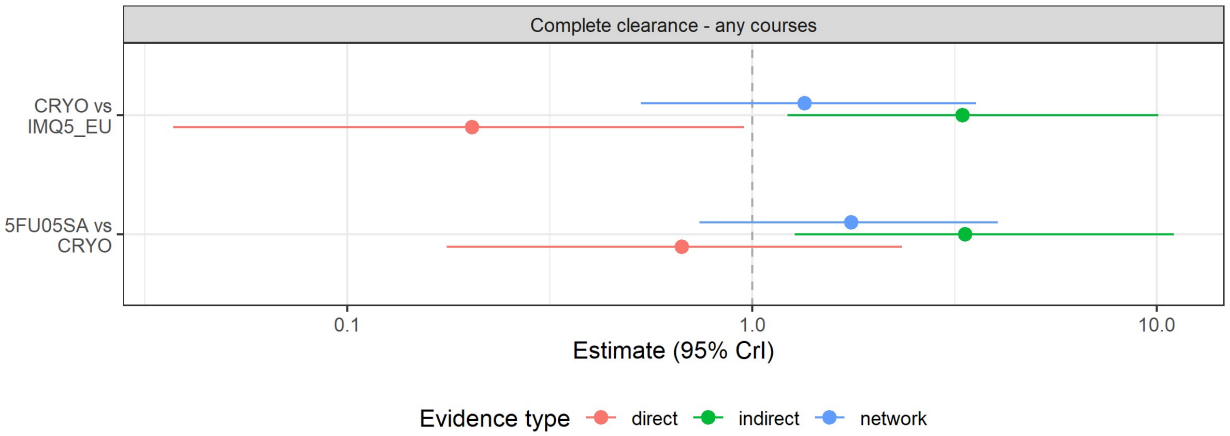
4.3 Assessment of Inconsistency

Inconsistency refers to unexplained heterogeneity (i.e. differing treatment effect estimates) between direct comparisons and indirect comparisons made possible by loops in the networks.

Here we estimate the posterior ORs between pairs of treatments for three scenarios: one where we only consider evidence when those treatments are head-to-head; the second where we only consider indirect evidence via shared comparators; and the third where we combine both forms of evidence (which is the result our network reports).

Supplementary Figure S6 shows the results of this inconsistency analysis for those pairs of treatments where both forms of evidence (direct and indirect) were available, and there was significant disagreement (p values <0.05) between the direct and indirect evidence.

We can see that the final network result balances the direct and indirect evidence and does so by upweighting the more confident of the two estimates. In general, indirect posterior ORs were consistent with direct posterior ORs, so the above inconsistencies had little effect on the overall outcome of the analyses.



Supplementary Figure S6. Inconsistency analysis – complete clearance (any courses)

5FU05SA - 5 fluorouracil 0.5% + salicylic acid 10%; CrI - Credible interval; CRYO - Cryotherapy; IMQ5_EU - Imiquimod 5% EU posology.

5 PRISMA Checklist for the review and NMA

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported in?
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	Manuscript title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Abstract has been constructed in accordance with JCM requirements
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Systematic review methods
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged	Table 1

Section/Topic	Item #	Checklist Item	Reported in?
		into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Results of the literature searches and screening & Supplementary Table S1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Figure S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Systematic review methods & Feasibility assessment methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Systematic review methods
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary Section S1.2
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Statistical analysis methods
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Systematic review methods
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	Statistical analysis methods
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • Handling of multi-arm trials; • Selection of variance structure; • Selection of prior distributions in Bayesian analyses; and • Assessment of model fit.	Statistical analysis methods
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Statistical analysis methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Systematic review methods & Feasibility assessment methods
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:	Sensitivity analyses of complete clearance

Section/Topic	Item #	Checklist Item	Reported in?
		• Sensitivity or subgroup analyses; • Meta-regression analyses; • Alternative formulations of the treatment network; and • Use of alternative prior distributions for Bayesian analyses (if applicable).	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results of the literature searches and screening & Figure 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 3 & Supplementary Figures S2–S5
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Results of the feasibility assessment
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table S5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	Tables 2–4
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	Figures 3 & Supplementary Figures S2–S5
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Supplementary Section S4.3 & Supplementary Figure S6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Results of the literature searches and screening
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	Sensitivity analysis: Single course data only Sensitivity analysis: studies

Section/Topic	Item #	Checklist Item	Reported in?
			assessing a treatment area of ≤25 cm2 only Sensitivity analysis: Single placebo node Sensitivity analysis: Studies assessing efficacy ≥8 weeks after treatment only
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	Limitations & Assumptions
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	See funding statement

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