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2 March 2015

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Dear Dr Keaney

Photodynamic treatment (PDT) for skin and mucosal cancer

Further to your letter of 12 November 2014 and the subsequent exchange of emails with Ms Mary Warner, we enclose a summary on photodynamic therapy (PDT) for the treatment of non-melanoma skin cancer.

It is evidence-based that the safety and efficacy of PDT has strengthened considerably since 1999. The Australasian College of Dermatologists supports MSAC in re-evaluation/reconsideration of public funding for this treatment.

Yours sincerely

Associate Professor Stephen Shumack OAM FACD FAICD
President

Enclosure

cc Ms Mary Warner
Director, Medical Services Section, Medical Specialist Services Branch
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Summary on photodynamic therapy for the treatment of nonmelanoma skin cancer

February 2015

Executive summary

This document provides a summary of the more recent randomised control trial (RCT) evidence on photodynamic therapy (PDT) for the treatment of nonmelanoma skin cancer.

Twelve RCTs were identified in actinic keratosis (AK); 6 were identified in basal cell carcinoma (BCC), 3 each in nodular BCC and superficial BCC; and 2 were identified in squamous cell carcinoma (SCC) in situ (Bowen's disease).

For actinic keratosis:

- *MAL-PDT was superior to placebo-PDT*
- *MAL+daylight-PDT was non-inferior to MAL+conventional-PDT*
- *There is variability in reporting on the effectiveness of MAL-PDT compared with cryotherapy*
- *MAL-PDT was nominally less effective than imiquimod or imiquimod + PDT*
- *MAL-PDT was nominally less effective than ALA-PDT with Ameluz®* (Biofrontera, Leverkusen, Germany)
- *Conventional-MAL-PDT was nominally less effective than AFL-PDT or AFL-daylight-PDT*

For basal cell carcinoma:

- *MAL-PDT was superior to placebo-PDT*
- *MAL-PDT was inferior to surgery*
- *No statistical differences between MAL-PDT and cryotherapy*
- *Imiquimod was superior to MAL-PDT*
- *No significant differences between 5-FU and MAL-PDT*
- *Subgroup analysis demonstrated that MAL-PDT was superior to imiquimod for sBCC on the lower extremities*

For squamous cell carcinoma in situ (Bowen's disease):

- *MAL-PDT was significantly more effective that cryotherapy*
- *MAL-PDT was nominally more effective than 5-FU*
- *Er:YAG AFL-PDT was significantly more effective than MAL-PDT*

Table of Contents

1. Introduction

In 1999, the Medical Services Advisory Committee (MSAC) concluded there was a lack of sufficient evidence to support the decision for public funding of photodynamic therapy (PDT) for the treatment of skin and mucosal cancer.

The use of PDT combines a drug (photosensitiser or photosensitising agent) with a specific type of light to kill target cells. Methyl aminolevulinate (as hydrochloride), Metvix®, is a topical photosensitising agent that is used in PDT.

As of August 2014, the Therapeutic Goods Administration (TGA) approved indications for Metvix® were:

- treatment of thin or non-hyperkeratotic and non-pigmented actinic keratosis (AK) on the face and scalp when other registered therapies are unacceptable
- primary treatment of superficial and/or nodular basal cell carcinoma (BCC) where surgery is considered inappropriate
- treatment of biopsy-proven squamous cell carcinoma (SCC) in situ (Bowen's disease), where surgery is considered inappropriate.

Treatment consists of topical application of Metvix® cream to the target field followed, after an incubation period of three hours, by exposure to red (wavelength 570-670 nm) light-emitting diode (LED) light via a suitable lamp (conventional-PDT; c-PDT). Light exposure activates photoactive porphyrins produced intracellularly from methyl aminolevulinate, which subsequently leads to a cytotoxic process, via the production of reactive oxygen species, within the target cells. In some circumstances, patients with AK may be treated with Metvix® followed by exposure to natural daylight (d-PDT), negating the need for a suitable red LED light lamp.

This document provides a summary of the current randomised control trial (RCT) evidence on PDT for the treatment of nonmelanoma skin cancer to investigate whether the evidence base has strengthened since 1999, to justify a reconsideration of the technology for public funding.

2. Reimbursement history

A timeline of the reimbursement history for PDT is summarised in Figure 1. Initially, submissions were presented to the Medical Services Advisory Committee (MSAC), as the PDT procedure is performed by a dermatologist with a lamp. In 2003, MSAC referred the application for Metvix® PDTto the Pharmaceutical Benefits Advisory Committee (PBAC), with the view that the major cost in relation to the reimbursement of PDT was the use of Metvix® during the treatment process. Three submissions for Metvix® to the PBAC submitted in 2005, 2007 and 2008 resulted in rejections. It is currently uncertain if future reimbursement applications for PDT and/or Metvix® will require a submission to PBAC, MSAC or a co-dependent submission to both the PBAC and MSAC.

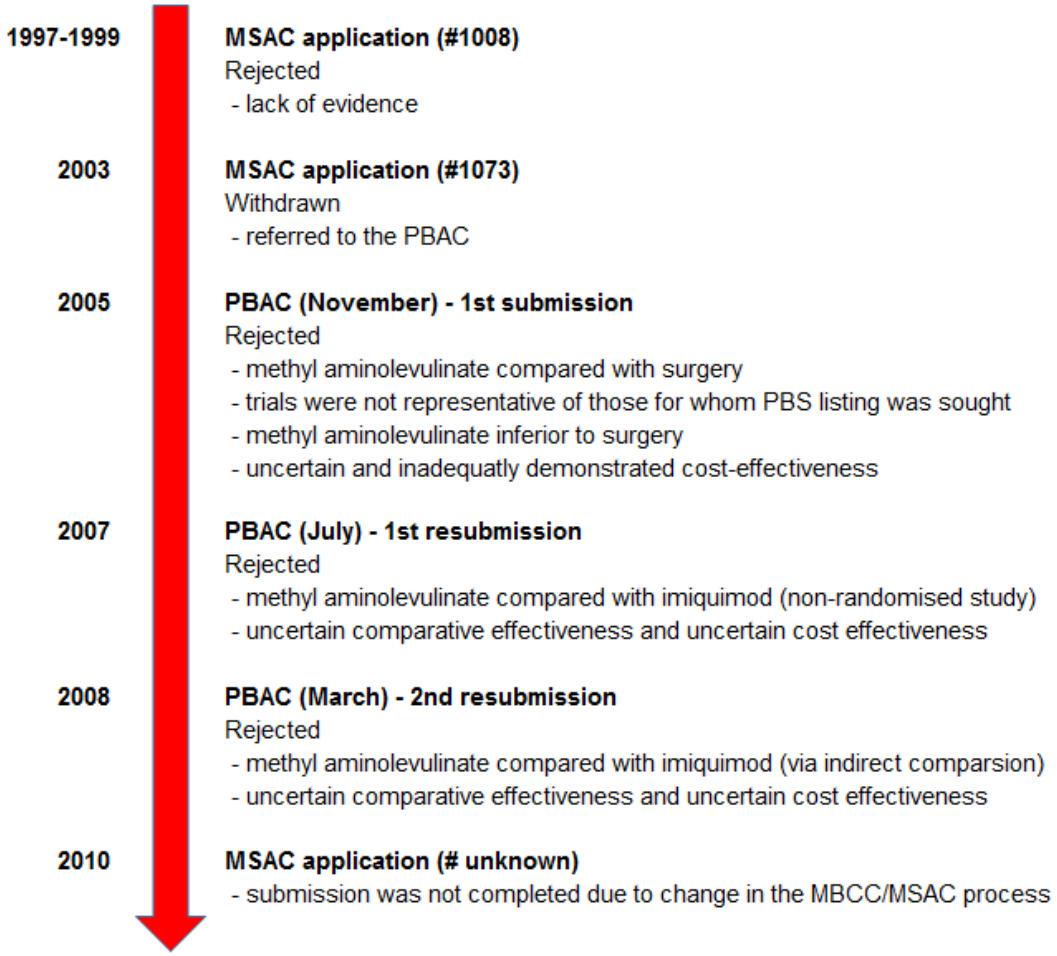

Figure 1 Reimbursement history timeline for PDT

3. Clinical summary

Overall,

- 12 RCTs were identified in 13 papers in AK, including a 6 and 12 month follow-up (Dirschka 2013) to one of the RCTs (Dirschka 2012).
- 3 RCTs were identified in 3 papers in nBCC - T303 [Rhodes 2004]; T307 and T308 [Foley 2009]. Rhodes 2007 was the 5 year follow-up to Rhodes 2004.
- 3 RCTs were identified in 4 papers in sBCC. Subgroup analyses for one RCT (Arits 2013) was also identified (Roozeboom 2014).
- 2 RCTs were identified in 2 papers in SCC in situ.

Overall,

- placebo-PDT treatment arm was the most used comparator followed by cryotherapy
- AK had the highest number of different comparators
- other comparators included diclofenac and hyaluronic acid and trichloroacetic acid

Actinic keratosis

- *MAL-PDT was superior to placebo-PDT (Freeman 2003, Pariser 2003)*
- *MAL+daylight-PDT was non-inferior to MAL+conventional-PDT (Rubel 2014)*
- *There is variability in reporting on the effectiveness of MAL-PDT compared with cryotherapy (Szeimies 2002, Freeman 2003, Morton 2006, Kaufmann 2008)*
- *MAL-PDT was nominally less effective than imiquimod or imiquimod + PDT (Serra-Geillen 2012)*
- *MAL-PDT was nominally less effective than ALA-PDT with Ameluz®* (Biofrontera, Leverkusen, Germany) *(Dirschka 2012)*
- *Conventional-MAL-PDT was nominally less effective than AFL-PDT (Choi 2015) or AFL-daylight-PDT (Togsverd-Bo 2015)*

At the time of this clinical summary, Metvix® had not been considered by the PBAC for the treatment of AK.

The current review process presented seven RCTs, of which three compared MAL-PDT with cryotherapy (Szeimies 2002, Morton 2006, Kaufmann 2008); one compared MAL-PDT with placebo-PDT (Pariser 2003); one compared MAL-PDT with cryotherapy and placebo-PDT (Freeman 2003); one compared MAL-PDT with imiquimod and PDT + imiquimod (Serra-Guillen 2012); and one compared MAL-PDT with ALA-PDT and placebo-PDT (Dirschka 2012 and Dirschka 2013).

An additional five RCTs conducted in patients with AK are considered relevant. Comparators from these RCTs included MAL+daylight-PDT [MAL-d-PDT] (Rubel 2014); diclofenac and hyaluronic acid [DHA] (Zane 2014); ablative fractional laser-assisted-PDT [AFL-PDT] (Choi 2015); trichloroacetic acid [TCA] (Di Nuzzo 2015) and MAL+d-PDT, ablative fractional laser-assisted-daylight-PDT [AFL-d-PDT] and AFL alone (Togsverd-Bo 2015).

A summary of RCTs conducted in patients with AK is presented in Table 1. Further information on each RCT is presented in Appendix A RCTs for actinic keratosis.

Table 1 List of RCTs conducted in patients with actinic keratosis

Author (year)	Intervention	Comparator/s
Szeimies (2002)	MAL-PDT	cryotherapy
Freeman (2003)	MAL-PDT	cryotherapy; placebo-PDT
Pariser (2003)	MAL-PDT	placebo-PDT
Morton (2006)	MAL-PDT	cryotherapy
Kaufmann (2008)	MAL-PDT	cryotherapy
Serra-Guillen (2012)	MAL-PDT	imiquimod; PDT + imiquimod
Dirschka (2012)	MAL-PDT	ALA-PDT; placebo-PDT
Dirschka (2013)[a]	MAL-PDT	ALA-PDT; placebo-PDT
Rubel (2014)	MAL+c-PDT	MAL+d-PDT
Zane (2014)	MAL-PDT	DHA
Choi (2015)	MAL-PDT	AFL-PDT
Di Nuzzo 2015	MAL-PDT	TCA 50%
Togsverd-Bo (2015)	MAL+c-PDT	MAL+d-PDT; AFL-d-PDT; AFL

Abbreviations: AFL, ablative fractional laser; c-PDT, conventional-photodynamic therapy; d-PDT, daylight-photodynamic therapy; DHA, diclofenac and hyaluronic acid; MAL, methyl aminolevulinate; PDT, photodynamic therapy; TCA, trichloroacetic acid

[a.] 6 and 12 month follow-up to Dirschka (2012)

MAL-PDT vs. placebo-PDT

(Freeman 2003, Pariser 2003, Dirschka 2012, Dirschka 2012)

- MAL-PDT is statistically superior to placebo-PDT at 3 months
- Cosmesis favoured MAL-PDT compared to placebo-PDT
- MAL-PDT resulted in more reported AEs than placebo-PDT

MAL-PDT vs. cryotherapy

(Szeimies 2002, Freeman 2003, Morton 2006, Kaufman 2008)

- There is inconsistent reporting on the effectiveness of MAL-PDT compared with cryotherapy, with two sessions of MAL-PDT more effective than single-freeze thaw cryotherapy and double-freeze thaw cryotherapy more effective than a single session of MAL-PDT
- Cosmesis statistically favoured MAL-PDT
- MAL-PDT didn't always result in more reported AEs

MAL-PDT vs. imiquimod

(Serra-Guillen 2012)

- MAL-PDT was nominally less effective than imiquimod
- Cosmesis and tolerance nominally favoured MAL-PDT

Basal cell carcinoma

- *MAL-PDT was superior to placebo-PDT (Foley 2013)*
- *MAL-PDT was inferior to surgery (Rhodes 2004, Rhodes 2007, Szeimies 2008)*
- *No statistical differences between MAL-PDT and cryotherapy (Basset-Seguin 2008)*
- *Imiquimod was superior to MAL-PDT; no significant differences between 5-FU with either imiquimod or MAL-PDT (Arits 2013)*
- *Subgroup analysis demonstrated that MAL-PDT was superior to imiquimod for sBCC on the lower extremities (p=0.003) (Roozeboom 2014).*

At the time of this clinical summary, Metvix® had been considered for listing by the PBAC for the treatment of superficial BCC (sBCC) or nodular BCC (nBCC) in November 2005 and for sBCC in July 2007 and March 2008. All three submissions for listing were rejected by the PBAC (See Reimbursement history).

Four clinical trials for Metvix® have been presented; T303 [Rhodes 2004, Rhodes 2007], T304 [Basset-Seguin 2008], T307 and T308 [Foley 2009].

Six RCTs for BCC have been published; three each for nBCC (Rhodes 2004, Rhodes 2007 and Foley 2009) and sBCC (Basset-Seguin 2008, Szeimies 2008 and Arits 2013). Three publications of two RCTs compared MAL-PDT with surgical excision (Rhodes 2004, Rhodes 2007 and Szeimies 2008); one RCT compared MAL-PDT with cryotherapy (Basset-Seguin 2008); two RCTs compared MAL-PDT with placebo-PDT (Foley 2009) and one RCT compared MAL-PDT with imiquimod or 5-FU (Arits 2013).

One publication (Roozeboom 2014) presented subgroup analyses of Arits 2013, a single-blind, non-inferiority, randomised trial of MAL-PDT vs. imiquimod.

A summary of RCTs conducted in patients with BCC is presented in Table 2. Further information on each RCT is presented in Appendix B RCTs for basal cell carcinoma.

Table 2 List of RCTs conducted in patients with basal cell carcinoma

Study ID/ Author (year)	BCC	Intervention	Comparator/s
T303/Rhodes (2004)[a]	nodular BCC	MAL-PDT	surgical excision
Rhodes (2007)[b]	nodular BCC	MAL-PDT	surgical excision
T304/Basset-Seguin (2008)[c]	superficial BCC	MAL-PDT	cryotherapy
Szeimies (2008)	superficial BCC	MAL-PDT	surgical excision
T307/T308/Foley (2009)[d]	nodular BCC	MAL-PDT	placebo-PDT
Arits (2013)[e]	superficial BCC	MAL-PDT	imiquimod; 5-FU

Abbreviations: 5-FU, fluorouracil; BCC, basal cell carcinoma; MAL, methyl aminolevulinate; PDT, photodynamic therapy; PSD, public summary document

a. Rhodes 2004 is the full publication to T303
b. 5 year follow-up to Rhodes (2004)
c. Basset-Seguin 2008 is the full publication to T304
d. Foley 2009 is the full publication to T307/308
e. Subgroup analyses for this trial has been published separately (Roozeboom 2014).

MAL-PDT vs. surgical excision

nBCC (Rhodes 2004, Rhodes 2007)

- MAL-PDT is non-inferior to surgery at 3 months. Time-to-event analysis showed that surgery was more favourable than MAL-PDT in the long-term
- No statistically significant differences between treatments in recurrence rates
- Cosmesis favoured MAL-PDT compared to surgical excision up to 12 months and continued (statistically significantly) for up to 5 years after last treatment
- MAL-PDT resulted in more reported AEs than surgery

sBCC (Szeimies 2008)

- MAL-PDT is non-inferior to surgery at 3 months
- 9.3% of lesions recurred at 12 months for MAL-PDT and none for surgery
- Cosmesis was statistically superior for MAL-PDT compared to surgery
- MAL-PDT resulted in more reported AEs than surgery

MAL-PDT vs. cryotherapy

sBCC (Basset-Seguin 2008)

- Overall lesion complete response rates did not differ significantly (p = 0.49)
- No significant difference in the overall lesion recurrence rate (p=0.86)
- Cosmetic outcome was significantly superior for MAL PDT at 3 months after the last treatment (p=0.0005)
- MAL-PDT and cryotherapy had similar reports of AEs

MAL-PDT vs. placebo-PDT

nBCC (Foley 2009)

- Histologically verified lesion complete response rates following PDT were superior after treatment with MAL-PDT compared with placebo-PDT (73% vs. 27%)
- Cosmetic outcome, slightly favoured MAL-PDT over placebo-PDT (98% vs. 93%)
- More AEs were reported for MAL-PDT compared to placebo-PDT

MAL-PDT vs. imiquimod

sBCC (Arits 2013, Roozeboom 2014)

- Imiquimod was superior to MAL-PDT
- No significant difference in aesthetic outcome
- MAL-PDT reported less SAE than imiquimod
- Subgroup analysis demonstrated that MAL-PDT was superior for sBCC on the lower extremities (p=0.003)

Squamous cell carcinoma in situ (Bowen's Disease)

- *MAL-PDT was significantly more effective that cryotherapy (Morton 2006)*
- *MAL-PDT was nominally more effective than 5-FU (Morton 2006)*
- *Er:YAG AFL-PDT was significantly more effective than MAL-PDT (Ko 2014)*

At the time of this clinical summary, Metvix® had not been considered by the PBAC for the treatment of biopsy-proven SCC in situ (Bowen's disease).

One randomised, placebo-controlled study, with follow-up at 3 and 12 months after last treatment, has been published (Morton 2006). One additional randomised study with 12-month follow-up, was considered to be relevant (Ko et al 2014).

The use of Metvix® for the treatment of SCC in situ (Bowen's disease) has been investigated in two RCTs; one comparing MAL-PDT with cryotherapy or 5-FU and the other comparing MAL-PDT with Er:YAG AFL-assisted MAL-PDT (Er:YAG AFL-PDT).

A summary of RCTs conducted in patients with SCC in situ (Bowen's disease) is presented in Table 3. Further information on each RCT is presented in Appendix C.

Table 3 List of RCTs conducted in patients with squamous cell carcinoma (Bowen's disease)

Author (year)	Intervention	Comparator/s
Morton (2006)	MAL-PDT	cryotherapy; 5-FU; placebo-PDT
Ko (2014)	MAL-PDT	Er:YAG AFL-PDT

Abbreviations: 5-FU, fluorouracil; Er:YAG AFL, erbium:yttrium-aluminium-garnet ablative fractional laser; MAL, methyl aminolevulinate; PDT, photodynamic therapy

MAL-PDT vs. cryotherapy or 5-FU

(Morton 2006)

- Sustained lesion response rates at 12 months were significantly higher for MAL-PDT than those for CRY (P=0.47) and higher (although not statistically so) than those for 5-FU (P=0.19).
- Cosmetic outcome at 3 months was superior with MAL-PDT compared with the other treatments and was maintained at 12 months.
- Most treatment-related local events reported with MAL-PDT were mild or moderate, with a lower rate of severe local events compared to cryotherapy.

MAL-PDT vs. Er:YAG AFL-PDT

(Ko 2014)

- Er:YAG AFL-PDT was significantly more effective (93.8%) than MAL-PDT (73.1%), in terms of overall response rate, at 3 months (P = 0.031).
- Recurrence rate was significantly lower for Er:YAG AFL-PDT (6.7%) than MAL-PDT (31.6%) at 12 months (P = 0.022).
- No significant difference was found between Er:YAG AFL-PDT and MAL-PDT in terms of cosmetic outcomes or safety.

4. Conclusion

The evidence base for the use of PDT for the treatment of nonmelanoma skin cancer has increased. With regards to using this evidence to justify reconsideration for public funding for this technology:

- There is evidence supporting the superiority of MAL-PDT compared to placebo-PDT for AK and BCC. Cosmesis and tolerability also favoured MAL-PDT compared to placebo-PDT in both indications.

- A recent trial has reported imiquimod to be superior to MAL-PDT in the treatment of sBCC. However, a subgroup analysis on these data has suggested that MAL-PDT may be a superior treatment for sBCC on the lower extremities compared to imiquimod.

- There appears to be a relative paucity of relevant RCT evidence on the use of PDT in SCC in situ. However there is evidence to suggest that MAL-PDT may be significantly more effective than cryotherapy in this indication, with promising results with regards cosmetic and AEs outcomes.

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Appendix A RCTs for actinic keratosis

Details of RCTs for actinic keratosis

Author (year)	Study design	Intervention	Comparator	Lesion response	Recurrence rate	Cosmetic outcome[a]	Safety
Szeimies (2002)	MN, MC, R, OL	MAL-PDT (single session) (N=102)	cryotherapy (double freeze-thaw) (N=100)	LCR: 68.7% vs 75.3% (3 months)	NR	96.3% vs 80.9% P=0.035	AE: 43% vs 26%
Freeman (2003)	MC, R, PC	MAL-PDT (2 sessions) (N=88)	cryotherapy (single freeze-thaw) (N=89)	LRR: 91% vs 68% P<0.001 (3 months)	NR	83% vs 51% (p<0.001) (3 months)	AE: 69.5% vs 35%
			placebo-PDT (N=23)	LRR: 91% vs 30% P<0.001 (3 months)	NR	NR	AE: 69.5% vs. 28.5%
Pariser (2003)	MC, R, DB, PC	MAL-PDT (N=42)	placebo-PDT (N=48)	LCR: 89% vs 38% P=0.001 (3 months)	NR	97% and 91% (3 months)	AE: 90% vs 58%
Morton (2006)	MC, R, intra-individual Treatment repeated at W12 in lesional non-response	MAL-PDT (N=119)	cryotherapy (N=119)	LRR: 84.4% vs 74.5% (12 weeks) 86.7% vs 83.9% (24 weeks)	NR	70.8% vs. 57.4% (12 weeks) 77.2% vs. 49.7% (24 weeks)	Skin-related AE: 62.2% vs. 72.3%

Author (year)	Study design	Intervention	Comparator	Lesion response	Recurrence rate	Cosmetic outcome[a]	Safety
Kaufmann (2008)	MC, C, R, OL, intra-individual	MAL-PDT (N=121)	cryotherapy (N=121)	LRR: 75% vs 87% P=<0.001 (24 weeks)	NR	79% vs 56% P=<0.001 (24 weeks)	≥1 AE: 45% vs 63%
Serra-Guillén (2012)	R, C	MAL-PDT (N=40)	imiquimod (N=33)	CCR: 10% vs 27% (4 months)	NR	90% vs 61%	37.5% vs 24% ('good' tolerance)
			MAL-PDT+ imiquimod (N=32)	CCR: 10% vs 37.5% (4 months)	NR	90% vs 84%	37.5% vs 22% ('good' tolerance)
Dirschka (2012)	MC, R, PC,	MAL-PDT (N=246)	ALA-PDT (N=248)	Total clearance: 83.2% vs 90.4% (12 weeks)	NR	45.2% vs 43.1%	TEAE: 98.0% vs 96.4%
			placebo-PDT (N=76)	Total clearance: 83.2% vs 37.1% (12 weeks)	NR	45.2% vs 36.4%	≥1 AE: 98.0% vs 72.4%
Dirschka (2013)[a]	MC, R, PC,	MAL-PDT (N=240)	ALA-PDT (N=241)	NR	6.6% vs 7.0% (6 months) 25.4% vs 21.7% (12 months)	42.7 vs 39.7% (6 months)	11.3% vs. 11.6%
			placebo-PDT (N=68)	NR	6.6% vs 3.6% (6 months)	42.7% vs 34.8% (6 months)	11.3% vs. 8.8%
Rubel (2014)	R, intra-individual	MAL+d-PDT (N=100)	MAL+c-PDT (N=100)	LCR: 89.2% vs 92.8% (NI) (12 weeks)	NR	Very satisfactory and similar for both treatments	AEs: 39% vs 59%
Zane (2014)	R, OL	MAL-PDT (N=100)	DHA (N=100)	LRR: 85.9% vs 51.8% (90 days)	NR	64% vs 17% ('excellent') 31% vs 75%	Neither serious short-term nor long-term adverse events were

Author (year)	Study design	Intervention	Comparator	Lesion response	Recurrence rate	Cosmetic outcome[a]	Safety
				P<0.0001 56.5% vs 20.9% (1 year) P=0.0012		('good')	reported.
Choi (2015)	R	3h-MAL-PDT (N=33)	3h-AFL-PDT (N=31)	CRR: 65.5% vs 91.5% (3 months)	22.1% vs 7.5% P=0.002 (12 months)	80.6% vs 87% (12 months)	No significant differences in adverse events between the groups
			2h-AFL-PDT (N=29)	CRR: 51.1% vs 84.8% (12 months)	22.1% vs 12.1% NS (12 months)	80.6% vs 80.6% (12 months)	
Di Nuzzo (2015)	R, intra-individual	MAL-PDT (N=13)	TCA 50% (N=13)	Clearance rate: 5.3% vs 17.6% (12 months)	5.3% vs 17.6% (12 months)	100% vs 15%	TCA 50% caused hypopigmentation in 85% of patients.
Togsverd-Bo (2015)	R, intra-individual	c-PDT (N=16)	d-PDT (N=16)	LCR: 50% vs 46% (3 months)	NR	AFL-d-PDT was more favourable compared with d-PDT, c-PDT and AFL (P < 0.01) (3-month)	The severity of the inflammatory skin reactions following study treatments was significantly different P<0.001.
			AFL-d-PDT (N=16)	LCR: 50% vs 74% (3 months)	NR		
			AFL (N=16)	LCR: 50% vs 5% (3 months)	NR		

Abbreviations: AFL, ablative fractional laser; c-PDT, conventional-photodynamic therapy; C, comparative; CCR, complete clinical response; d-PDT, daylight-photodynamic therapy; DB, double-blind; DHA, diclofenac and hyaluronic acid; LCR, lesion complete response; LRR, lesion response rate; MAL, methyl aminolevulinate; MC, multicentre; MN, multinational; NR, not reported; OL, open-label; PC, placebo controlled; PDT, photodynamic therapy; R, randomised; TCA, trichloroacetic acid

a. Good or excellent; investigator rated

b. 6 and 12 month follow-up of Dirschka 2012

Appendix B RCTs for basal cell carcinoma

Details of RCTs for basal cell carcinoma

Trial ID/ Author (year)	Study design	Patients	Intervention	Comparator	Response for lesions	Recurrence of lesions	Cosmetic outcome[a]	Safety
T303/Rhodes (2004)	MC, R, NI	N=101 [ITT] Histologically confirmed, primary nBCC	MAL-PDT (N=52 [ITT])	excision surgery (N=49 [ITT])	LCR: 91% vs. 98% P=0.25 (NI) (3 months)	Tumour free: 83% vs. 96% P=0.15 (12 months) 60% vs. 85% (24 months)	82 % vs. 33% P=0.001 (3 months) 79 % vs. 38% P=0.001 (12 months) 83 % vs. 41% P=0.001 (24 months)	AE: 52% vs. 29% P=0.03
Rhodes (2007) [5-year follow-up of Rhodes 2004]	MC, R	N=97 [PP] Histologically confirmed, primary nBCC	MAL-PDT (N=50 [PP])	excision surgery (N=49 [47])	LCR: 76% vs. 96% P=0.01 (5 years)	4% vs. 0% (1 year) 10% vs. 0% (2 years) 14% vs. 2% (3 years) 14% vs. 4% (4 years) 14% vs 4% (5 years) P=0.09	87 % vs. 54% P=0.007 (5 years)	NR
T304/Basset-Sequin (2008)	MC, R, Phase III	N=120 sBCC	MAL-PDT	cryotherapy	LCR: 97.1% vs. 94.9%; NS (3 months) 75% vs. 74% P=0.90 (5 years)	22% vs. 20%; NS (5 years)	30% vs. 4% P=0.0005 (3 months) 50% vs. 16% P=0.00078 (12 months)	AE: 73% vs. 79%
Szeimies (2008)	MC, R, OL	N=196 sBCC	MAL-PDT	excision surgery	LCR: 92.2% vs. 99.2% (3 months)	9.3% vs. 0%. (12 months)	92.8% vs. 51.1% P<0.001 (12 months)	AE: 37% vs. 14.6%

Trial ID/ Author (year)	Study design	Patients	Intervention	Comparator	Response for lesions	Recurrence of lesions	Cosmetic outcome[a]	Safety
T307/T308/ Foley (2009)	MC, R, Phase IV, DB	N=131 nBCC	MAL-PDT	placebo-PDT	LCR: 73% vs. 27% (S)	NR	98% vs. 93%	AE: 91% vs. 66%
Arits (2013)	MC, R, SB, NI	N=601 Histologically confirmed, sBCC	MAL-PDT (N=202)	imiquimod (N=198)	PRR: 72.8% vs. 83.4% P=0.021 (3 and 12 months)	NR	62.4% vs. 61.4% 0.84 (12 months)	SAE: 0% vs. 4.8%
				5-FU (N=201)	PRR: 72.8% vs. 80.1% p=0.120 (3 and 12months)	NR	62.4% vs. 57.5% 0.33 (12 months)	SAE: 0% vs. 2.1%

Abbreviations: 5-FU, fluorouracil; DB, double-blind; LCR, lesion complete response; MAL, methyl aminolevulinate; MC, multicentre; nBCC, nodular basal cell carcinoma; NI, non-inferiority; NR, not reported; OL, open-label; PDT, photodynamic therapy; PRS, patient response rate; R, randomised; SB, single-blind; sBCC, superficial basal cell carcinoma;

[a.] Good or excellent; investigator rated

Appendix C RCTs for squamous cell carcinoma in situ (Bowen's disease)

Details of RCTs for squamous cell carcinoma in situ (Bowen's disease)

Author (year)	Study design	Patients	Intervention	Comparator	Lesion response	Recurrence	Cosmetic outcome[a]	Safety
Morton (2006)	MC, R, PC	N=225 Histologically confirmed SCC in situ and no evidence of progression	MAL-PDT (N=124)	cryotherapy (N=91)	LCR: 93% vs. 86% (3 months) 80% vs. 67% P=0.047 (12 months)	15% vs. 21% (12 months)	94% vs. 66% (3 months)[b]	≥1 AE: 63% vs. 49% Severe AE: 6% vs. 12%
				5-FU (N=36)	LCR: 93% vs. 83% (3 months) 80% vs. 69% P=0.19 (12 months)	15% vs. 17% (12 months)	94% vs. 76% (3 months)[b]	≥1 AE: 63% vs. 77%
				placebo-PDT (N=24)	LCR: 93% vs. 21% (3 months)	15% vs. 50% (12 months)	NR	≥1 AE: 63% vs. 59%
Ko (2014)#	R	N=21 (total of 58 BD lesions)	MAL-PDT	Er:YAG AFL-MAL-PDT	Overall RR: 73.1 % vs. 93.8% P = 0.031 (3 months)	31.6% vs. 6.7% P=0.022 (12 months)	No significant differences	

Data from abstract only

Abbreviations: 5-FU, fluorouracil; BD, Bowen's Disease; Er:YAG AFL, erbium:yttrium-aluminium-garnet ablative fractional laser; LCR, lesion complete response; MAL, methyl aminolevulinate; MC, multicentre; PC, placebo-controlled; PDT, photodynamic therapy; R, randomised; RR, response rate; SCC, squamous cell carcinoma

a. Good or excellent; investigator rated

b. Maintained at 12 months