Independent Review

Imiquimod for the Treatment of Solar Keratoses

The names of reviewers have been withheld, consistent with PBAC procedures

Submission date 16/1/2009

Executive Summary

The purpose of this independent review is to assess the efficacy and cost effectiveness of 5% imiquimod cream (Aldara™) for the treatment of solar keratoses (SK) of the face and scalp. We find that imiquimod is superior to placebo in reducing visible SK lesions and is therefore efficacious within this scope. However, there are no reliable studies to demonstrate that imiquimod is superior to its main comparators, 5-flurouracil and cryotherapy. In view of a lack of demonstrated superiority over comparators, the most appropriate pharmaco-economic analysis is a cost minimization analysis. We find that imiquimod is inferior to comparators in terms of cost. Finally, we assessed the safety of imiquimod. We find that there is a lack of safety data for treatment surface areas exceeding 25 cm^2, which is consistent with the opinion of the TGA and the allowed treatment area in the TGA-approved prescriber information. For treatment areas up to 25cm^2 imiquimod has both local and systemic side effects but there are usually within a clinically acceptable range. The 25cm^2 TGA-approved treatment area is likely to be impractical for single course treatment of sun-exposed areas of the face and/or scalp where application of drug to 10 to 20 times this surface area is required. The logical comparator drug, 5-flurouracil, is approved for treatment areas up to 500 cm^2.

1. Scope of this review

The scope of this independent review is assess the application to extend the listing of imiquimod (Aldara™) 5% cream sachets on the Pharmaceutical Benefits Scheme (PBS) as a field therapy for multiple solar keratoses (SK) lesions of the face and scalp.

Requested PBS listing: IMIQUIMOD, cream 50mg per g (5%), 250 mg single use sachets, 12, Aldara®, iNOva Pharmaceuticals (Aust) Pty Ltd – extension to listing to include use as a field therapy for solar keratosis.

Name, Restriction, Manner of administration and form	Max Qty.	No. Repeats	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
imiquimod, cream 50mg per g (5%) 250mg single use sachets	12	1	$159.87	Aldara ™	iNova Pharmaceuticals (Aust) Pty Ltd
Section 85 Authority required					
Solar keratosis on the face or scalp in a patient with normal immune fuction who has multiple clinically evident SK lesions and requires topical drug treatment as field therapy. The patient or carer must be able to understand and administer the imiquimod dosing regimen. No applications for increased maximum quantities and/or repeats will be authorised.					

As per the request from the sponsor of the application, iNova Pharmaceuticals (Australia) Pty Ltd (iNova), this review has focused on the following questions:

- Is there value in treating SK?
- Is there certainty of imiquimod's comparative effectiveness?
- Is there a safety issue with imiquimod as a true field therapy?
- Is imiquimod a cost-effective therapy for SK?

1.1 General process of the review

The submission documents (executive summary, sections A-E and the attached literature) as well as the PBAC documents were reviewed in detail. In addition, a PubMed search was performed seeking general reviews and guidelines for the treatment of SK as well as looking for specific publications that have examined imiquimod as a therapy for SK.

In the conduct of this review the Convenor instructed that only documents and published papers available to the Pharmaceutical Benefits Advisory Committee (PBAC) when it assessed the application to extend the listing of imiquimod on the PBS could be included. Therefore, information that has become available since April 2008 has not been sought or considered in the review process. No new information or other information directly

concerning imiquimod was considered that was not available to the PBAC. No external consultation was conducted.

At the request of the Convenor, a statistician expert in clinical trials was engaged to review the powering and data analysis of a pivotal trial referenced in the application, and their full report is appended (Appendix 1).

The primary reviewer XXXXXXX was assisted by their Research Associate XXXXXX in the conduct of the review, the review of the literature and the review of the submission documents. The primary reviewer prepared the final document and the primary reviewer alone wrote the conclusions.

2. Background

2.1 Solar Keratoses (SK)

SK are rough scaly lesions of the epidermis that occur on sun-exposed areas of skin, most notably the face, scalp and the dorsum of the hands and arms (1). The reasons for treatment are cosmetic and/or to decrease the chance of an SK lesion progressing to squamous cell carcinoma (SCC) of the skin. Because of the association between SK and SCC, SK lesions are considered by some to represent a *carcinoma-in-situ*. The rate at which SK progress to SCC is not accurately known and is likely impacted on by whether the predominant exogenous risk factor for SK, namely unprotected sun exposure, continues or not. Literature figures for the rate of progress of SK to SCC vary. For an individual lesion, the risk was assessed as being > 0.1 to 0.24% per year (2,3). Extrapolation of this data to account for the fact that the majority of individuals will have more than one SK, the risk of progression to SCC over a period of 10 years is thought to be between 6 and 10% (4). Once SCC has occurred the risk of development of metastatic cancer is between 0.5 and 3.3% (5,6). Based on these figures the 10 year risk of an individual developing metastatic SCC arising from SK is in the range of 0.03 to 0.33%. While approximately 60% of SCC of the skin is thought to arise from SK, the remaining 40% arises *de novo*, with no pre-existing SK (2,7,8).

It is important to recognise that SK can spontaneously regress without pharmacologic or ablative therapy. In an Australian study, Thompson, *et al*, (6) reported that regular use of sunscreen with a SPF of 17 over a single summer caused a mean loss of 60% of existing SK lesions and a reduction in new lesions as compared to a control group. Thus, reduction of the predominant exogenous risk factor for SK, UV light exposure, should always form the cornerstone of the management of this condition.

2.2 Imiquimod

Imiquimod is an imidazoquinoline (Figure 1) thought to exert its effect on skin lesions such as SK by acting as an immune modifier. When applied topically clinical trials have demonstrated activity against SK, basal cell carcinoma and genital warts. The exact mechanism by which these effects are achieved remains unknown. Imiquimod has been identified as a toll-like Receptor 7 (TLR7) agonist (8), a signalling pathway that increases the production of some cytokines, particularly interferon-α. It is unclear if this contributes to its therapeutic action, but is seems likely that interferon-α production contributes to its systemic side effects given that these are very similar to those known to occur with interferon-α therapy (e.g.; flu-like symptoms, fatigue, headaches, myalgia).

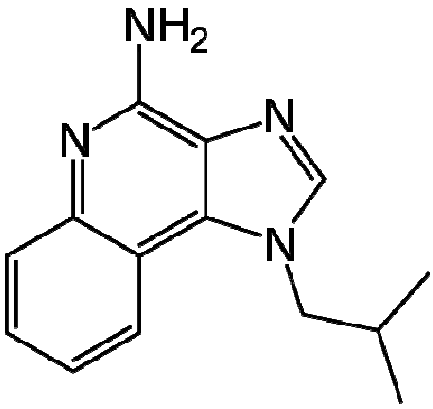

Figure 1. Structure of imiquimod

For SK, 5% imiquimod topical cream (Aldara™) has marketing approval in Australia for treatment of lesions of the scalp and face with a maximum application area of 25 cm^2. The drug is supplied as a box of twelve 250 mg single use sachets. A typical treatment regime is to apply a portion of one sachet to a treatment area not exceeding 25 cm^2 three times per week for 4 weeks, using a fresh sachet for each application. After a 4-week break, if SK lesions persist (80% of cases) a further 4 weeks of treatment is undertaken, which requires a second box of 12 sachets. The current cost of a box of 12 sachets is $158.97

Presently, there are three major limitations of imiquimod as a therapy for SK:

(i) The small treatment area of 25 cm^2 is likely to prove impractical for most patients who will require a more extensive “field therapy” of sun-exposed areas of the face and scalp. Most trials of this drug have been restricted to 25 cm^2, within a single study reporting a treatment area of 50 cm^2 (H2H study). Typical field therapy for SK

requires a treatment area of 10 to 20 times that currently approved by the TGA for imiquimod. This is discussed in more detail in *section 6.2*.

(ii) There are local and systemic side effects associated with treatment. These are covered in detail in *section 5* of this review.

(iii) Long-term outcome data is lacking. This is covered in *section 3.3*.

2.3 Comparator therapies

Two other therapies are in widespread use for treatment of SK; cryotherapy and topical 5-flurouracil (5-FU). Of these, 5-FU is the logical comparator therapy for imiquimod being a topically applied pharmacologic therapy. Treatment of SK with 5-FU is accomplished by a daily application of 5-FU emulsion for 3 to 4 weeks to a maximum treatment field of 500 cm^2. Adverse reactions are local and most often consist of an erythema of the treatment field resembling sunburn, followed by blistering, peeling and cracking of the skin. 5-FU is supplied in a 20 g tube costing $45.56, with one tube usually being sufficient for a treatment course.

3. Is there value in treating SK?

The iNova Independent Review Request reads (in part):

1) Is there value in treating SK?

"…the value of treating solar keratosis has not been conclusively established by the submission" (PBAC Short Minutes, pg 2).

The submission seeks PBS listing for imiquimod as a field treatment for a type of SK representing skin field cancerisation. This affects a minority of SK patients who have multiple coalescing clinical (visible) and subclinical (non-visible) lesions continually arising against a background of moderate to severe solar damaged skin. The disease form presents as a painful, itchy and unsightly condition with associated morbidity and is potentially disfiguring. Irrespective of potential progression to SCC, there is also a growing trend to manage multiple SK lesions as an in situ malignancy in its own right as part of a continuum of disease to manage field change.

For these reasons, the clinical rationale and value of treating SK is widely recognised in the literature, current guidelines and clinical practice, and so **a prima facie case for conclusively establishing the value of treating SK already exists.** This was detailed in the submission (*pgs 19-23*), Expert Advice (*Submission Attachment 4*) and in both iNova's pre-Subcommittee and pre-PBAC responses.

While some SK lesions can regress, the requested listing for imiquimod in specifying "field therapy" identifies patients with more extensive or severe disease arising from field cancerisation. In these patients it would be highly unlikely and most unusual for significant amounts of their disease to regress, and so the PBAC's concern that these multiple lesions can spontaneously regress is unfounded. This is why a topical field therapy such as imiquimod is required to manage the condition.

The value of treating SK, particularly in the target PBS patient population, has been conclusively established.

3.1 Improving health outcomes?

The submission states that there is value of treating SK because:

- *The submission seeks PBS listing for imiquimod as a field treatment for a type of SK representing skin field cancerisation.*

The concept of field cancerisation has previously been described for the oropharynx, gastro-intestinal tract, bladder and cervix. Some authors (10) describe SK as a field disease as well, e.g., not limited to a single clinically apparent lesion. Lesions within a field may be subclinical (not visible), and have been characterised by molecular biological techniques (genetic mutations, clonality in areas of field change). These observations provide a scientific rationale for the treatment of a field, such as the face or scalp, as opposed to the treatment of individual visible lesions. While an interesting concept the clinical relevance remains uncertain in the absence of robust long term studies comparing outcomes from local verses field approaches.

In clinical practice, the choice of treatment is more likely to be based on the number of visible SK lesions. Two broad therapeutic approaches are described in the literature; lesion specific therapies and field therapies. In the US, 90% of all SK is treated with locally ablative therapies, mainly cryotherapy, but the proportion of face and scalp lesions treated by each of these approaches is not known. Field therapy treats an entire anatomic area in which there are visible lesions, such as sun-exposed areas of the face and/or scalp. This allows treatment of all visible lesions within the field but also sub clinical lesions that may be presumed to the present within the UV damaged skin.

- *It is painful, itchy and unsightly condition with associated morbidity and is potentially disfiguring.*

Most SK lesions are asymptomatic and only apparent on close inspection, with only a minority causing pruritus or burning sensations. While it can be argued that severe SK cases can affect quality of life, no studies have been done on health outcomes or incremental QALYs gained from treatment of SK.

- *Irrespective of potential progression to SCC, there is a growing trend to manage multiple SK lesions as an in situ malignancy in its own right as part of a continuum of disease to manage field change.*

Should SK be treated? This is the question raised by Spencer et al (11) pointing out that therapeutical attitudes vary between countries. The rationale for treating SK would be their potential to progress to invasive SCC. However the risk of progression is extremely low and those lesions are mainly treated for other reasons such as cosmesis and symptomatic relief.

Various authors point out that the most important aspect of the management of SK is to reduce/prevent further sun damage by ensuring appropriate outdoor clothing and hats, the use of sunscreens and the avoidance of sun exposure during times of high UV intensity. The regular use of sunscreen not only prevents the development of SK, but also hastens the remission of existing clinically apparent SK lesions (6).

SK has the potential to progress to, but is by no means an obligate precursor of SCC. Most lesions do not progress and remain stable with up to 26% spontaneously regressing without treatment. Moreover 40% of SCC does not arise from SK. It is impossible to determine which SK lesions may progress to SCC and predictions on the progression from SK to SCC vary widely (ranging from 0.075–0.096% per SK lesion per year to 1-10.2% over 10 years per person). A well-designed Australian prospective longitudinal study suggested that the yearly rate of progression of an SK lesion to invasive SCC in an average-risk person in Australia is between 8 and 24 per 10,000 (2).

Treating SK in order to prevent SCC has been associated with a strength of recommendation taxonomy SORT evidence rating of "C" (1) meaning "*consensus, disease oriented evidence, usual practice, expert opinion or case series*" (as opposed to "A: consistent good quality patient-oriented evidence" or "B: inconsistent or limited-quality patient-oriented evidence" (http://www.aafp.org/afpsort.xml). It is our understanding that the application to have imiquimod listed on the PBS does not include prevention of SCC as a primary objective, as no data is available relating to the efficacy of imiquimod in this context. The pharmaco-economic model is based on SK lesions and disease-free (recurrence-free) years as the main outcomes, without subsequent conversion to SCC and an associated SCC case fatality rate. The submission states that although SK is associated with a small but recognisable rate of progression to SCC, the longer-term rate of progression to SCC, metastasis and the resulting effect on mortality have not been considered in the analysis. The reason mentioned for this is that *"this was considered too far beyond the objectives of the key efficacy trials and imiquimod does not have an approved indication for SCC"*.

We agree that it is not possible to assess imiquimod as a therapy to prevent SCC-related adverse health outcomes due to absence of supporting data. Moreover, as covered above, the rate of progression of SK to adverse SCC-related health outcomes is very low.

3.2 QALYS and quality of life

Quality-adjusted life year (QALY) takes into account both quantity and quality of life generated by healthcare interventions. Quality of life was not measured in the various studies provided in the submission.

The submission states that a systematic review of the literature using Medline and Embase was undertaken to see if utilities could be found to translate the results into QALYS for a cost-utility analysis. The outcome was that "very little research has been done on quality of

life in solar keratosis (SK)" and "no utility studies were identified in the published literature", so that the submission did not attempt to transform the economic results into a cost per QALY context (*Transformation of disease-free years to QALYs was not undertaken in the Markov model due to non-availability of utility values for SK from the trials or published literature.)*

3.3 Duration of the effect and re-treatment

The duration of the treatment effect is uncertain. A short description in a publication not cited in Medline (Skin and Aging) describes follow-up of imiquimod treated SK of the face and/or scalp for a mean of 20 months (12) while another study followed a larger cohort of subjects for a median of 16 months (13). Only the later study can be considered to provide useful data, They found that after a median of 16 months, 24.7% (19 of 77) of the patients administered imiquimod three times per week and 42.6% (23 of 54) of the patients administered imiquimod two times per week had a recurrence of SK (the appearance of at least one AK lesion) in the original treatment area. No reliable data is available on the duration of the effect of treatment beyond 16 months.

3.4 Conclusion

In summary, there is value in treating SK if it prevents SCC-related adverse health outcomes, if it improves quality of life for SK sufferers, and if it has long-term beneficial effects. It is not possible to assess imiquimod as a therapy to prevent SCC-related adverse health outcomes due to absence of supporting data, and the rate of progression of SK to adverse SCC-related health outcomes is very low. There have been no studies about QALYs in relation to SK. The studies do not give any indication of the duration of the treatment effect beyond 16 months. Accordingly it is not possible to demonstrate there is value in treating SK.

4. Is there certainty of imiquimod's comparative effectiveness?

The iNova Independent Review Request reads (in part):

2) Is there certainty of imiquimod's comparative effectiveness?

"…the pivotal H2H trial involved only a very small number of patients, was unblinded, and appears to have had as its primary outcome an assessment of oncogenes…" (PBAC Short Minutes, pg 1,2).

The most important efficacy measure in the H2H study by Krawtchenko et al 2007 was the sustained (field) clearance rate. This was defined as the percentage of patients in each group with 100% initial and sustained lesion clearance and no new lesions in the treated area 12 months post-treatment. Total field clearance of

treated lesions and new lesions arising at a later time is the ultimate aim of field therapy and the most rigorous outcome for measuring treatment success. This is the only published SK study of which we are aware that has measured this key outcome.

In this randomised study, imiquimod was superior to both topical 5-FU and cryotherapy in achieving sustained (field) clearance of treated SK lesions and new lesions. The highly significant difference favouring imiquimod whereby 73% of patients achieved sustained total field clearance 12 months post treatment compared with 5-FU (33%; p=0.01) and cryotherapy (4%; p<0.0005) based on all enrolled study patients is strong direct evidence. The H2H study is also supported by the European regulatory agency (EMEA) who has accepted that this study represents convincing evidence for the difference between imiquimod and topical 5-FU such that another comparative study involving 5-FU is not required (***Attachment 2***). Note that the H2H study became available long after TGA approval for imiquimod's use in SK.

The H2H study was sufficiently powered to detect a statistically significant difference in sustained clearance between imiquimod and each comparator, and the sample size was appropriate as it contained the requisite number of patients in each treatment group to detect the magnitude of difference found, which favoured imiquimod. [redacted]

Regarding blinding, the study was appropriately designed as an open-label trial. Firstly, it is not possible to blind a medical procedure, i.e. cryotherapy. Secondly, blinding the study medications which were self-administered would be problematic and hazardous, requiring double dummy technique and double application with greater risk of application errors, which has safety implications. Indeed, 5-FU was applied twice a day over 4 weeks at maximal dosage per the approved Product Information versus imiquimod applied three times per week for one or two 4 week cycles.

Measures to reduce potential bias in the H2H study included patient randomisation and the evaluation of histology results by two independent dermatopathologists.

In addition to clinical outcomes, the oncogene results are important because they provide genetic support for the highly significant field clearance result favouring imiquimod over each comparator. As explained in iNova's pre-Subcommittee response, p53 and $p16^{INK4A}$ mutations relating to SK were cleared or reduced after treatment in 62% (16/26) and 65% (17/26) of imiquimod patients, respectively. This compares with 25% (6/24) and 33% (8/24) of 5-FU patients and 16% (4/25) and 12% (3/25) of cryotherapy patients. Both results favouring imiquimod were significantly different from those of 5-FU and cryotherapy groups on an intent-to-treat basis (p53 mutation p=0.0004; $p16^{INK4A}$ mutation p=0.0003). Topical 5-FU and cryotherapy did not differ from each other for either mutation. The genetic evidence also increases confidence that 12 months follow-up post treatment is sufficient time to assess what SK looks like longer term in comparing each therapy.

The reviewer should also be aware of these points:

- The H2H study results are supported by the body of evidence reporting low recurrence for imiquimod and high recurrence rate for 5-FU in treating SK. This evidence was provided in the submission and appears in the European Guidelines (Stockfleth & Kerl 2006) for managing SK that were discussed in the submission and provided as a published reference.

- The head to head H2H study, along with several large randomised double blind placebo controlled studies presented in the submission AND analysed further in a comprehensive statistical report providing pooled efficacy and safety results (*Submission Attachment 10*), **collectively represent more evidence for SK than was provided for the current sBCC listing which had no active comparator trial.**

- The imiquimod clinical results in the H2H study are more favourable than those in the placebo controlled studies. As discussed in the submission, this may be explained by the fact that more than 80% of imiquimod patients in the H2H study received the second 4 week cycle of treatment versus approximately one third of those in the placebo controlled cyclic studies.

Three published meta-analyses (14-16) demonstrate that imiquimod is an effective therapy for SK of the face and scalp as compared to placebo in terms of clinical clearance of lesions in treatment areas up to 25 cm^2. However, there is a paucity of data comparing imiquimod with other topical agents such as the active topical comparator 5-FU, with only 2 small randomized controlled trials (RCTs) available. The superiority of imiquimod compared to 5-FU is based on a single unblinded RCT [published as Krawtchenko N, *et al*, 2007 (17)], variously referred as the "pivotal" or "H2H study" or "Stockfleth 2007" in the iNova submission folder, section B). A critical analysis of the studies comparing imiquimod with its main comparators (5-FU and cryotherapy) has been performed as part of this review.

4.1 Comparison imiquimod vs 5-FU vs cryotherapy: Krawtchenko N, et al, 2007 (17) (H2H study)

This is a 3-arm study comparing imiquimod 3 times a week for 2 cycles of 4 weeks (separated by a 4-week pause), 5-FU twice daily for 4 weeks and cryotherapy. The study is presented as the key head-to-head study in the submission. Most conclusions on the superiority of imiquimod over its comparators, as well as the pharmaco-economical analysis solely rely on the results of this single study. We will describe hereafter several significant methodological and scientific limitations in this study.

4.1.1 Methodological bias

4.1.1.1 Exclusion criteria

Any use of a topical drug for SK is considered as an exclusion criterion if used less than 4 weeks before the start of the study (section B Table B4.2 p 43, attachment 6 p 16) (note; 2 weeks is mentioned in the published version of this study). Any enrolled patient may have therefore received one of the studied treatments at least 2 to 4 weeks prior to the start of the therapy, without any distinction to the treatment group where the patient is assigned. The data show that 65% of patients in the imiquimod group were previously treated for SK, 62% in the 5-FU group and 60% in the cryotherapy group "generally less than once a year and on average in the last one 1.5-2 yrs before the study" (p44). In the clinical study report (Attachment 6, p 30), table 16 shows that mean time since last treatment (years) was 1.6 (SD 2.43) in the imiquimod group (min 0.1 max 10), and 1.4 (SD 2.22) in the 5-FU group (min 0.2 max 8). Therefore, some patients received a topical treatment 6 weeks before the start of the study in the imiquimod group and 12 weeks before in the 5-FU group. In our

opinion, the long-term effect of any previous treatment cannot be excluded and precise details on the timing and type of treatment received in individual patients are missing.

A wide range of co-morbidities is described as exclusion criteria (clinically significant, unstable, cardiovascular or immunosuppressive, haematological, hepatic, neurological, renal, endocrine, collagen vascular, or gastrointestinal abnormalities or disease, Table B4.2 p 43). In our opinion, this might not reflect the patient population where SK is prevalent (older patients) and the results may difficult to translate to the clinical setting. Safety data may also have to be reinterpreted in this context.

4.1.1.2 Assessment of the initial response at 4 weeks post treatment

The initial test of cure has been performed at different time points depending on the therapy (week 6 for cryotherapy, week 8 for 5-FU, week 16 for imiquimod). The longer time frame until assessment may have been in favour of imiquimod when one considers that some lesions may regress spontaneously. Section 5.3.2.2, page 3 of attachment 6 reveals that the definition of the 4 weeks post treatment (W4) has been modified during the course of the study. At 4 weeks post treatment this study showed that 5-FU therapy resulted in complete clearance in 96% of treated patients whereas the imiquimod complete clearance rate was 54%. However the definition of the W4 visit was reconsidered (i.e., the visit that investigators considered to be the evaluation of treatment visit even if conducted more than 4 weeks after the last treatment application). When this new definition was applied to imiquimod, the complete response to imiquimod increased to 85%. The scientific rationale of the protocol modification in the definition has not been described in the published paper or in section B where only the favourable 85% is presented.

4.1.1.3 Assessment of the cosmetic outcome

This was not blinded for the physician or the patient.

4.1.1.4 Baseline characteristics

No statistical comparison of the groups (p values) is reported. It appears that the mean number of lesions was higher in the 5-FU group compared to imiquimod (8.3 vs 7.9). The 95% CI of the results was not provided. The representation of Fitzpatrick's skin phototype appears to be unequal between groups as well. 29% of patients had a phototype 1 in the 5-FU group verses 8% in the imiquimod group. This may represent a bias in favour of imiquimod.

4.1.1.5 Histological assessment

This appears more favourable to the imiquimod group than the clinical assessment. The punch biopsy size covers 4 mm of skin when the skin has been treated over a 50 cm^2 zone. Considering the unblended nature of the sampling procedure, the validity of the results is open to question.

4.1.2 Statistical bias

An expert bio-medical statistician was appointed to provide opinion on study design and powering as well as data analysis and interpretation. She identified serious flaws in design, power and analysis. The full report is presented in *Appendix 1*:

4.1.2.1 Changes in the reported primary outcome variables

The primary endpoint mentioned is the study synopsis (attachment 6, p2) and the objectives (p13) were the assessment of different oncogenes. They are not mentioned further in section B p 36 of the submission where the main outcomes mentioned are sustained clearance of SK, and secondary clearance at TOC, recurrence, global skin quality and safety. Interestingly, in the published version of this study, the last sentence of the introduction says; “besides we determined oncogenes from the biopsy specimen, the results will be presented elsewhere”. We are not certain where ‘elsewhere’ refers to. The presence of multiple outcome variables and inconsistent handling of outcome data severely diminishes an already flawed study.

4.1.2.2 Original number of primary outcome variables and sample size implications

It is highly unusual to have more than 2 or possibly 3 primary outcome variables in a randomised trial. Whenever there is more than one primary outcome variable, issues of multiple comparisons and the appropriate adjustment of p-values and sample size need to be considered. In this case the sample size statements are inadequate, as there is no clear statement of the null hypotheses, nor of the precise nature of the alternatives being investigated, nor of the power required.

Even with a single primary outcome of the proportion responding positively to just one gene being considered, the study lacks power. Over 30 subjects per treatment are required to achieve 80% power of detecting a difference ≥0.2 in Treatment A verses Treatment B proportions, and may be considerable larger depending on the actual proportions being considered.

4.1.2.3 Analysis and conclusions

Significant p-values from tests of homogeneity of distributions across all three treatment groups are reported, but there is no statistical difference between the individual treatments.

4.1.3 Validity of the chosen surrogate markers.

INova:

In addition to clinical outcomes, the oncogene results are important because they provide genetic support for the highly significant field clearance result favouring imiquimod over each comparator. As explained in iNova's pre-Subcommittee response, p53 and $p16^{INK4A}$ mutations relating to SK were cleared or reduced after treatment in 62% (16/26) and 65% (17/26) of imiquimod patients, respectively. This compares with 25% (6/24) and 33% (8/24) of 5-FU patients and 16% (4/25) and 12% (3/25) of cryotherapy patients. Both results favouring imiquimod were significantly different from those of 5-FU and cryotherapy groups on an intent-to-treat basis (p53 mutation p=0.0004; $p16^{INK4A}$ mutation p=0.0003). Topical 5-FU and cryotherapy did not differ from each other for either mutation. The genetic evidence also increases confidence that 12 months follow-up post treatment is sufficient time to assess what SK looks like longer term in comparing each therapy.

The value of oncogenes and p53 and primary endpoints is highly debatable. No data is presented to support the usefulness of these biomarkers as surrogates for clinically useful endpoints. When biomarkers are used in this way a minimum expectation is the presentation of receiver-operator curves (ROC) linking the biomarker to a clinical outcome. Indeed, great caution should be applied when biomarkers are used to evaluate the efficacy of a drug where the mechanism of action is unclear. Recent literature suggests more than one possible mechanism of action of imiquimod, including inhibition opioid growth factor and activation of TLR7/8. Thus, these biomarkers may have no significance.

Genes p53, p16, ras and 5 new epithelial oncogene candidates are mentioned in the study protocol (p3), but results for only p53 and p16 are reported in the Clinical Study Report (p13). The conclusions of the study are negatively affected by the absence of any information regarding 6 of the 8 stated primary outcome variables.

Complete clearance is a surrogate marker of the cosmetic result and does not reflect the propensity to develop SCC.

4.1.4 Assessment of recurrence and new lesions

The definitions of recurrence and new lesions are unclear. The patients included in the assessment of recurrence are only those that achieved complete (100%) clearance. The patients who did not respond completely to the initial therapy (some might have had partial clearance up to 99%) were excluded from analysis and were more frequent in the imiquimod group than the 5-FU group. The number of patients with complete clearance considered in the imiquimod group for assessment of recurrence was furthermore equal to 14 (54%, original definition of 4 weeks post treatment response) and not 22 (85%, new definition in

favour of imiquimod). Therefore the lower number of responders at 4 weeks has reduced the percent of recurrence in the imiquimod group. Moreover, the authors say that a more accurate outcome for immediate response is the histological assessment at 1 year, but do not provide this information.

4.1.5 Other limitations

The surface area of skin treated in this study (i.e. 50 cm^2) is twice that of the maximum recommended in Australia (max 25 cm^2), as per TGA-approved prescriber information for imiquimod. This surface area limitation is not peculiar to Australia and is based on available safety data. A surface area of 25 cm^2 is insufficient to treat sun-exposed areas of the face or scalp, with 10 to 20 times this surface area being a more realistic value. In this context we recommend that the sponsor clarify what is meant by "field therapy" in their submission to the PBAC.

4.1.6 Conclusion

The limitations of the H2H study (published as *Krawtchenko N, et al, 2007*) covered above and in the statistician's report contained in *Appendix 1* mean that this study cannot demonstrate that imiquimod is superior to its main comparators, 5-FU and cryotherapy

4.2 Critical analysis of the results

4.2.1 Acute clearance at Test of Cure (TOC) and sustained clearance

The iNova Independent Review Request states:

> The most important efficacy measure in the H2H study by Krawtchenko et al 2007 was the sustained (field) clearance rate. This was defined as the percentage of patients in each group with 100% initial and sustained lesion clearance and no new lesions in the treated area 12 months post-treatment. Total field clearance of
>
> treated lesions and new lesions arising at a later time is the ultimate aim of field therapy and the most rigorous outcome for measuring treatment success. This is the only published SK study of which we are aware that has measured this key outcome.
>
> In this randomised study, imiquimod was superior to both topical 5-FU and cryotherapy in achieving sustained (field) clearance of treated SK lesions and new lesions. The highly significant difference favouring imiquimod whereby 73% of patients achieved sustained total field clearance 12 months post treatment compared with 5-FU (33%; p=0.01) and cryotherapy (4%; p<0.0005) based on all enrolled study patients is strong direct evidence. The H2H study is also supported by the European regulatory agency (EMEA) who has accepted that this study represents convincing evidence for the difference between imiquimod and topical 5-FU such that another comparative study involving 5-FU is not required (***Attachment 2***). Note that the H2H study became available long after TGA approval for imiquimod's use in SK.

It is unclear how 19 patients in the imiquimod group could have had no SK lesion at the post treatment visit and follow-up 1 (6 months) and 2 (12 months) when only 13 patients had a complete clearance at 12 months among those completely cleared at 4 weeks post treatment (4WPT) (See table).

Clearance	imiquimod N=26	5-FU N=24	cryotherapy N=25
4WPT[a] all lesions at baseline cleared and no new lesions	14/26 (54%)	23/24 (96%)	17/25 (68%)
Acute TOC[c]	**22/26 (85%)**	**23/24 (96%)**	**17/25 (68%)**
Sustained response[a] complete clearance at month 12 among those who had complete clearance at TOC	13/14 (93%) or 13/22 (59%) depending on the definition of TOC	13/23 (56%)	7/17 (41%)
Sustained clearance rate[b,c] Observed when a patient presented with no SK (i.e.; neither pre-existing lesion, nor recurrent lesion, nor new lesion) at TOC and follow-up visits at month 6 and 12.	**19/26 (73%)**	**8/24 (33%)**	**1/25 (4%)**

[a] clinical study report H2H table 23 p35, *unpublished*
[b] clinical study report H2H table 22 p34
[c] published results

in **bold** rates used in the economic analysis

4.2.2 Recurrence and New lesions

Outcome	imiquimod	5-FU	cryotherapy
Recurrence (at least 1 lesion)			
6 months	0/23 (0%)	7/24 (29%)	8/25 (32%)
12 months	0/23 (0%)	11/24 (46%)	12/24 (50%)
12 months for cleared patients at TOC *	3/22 (14%)	10/23 (43%)	10/17 (59%)
New Lesion			
6 months	2/26 (8%)[a] vs 5/26 (19%)[b]	6/24 (25%)	16/25 (64%)
12 months	1/26 (4%)[a] vs 4/26 (15%)[b]	10/24 (42%)	21/25 (84%)

[a] publication Krawtchenko et al (17); [b] clinical study report

The submission (page 55 section B) states that *"it should also be noted that the recurrence rates quoted in the Krawtchenko publication (17) differs slightly to that reported in the clinical study report within a 1-2 patient variance, however importantly the conclusions are the same. This difference is likely due to the nature of the disease with lesions recurring and new lesions appearing/regressing, interpretation and differing definitions for the different assessments time points e.g. 4 weeks post treatment vs TOC".*

In our opinion, the validity of the "sustained clearance rates" needs to be more fully discussed, taking into account the nature of the disease itself and the possibility of regression of lesions without any treatment, a well established phenomenon.

Furthermore, the exact calculation of those rates is difficult to follow in the submission with numerous contradictions within the clinical study report, as well as with the publication of *Krawtchenko, et al,* (17). If ones take into account the sustained response at 12 months, 59% of patients receiving imiquimod and 56% receiving 5-FU achieved a sustained response, as opposed to the published sustained clearance rates of 73% verses 33% in favour of imiquimod. It is only these higher rates that have been used in the submission for the purpose of the pharmaco-economical analysis, and they create a bias in favour of imiquimod.

4.3 Comparison imiquimod vs cryotherapy: Foley trial (18)

This is an unblinded randomised controlled study comparing the 12 month-post-treatment efficacy of cryotherapy verses imiquimod. It is referred as “a supportive study” in the submission because multiple treatment sessions of cryotherapy were allowed during 12 months as compared to 1-2 sessions in *Krawtchenko, et al*. We disagree with the statement that “in clinical practice patients are more likely to receive a single session” (p47 section B). In our opinion multiple cryotherapy sessions reflect more adequately the current practice in Australia.

Cryotherapy regimen	Duration of treatment	Duration of follow-up
H2H trial (17) - 196C liquid nitrogen spray One session (20-40s)	1 session; a second session possible if lesions not cleared within 2 weeks	TOC, 6 and 12 months
Foley Trial (18) single freeze-thaw cycle One session (10s) up to 10 lesions per session.	1 session with up to 3 repeat sessions every 3 months based on response at 3, 6 or 9 month follow-up visits.	3, 6, 9 and 12 months

71 patients were included, 36 received cryotherapy and 35 imiquimod. More patients in the cryotherapy group had type I skin type as compared to the imiquimod group (39% vs 20%). This is a bias in favour of imiquimod.

The drop out rate from the study was high. Five patients withdrew in the cryotherapy group and 10 in the imiquimod group. The ITT population described in the submission is not the true ITT population but corresponds to the treated population only (n=62). When recalculating the response rate with the correct ITT denominator (see table), cryotherapy appears to be superior to imiquimod for both the patient and the lesion sustained response after 12 months. Therefore the claim that there was no difference between cryotherapy and imiquimod after ITT analysis (section B page 58) cannot be supported.

12 months patient sustained response:

Response	imiquimod	Cryotherapy
Submission		
Complete Responder	17/28 (61%)	28/34 (82%)
Partial Responder	7/28 (25%)	3/34 (9%)
Recalculated ITT		
Complete Responder	*17/35 (49%)*	*28/36 (78%)*
Partial Responder	*7/35 (20%)*	*3/36 (8%)*

3 and 12 months lesion sustained response (at 12 month follow-up, assessment of how many of those lesions judged to have completely responded at the three month review remained as having completely responded).

Response	imiquimod	Cryotherapy
Submission 3 months		
Complete Responder	245/280 (88%)	252/330(76%)
Partial Responder	33/280 (12%)	68/330 (21%)
Recalculated ITT 3 months		
Complete Responder	*245/340 (72%)*	*252/360(70%)*
Partial Responder	*33/340 (10%)*	*68/360 (19%)*
Submission 12 months		
Complete Responder	234/250 (94%)	306/310(99%)
Partial Responder	14/250 (6%)	4/310 (1%)
Recalculated ITT 12 months		
Complete Responder	*234/340 (69%)*	*306/360 (85%)*
Partial Responder	*14/340 (4%)*	*4/360 (1%)*

Italics: recalculated ITT analysis

4.4 Secondary comparisons: Placebo verses imiquimod studies

3 cyclic therapy randomised double blind vehicle controlled studies (1459, 1473 and 1487) and their 2 long term follow up studies (1518 and 1524) were considered in the submission as a secondary comparison of imiquimod verses placebo evaluating the acute 100% clearance rate. Patients were receiving imiquimod or vehicle 3 times per week for 4 weeks for 1 or 2 cycles of treatment.

Acute 100% clearance rates:

Studies	Patients enrolled	imiquimod n/N (%)	Placebo n/N (%)	Relative Risk [95% CI]	NNT
1459	82	18/39 (46%)	4/43 (9%)	5.0 [1.8, 13]	3
1473	246	66/123 (54%)	18/123 (15%)	3.7 [2.3, 5.8]	3
1487	259	71/129 (55%)	3/130 (2%)	24 [8, 74]	2
Meta-analysis of 1459+1473+1487	587	155/291 (**53%)**	25/296 (**8%**)	6.3 [4.3, 9.3]	2

The acute 100% clearance rate of imiquimod was statistically significantly superior to placebo (see table, meta-analysis NNT=2).

The proportion of patients who had 100% clearance after one 4-weeks cycle was 33%, and therefore **67%** required a second cycle of treatment. In the submission, these values were therefore used in the pharmaco-economic analysis comparing imiquimod verses placebo.

4.5 Comparison imiquimod vs 5-FU: Tanghetti E, et al, 2007 (19) (study excluded from the submission)

Another RCT has been performed comparing imiquimod to 5-FU (19). This study offers the advantage of physician blinding. The manufacturer of 5-FU, Valeant, provided a grant for this study. This study has been excluded but provided as a reference (section B2.2.2 p33) by iNova because the weekly dose of imiquimod was two-thirds of the recommended dose (2 times a week instead of 3). The treatment was, however, administrated uninterrupted for 16 weeks (as opposed to 2 x 4 weeks) so that the total number of applications was higher than that used in the *Krawtchenko, et al,* study (32 vs. 24 total applications). Moreover,

topical treatments within 2 months of the study were an exclusion criterion. No specific details on the co-morbidities excluded other than "any clinical laboratory value outside the normal range or any organic or psychological disease that could interfere with the outcome or interpretation of the study results" is provided. Patient baseline characteristics (such as skin type or age) were not provided. Results were based solely on clinical assessment and the follow-up was performed at the same time points for the 2 therapies: baseline and weeks 4, 8, 12, 16 and 24 weeks. Despite the small sample size of the study, large differences were noticed in favour of 5-FU (complete clearance at week 24: 84% in the 5-FU group vs 24% in the imiquimod group, $p<0.01$).

Like the H2H study, this study is also flawed but has the advantage of having a simple clinically relevant outcome variable and physician blinding. The data cannot be completely dismissed on the basis of inadequate imiquimod treatment, as the total dose of imiquimod administered is higher than that recommended by the manufacturer. However, like many studies in this area, patient numbers were relatively small with a total of 36 being randomised. Accordingly, this study fails to provide robust evidence on the relative efficacy of imiquimod verses 5-FU for the treatment of SK.

4.6 Conclusion:

iNova stated that:

> There is no clinical or statistical basis for the PBAC's concerns about the adequacy of the provided data. Indeed, the collective data submitted was more than adequate. In particular, the adequately powered H2H study that directly compared imiquimod and its main comparator, topical 5-FU, provides a higher level of evidence than was available for the sBCC listing, enabling certainty of imiquimod's comparative effectiveness in SK at both a clinical and genetic level.

We strongly disagree with this statement. This review highlights weak study design, inadequacy of data as well as significant statistical issues in the H2H study (published as *Krawtchenko, et al,* 2007). Also, it is not possible to draw firm conclusions as to the efficacy of imiquimod as compared to 5-FU given the contradictory results from 2 RCTs, both of which have methodological and scientific limitations. The claim for an "unequivocal" superiority of imiquimod over 5-FU (section B, p65) is not supportable. A suitably powered randomised double-blinded RCT with relevant endpoints and exclusion criteria is needed to scientifically confirm the relative efficacy of imiquimod and 5-FU.

5. Is there a safety issue with imiquimod as a true field therapy?

The iNova Independent Review Request reads:

> There is no safety issue with imiquimod's use as a field therapy for SK. The TGA has not signalled there is an issue following several years of market availability, nor has there been an ADRAC report for imiquimod, although safety reports are regularly submitted to the TGA.
>
> The submission requests use of imiquimod as a field therapy in accordance with the Product Information, and all relevant efficacy and safety data was presented. "Field therapy" in the requested listing, which identifies the target patient population eligible for imiquimod, is an established medical term addressing the histopathological changes associated with a more severe form of SK requiring treatment beyond the visible lesion. **This term is not related to, nor assumes, the size area of application for which doctors would consult the Product Information (PI) and other information sources.**

As covered earlier in this review, the usual meaning of "field therapy" is application of a therapy to an anatomic region. In the present context, we understand this term to mean application of the therapy to sun-exposed areas of the face and/or scalp. This typically represents a treatment field of 300 to 500 cm^2 for an adult patient. For the treatment of SK, we believe that the request from iNova for a field therapy could be misinterpreted in the clinical setting, given that a field therapy with 5-FU covers up to 500 cm^2 surface area (the whole face). Indeed a sachet of imiquimod can cover up to 380 cm^2 surface of skin. The term "field therapy" is in our opinion confusing to the physician and a drift to off label prescription is of concern given a lack of safety data for imiquimod for an area exceeding 25 cm^2. The present TGA approval for imiquimod is restricted to a surface area up to 25cm^2, which could be interpreted as being a local therapy. We recommend that the sponsor is asked to clarify their definition of a "field therapy" in the context of this submission. Also, the sponsor should be asked to clarify what is meant by "other information sources" and to give examples of such.

> The following points are relevant:
>
> - The 25cm^2 application recommended in the Dosage/Aministration section of the Product Information is based on clinical trials in which patients applied imiquimod to this size area, rather than safety concerns (see TGA Delegate advice, ***Attachment 4***). These were the only Phase 3 trials available at the time of TGA registration, whereas the H2H study and placebo controlled cyclic studies in the PBAC submission came later.

We disagree with the above statement. A phase II study (1402-IMIQ) has been performed to "evaluate the safety margins for systemic exposure of imiquimod with the maximum dose level, to the maximum treatment area, with the maximum dosing regimen to be used in the phase III studies evaluations SK". This study has shown that treatment of surface area greater than 25 cm^2 results in increased systemic bioavailability of imiquimod. Moreover, out of 58 subjects included, 7 withdrew because of adverse events.

In the “placebo controlled cyclic studies that came later”, the surface area treated with imiquimod was still 25cm^2.

To our knowledge, the only study where a larger surface area was treated (50 cm^2) is the H2H study. The main aim of this study was not assess the safety of the drug but the comparative efficacy, and only 26 patients were included. No proper safety data is therefore available to assess the safety of imiquimod for larger surface area than 25 cm^2.

- Imiquimod has been available for almost 10 years in Australia, of which SK has been a registered indication for 3 years. The Periodic Safety Update Report (PSUR) submitted to the TGA and discussed in the submission (pg. 77-78) estimates global patient exposure at 169 million patient-days from which no safety issues were found. All uses and application sizes from clinical studies and market experience are included in the PSUR, which concluded that only pharmacovigilance monitoring as a regulatory requirement is needed.

The PSUR concluded that pharmacovigilance monitoring is needed because no new safety issues appeared. It does not mean that there are no safety issues.

Section B7 of the submission claims that there is no evidence of delayed or rare adverse events with imiquimod in the treatment of SK, and it has been widely used in the treatment of sBCC, SK, external genital, perianal warts and condyloma acuminata since being commercially available in 1999. A total estimated patient exposure of 169 million patient-days is stated and there have been a total of 2,550 case reports of suspected adverse drug reactions of which 351 were serious.

Graceway Pharmaceuticals supplied reports to the global 11th PSUR 27 February 2006 to 26 February 2007 for imiquimod. 556 reports were received. The estimated patient exposure for the reporting period was 28 million patient-days.

Fatal/Life-threatening	2	59 Total serious
Serious unlisted (excl above)	49	
Serious listed	8	
Non-serious unlisted	278	497 Total non-serious
Non-serious listed	219	
	TOTAL:	**556**

Fifty-one new unlisted serious case reports were received during the reporting period. Some patients experienced more than one symptom; some symptoms were experienced by more than one patient. Reported unlisted reactions were as follows, in alphabetical order: Abdominal pain, Abortion spontaneous (2), Accidental Overdose, Anaphylactic reaction,

Angioneurotic Oedema, Application site bleeding, Application site discharge (2), Application site erosion, Application site infection, Arthritis, Arthritis reactive, Asthenia (2), Bacterial infection, Blood pressure, increased C-reactive protein, increased Cellulitis, Chest discomfort, Chest pain, Constipation, Coronary artery disease, Cough, Cutaneous lupus erythematosus, Death, Diabetes mellitus insulin-dependent, Dizziness Dyspnoea, Ectropion, Electrocardiogram Abnormal, Erythema Multiforme (3), Eye irritation, Exanthema generalised, Face oedema, Facial palsy, Herpes simplex, Hypoesthesia (2), Hypotension (2), Impaired Healing, Infection, Inflammation (2), Keratitis Leukocytosis, Lip exfoliation, Lip Ulceration, Local Reaction, Loss of consciousness, Lymphadenopathy (2), Lymphocytic Infiltration, Lymphoma, Lymphoproliferative Disorder, Mouth Ulceration (2), Mucositis Inflammation, Multi-Organ Failure, Muscle Spasms, Nausea (2), Neuropathic pain, Non-Specific Reaction, Ocular Hyperaemia, Oedema, Optic Neuritis, Oral Mucosal Blistering, Oral Mucosal Exfoliation, Pain in Extremity (2), Perivascular Dermatitis, Pharyngolaryngeal pain, Platelet count decreased, Pneumonia, Proptosis, Pruritus Ani, Pulmonary congestion, Rash erythematous (2), Rash papular, Red blood cell sedimentation rate increased, Rosacea, Sarcoma, Septic Shock, Skin disorder, Squamous Cell Carcinoma (2), Swelling Face, Swollen Tongue, Urinary retention, Vaginal laceration, Vulval ulceration, Vulvar erosion, Vision Blurred (2), Vitiligo, Vomiting, Vulvitis.

Their conclusions were that:

-No significant new safety information is revealed or suggested by the cases in this PSUR
-No safety signal is perceived, neither is any trend, which would require further investigation.
-No other action on safety grounds is warranted, other than continued pharmacovigilance.
-The benefit risk assessment for Aldara remains favourable.

- The PBAC claim that one imiquimod cream sachet can cover up to a 389cm^2 skin area is not valid since it comes from a non-efficacy study conducted on the disease free skin of two pigs and one human arm (Berman et al 2004).

This study shows that one single use imiquimod 5% sachet can cover up to 386cm^2 of skin, irrespective of the aim of the study (or the source of the skin). If the sponsor disagrees with this interpretation the sponsor should provide new data as to the skin surface area that one sachet of Aldara will cover. Suffice it to say that it will be significantly greater than 25 cm^2.

- All imiquimod studies in the PBAC submission demonstrated safety, which was no worse than 5-FU in the H2H trial that applied study cream to a 50cm^2 area (*Submission Attachment 6*).

We agree that no major safety concerns have been raised by the literature review available in the PBAC submission. The adverse drug reactions from the H2H study, the Foley trial (18)

and 3 placebo-controlled trials provided in the submission (section B.6.3) are summarised below:

Summary of adverse events (AE) reported in the H2H study:

	IMQ N=26			**5-FU N=24**			**Cryotherapy N=25**		
	n*	N	%	n*	N	%	n*	N	%
Patients with at least 1 AE		3	12		1	4		2	8
Patients with at least 1 SAE		1	4		0	0		1	4
Deaths		0	0		0	0		0	0
AEs – treatment period									
Feelings of weakness	2	1	4	0	0	0	0	0	0
Headache	1[c]	1[c]	4	0	0	0	1[b]	1[b]	4
Hypertension aggravated	0	0	0	1	1	4	0	0	0
Hyperthyroidism	0	0	0	1	1	4	0	0	0
Skin inflammation	1[a]	1[a]	4	0	0	0	0	0	0
AEs - follow-up period									
Skin lesion excision of SK	0	0	0	0	0	0	1	1	4
Skin lesion excision of basocellular carcinoma	0	0	0	0	0	0	2[o]	2[o]	8
Skin lesion excision	1[o]	1[o]	4	0	0	0	0	0	0
Squamous cell carcinoma of skin	1[o]	1[o]	4	0	0	0	0	0	0
Accidental puncture or laceration during a procedure, not elsewhere classified	0	0	0	0	0	0	1	1	4
Vertigo	0	0	0	0	0	0	1	1	4

* n= Number of events
All AEs except those indicated were classified as "not related".
a Classified as "possibly related".
b Classified as "probably related".
c Classified as "related".
o Outside of study treatment area.

Source: table 6.10 section B6.3.1 of the submission

All treatments were well tolerated according to the authors (6 patients reporting 14 AEs during the study period, 7 of these AEs in the treatment period in 4 patients). One patient in the imiquimod group interrupted treatment due to AEs (skin inflammation). 4 SAEs were

reported by two patients (4 episodes of skin lesion excisions leading to hospitalisation). One episode occurred in the imiquimod group (lesion excision for SCC outside the treatment area) and the other 3 others concerned one patient in the cryotherapy group (lesion excision for SK outside the treatment area and basocellular carcinomas). None of the patients died during the study period.

Summary of AE reported in the Foley trial (18):

Symptom	IMQ		Cryotherapy		Relative Risk	Relative Difference
	N=27*	(%)	N=33**	(%)	[95% CI]	[95% CI]
Pain/ Burning/ Stinging	13	(48.1)	17	(51.5)	0.935 [0.560 to 1.561]	-0.034 [-0.288 to 0.220]
Swelling/ Oedema	12	(44.4)	17	(51.5)	0.863 [0.505 to 1.475]	-0.071 [-0.324 to 0.183]
Redness/ Erythema	24	(88.9)	32	(97.0)	0.917 [0.792 to 1.061]	-0.081 [-0.213 to 0.051]
Blister Formation	0	(0.0)	10	(30.3)	0.00 n.e.	-0.303 [-0.460 to -0.146]
Weeping/ Exudate	5	(18.5)	9	(27.3)	0.679 [0.258 to 1.787]	-0.088 [-0.299 to 0.124]
Vesicles	1	(3.7)	1	(3.0)	1.222 [0.080 to 18.643]	0.007 [-0.085 to 0.099]
Erosion/ Ulceration	5	(18.5)	9	(27.3)	0.679 [0.258 to 1.787]	-0.088 [-0.299 to 0.124]
Scabbing/ Crusting	20	(74.1)	29	(87.9)	0.843 [0.652 to 1.090]	-0.138 [-0.337 to 0.061]
Flaking/ Scaling/ Dryness	24	(88.9)	32	(97.0)	0.917 [0.792 to 1.061]	-0.081 [-0.213 to 0.051]
Infection	2	(7.4)	1	(3.0)	2.444 [0.234 to 25.529]	0.044 [-0.071 to 0.159]
Bleeding	1	(3.7)	3	(9.1)	0.407 [0.045 to 3.696]	-0.054 [-0.175 to 0.067]
Peeling	11	(40.7)	14	(42.4)	0.960 [0.525 to 1.757]	-0.017 [-0.267 to 0.234]
Itching	17	(63.0)	17	(51.5)	1.222 [0.787 to 1.897]	0.114 [-0.135 to 0.364]
Other***	4	(14.8)	3	(9.1)	1.630 [0.399 to 6.661]	0.057 [-0.109 to 0.223]

* One participant who received imiquimod and completed the study was unable to attend the follow-up appointment during the cycle of treatment and therefore no symptom data can be included for this participant

** One participant who received cryotherapy and completed the study was unable to attend follow-up appointments one week after each cycle of treatment and therefore no symptom data can be included for this participant

*** Other symptoms reported after cryotherapy treatment included headaches (3) and a watery eye (1). Other symptoms reported after imiquimod treatment included headaches (2), sore or watering eyes (2), flu-like illnesses (2) and nausea (1),

The AEs were recorded one week after treatment for participants receiving cryotherapy and three weeks after treatment with imiquimod. This might have biased the results.

After cryotherapy more blister formation was reported (p=0.001), as well as more scabbing/crusting and erosion/ulceration but this was non significant (p=0.17 and 0.42 respectively). Inversely, more itching was experienced after imiquimod, but again this difference was not significant (p=0.37). The severity of pain/burning/stinging and swelling/oedema was similar in the 2 groups. Fewer participants experienced redness/erythema following imiquimod but it was more severe than with cryotherapy.

Summary of AE reported in placebo-controlled trials:

Study	**1487**			**1459**			**1473**		
	IMQ n=129	PBO n=130	p-value	IMQ n=39	PBO n=43	p-value	IMQ n=123	PBO n=123	p-value
≥ 1 AE	69 (53.5)	40 (30.8)	<0.001	12 (30.8)	11 (25.6)	0.631	72 (58.5)	66 (53.7)	0.521
Severe	6	4	0.540	0	1 (2.3)	0.276	3 (2.4)	6 (4.9)	0.500
Serious	1	4	-	0	0	-	3 (2.4)	4 (3.6)	-
Death	0	1	-	1 (2.6)	0	-	0	0	-
Application reaction **Itching at target site**	29 (22.5) 16 (12.4)	6 (4.6) 2 (1.5)	<0.001	4 (10.3)	4 (9.3)	0.047	27 (22)	7 (5.7)	<0.001
>1AE other than application reaction	52 (40.3)	35 (26.9)	0.026	9 (23.1)	11 (25.6)	1.000	58 (45.2)	63 (51.2)	0.610
Plausibility	38 (29.5)	8 (6.2)	<0.001	4 (10.3)	0	0.047	31 (25.2)	9 (7.3)	<0.001
Discontinuation due to AE	4 (3.1)	0	-	0	0	-	1 (0.8)	0	-

Values extracted from the clinical study reports of the studies 1459, 1473 and 1487.

These data show that patients receiving imiquimod are more likely to have application site reaction adverse events than patients receiving placebo. The incidence of adverse events other than application site reaction was also higher after imiquimod than placebo in the study 1487 (40.3% vs. 26.9%, p=0.026). Adverse events that were considered probably or possibly related to treatment and reported by at least 1 subject in the imiquimod group included: myalgia (3.1%), arthralgia (2.3%), headache (2.3%), asthenia (1.6%), malaise (1.6%), diarrhoea (1.6%), anorexia (1.6%), depression (1.6%), fatigue (0.8%), fever (0.8%), influenza-like symptoms (0.8%), leg pain (0.8%), rigors (0.8%), nausea (0.8%), infection

staphylococcal (0.8%), and rhinitis (0.8%); as compared to headache (0.8%), somnolence (0.8%), and tracheitis (0.8%) for the vehicle group.

> The PBAC comment about Phase 2 studies and systemic effects regarding larger treatment areas is inappropriate and irrelevant to the requested listing. These were dose finding studies reporting up to twice daily application for 16 weeks, with one or more sachets per application and often on limbs rather than face or scalp. The PBAC has focused on these earlier phase studies to assess safety rather than comparative safety data from the H2H study report and placebo controlled Phase 3 studies which all used the TGA approved three times weekly dose regimen relevant to clinical practice.

The fact that Phase II studies report systemic effects for larger treatment areas is an important finding. The purpose of dose-finding studies in drug development is to assess efficacy as well as safety. The aim of a Phase II study is to define the response (no effect, mean effective and maximal effective doses) and then take into account the tolerability to select the optimal therapeutic dose. These Phase II studies are the only studies available to assess the safety of imiquimod for treatment area greater than 25 cm^2, other than the H2H study. Comparative safety data from the H2H study are weak due to the small sample size of the study (this is discussed above).

> The PBAC comment about safety issues in Europe and amplification in the Australian setting is also inappropriate and without an evidence base. **There is no application area restriction for imiquimod's use in SK based on the European Product Information** (named Summary of Product Characteristics). The EMEA also has not identified any safety issues. iNova understands the *"safety issues reported"* in the PBAC short minutes comes from a Netherlands Pharmacovigilance Centre reporting four patients with severe local skin reactions (these effects are all in the Product Information), only one of whom used imiquimod for SK (*information supplied by the Pharmaceutical Benefits Branch to iNova post PBAC meeting and available on request*).

The severe adverse reactions reported by the Netherlands Pharmacovigilance centre have to be taken into account. They raised concerns in November 2007 regarding severe skin disorders (i.e., more severe than expected) after imiquimod cream 5%. They received four reports of severe local skin reactions with super infections or reactivated viral infections. These adverse drug reactions (ADRs) were reported in a short period of time after extension of the indication for imiquimod.

We disagree that safety issues in one country cannot be applied to another country such as Australia. Spontaneous reports of suspected ADR to national pharmacovigilance centres are a crucial element in the worldwide enterprise of pharmacovigilance and form the core of the World Health Organisation database. The Netherlands, like Australia, is predominantly caucasian, so safely signals are likely to be highly applicable to the local situation.

iNova does not believe there is a need to provide safety data to the PBAC on imiquimod's use in areas greater than 50cm^2 when this is not consistent with the Product Information, or the H2H study comparing against 5-FU, or Phase 3 clinical studies, nor promoted by our company. The TGA also has not flagged there is a safety issue. To provide such data is beyond the scope of the submission.

In Australia, the TGA registered PI for treatment of SK with imiquimod has been limited to surface area up to 25 cm^2 based on safety concerns raised in Phase II studies and a lack of data beyond this treatment area. No reliable supporting data is available in the literature or from iNova for field therapy for surface areas greater than 25 cm^2, so that the prevalence of local/systemic side effects for larger treatment fields is unknown.

A significant concern is that there is enough drug in a sachet to treat up to 386 cm^2 of skin and that there is no effective protection against a patient applying a whole sachet other than their own intelligence and the warning on the packet. It must be assumed there is a probability that some patients will apply considerably more than the recommended 25cm^2.

6. Is imiquimod a cost-effective therapy for SK?

The iNova Independent Review Request says:

> The economic model was created to evaluate SK as a disease in its own right. While it is possible and logical that treating SK should lead to a reduction in SCC, there is no robust evidence for this and the submission does not make this claim. Imiquimod is not licensed for SCC and the submission is NOT seeking consideration for any possible positive effect on SCC prevention. For these reasons, although the more SK lesions there are the greater the potential risk of SCC, the submission economic model does not transform SK to SCC and so the model time frame is appropriate and adequate for SK.
>
> The model provides incremental cost-effectiveness (CE) ratios one year and three years post treatment, both periods representing ample time for testing sustained clearance. In sensitivity analysis the same sustained clearance rate for imiquimod as for comparators was conservatively assumed for years 2 and 3. This still resulted in acceptable CE ratios, indicating the model is robust and that the 12 month clearance rate largely influences cost-effectiveness.
>
> The PBAC's comment that SK has a much longer course is speculative. The greatest risk of SK recurrence is within the first 12 months post treatment and, consistent with this, the economic model was not sensitive to the recurrence rate beyond 12 months. Also relevant is the gene mutation evidence from the H2H study, from which it is biologically plausible that the clinical difference favouring imiquimod 12 months post treatment is representative of comparative longer term outcomes.
>
> In the absence of utility values measuring quality of life impact of SK treatment, the economic model measured cost-effectiveness in terms of cost per solar keratosis recurrence free year. This is similar to the approach that was used for the sBCC listing since SK, like sBCC, is a condition in its own right impacting on morbidity rather than survival. There is inconsistency in the PBAC accepting cost per sBCC recurrence free year and not cost per solar keratosis recurrence free year.
>
> Other clinical/economic matters raised by the ESC (*PBAC Short Minutes, pg 2, 4th paragraph*) were addressed in iNova's pre-Subcommittee and pre-PBAC responses, and iNova trusts the Reviewer will peruse these documents during his/her assessment. The economic model was shown to be very robust when testing various parameters, even those performed by the Evaluator.

Imiquimod is a cost-effective field therapy for SK based on head to head data showing superior sustained clearance compared with topical 5-FU and a robust economic model producing acceptable CE ratios, which are comparable to those shown for the sBCC listing.

Firstly, we note that the preferred economic analysis is cost-utility (refer PBAC guidelines) where health outcomes in terms of life years gained are the key measurement – commonly

incremental QALY gained. Earlier we have discussed the absence of these measurements, and the consequent difficulties in demonstrating the value of treating SK. It also means that the sponsor is not able to use a cost utility analysis for the economic modelling.

Instead they have used a cost effectiveness analysis, where the objective is to assess the incremental cost per extra unit of health outcome achieved (refer PBAC guidelines) and test whether Imiquimod offers more of a given health outcome than the main comparator.

6.1 Cost effectiveness

In the submitted economic evaluation, a cost effectiveness (CE) analysis using cost per patient-year in remission (disease-free/recurrence-free) over a 3-year timeframe was provided in the form of incremental CE ratio. The economic evaluation was performed using a Markov model. The model was structured with an optional extra level of salvage treatment of resistant lesions not cleared with short-term therapy. The rates of initial SK clearance and sustained clearance failure were derived from the "key imiquimod studies" (17, 18) and placebo controlled studies 1459, 1473, 1487, 1518 and 1524.

6.1.1 Clearance rates used in the model

6.1.1.1 Acute clearance rates:

The submission claims that the initial acute clearance rates with 5-FU and cryotherapy were not statistically different from imiquimod. An overall "pooled clearance rate" for all three treatments combined was therefore used in the primary analysis in the model.

As described above, the initial acute clearance rates vary widely depending on the definition of the TOC visit (see table) and this represents a bias in favour of imiquimod.

Moreover, it appears inadequate to claim equivalence because of the absence of a statistically significant difference between treatments. A lack of significant difference might occur when trials are too small to demonstrate a real difference in the effects of the interventions. This bias clearly is in favour of imiquimod for the comparison with 5-FU (see table).

	imiquimod	5-FU	cryotherapy
4WPT	14 (54%)	23 (96%)	17 (68%)
Acute TOC	22 (85%)	23 (96%)	17 (68%)
Pooled acute clearance rate	**82.7%**	**82.7%**	**82.7%**

Rate used in the submission

6.1.1.2 Sustained clearance failure rates:

As the acute clearance rates were pooled, the pharmaco-economic model relies only on the sustained response. As mentioned previously, the validity of the "sustained clearance rates" needs to take into account the spontaneous regression rate of lesions in the absence of treatment and subject behaviour, such as continued sun exposure. Therefore the sustained rates have some inherent weaknesses that must be carefully accounted for in the construction of pharmaco-economic models. In addition, the calculation of these rates was difficult to follow in the submission with numerous contradictions within the clinical study report, as well as with the publication of *Krawtchenko, et al*.

In the pharmaco-economic analysis, the sustained clearance rate was transformed into a sustained clearance failure rate then into a quarterly sustained clearance failure rate (see table). The submission explains that those rates were converted to quarterly rates by an exponential calculator "for greater accuracy and flexibility". It was not possible to follow the methodology for calculating sustained clearance failure rates, and the calculation method for the quarterly rates is not provided.

Accordingly, the balance of this analysis uses the assumption that Imiquimod has a 73% sustained clearance rate, compared to 33% for 5-FU. As discussed above the more accurate figures are 59% and 56%, so all the following analysis has an inbuilt significant bias towards Imiquimod.

	imiquimod	5-FU	cryotherapy
Sustained clearance rate	19 (73%)	8 (33%)	1 (4%)
Sustained clearance failure	(22-19)/22 13.6%	(23-8)/23 65.2%	(17-1)/17 94.1%
Quarterly sustained clearance failure rate	**3.59%**	**23.19%**	**50.71%**
Disaggregated components of sustained clearance rates			
Recurrence rate	3/22	10/23	10/17
New lesions	0/22	5/23	6/17

From H2H trial (17)

Rates in **bold** used in the economic model

6.1.1.3 Imiquimod and placebo

In the economic model comparing imiquimod with placebo, the actual acute clearance rates (from studies 1459, 1473 and 1487) were used, whereas the sustained recurrence rates of imiquimod (27.3%) were used for placebo. The submission said that no significant difference between imiquimod and placebo was demonstrated, but the actual sustained recurrence rate of placebo was 47.1%. This provides a bias in favour of imiquimod.

	imiquimod	placebo
Acute TOC	53.3%	8.4%
Sustained clearance rate (%)	27.3%	27.3%
Quarterly clearance rate (%)	7.66%	7.66%

6.1.1.4 Extrapolation of 12-month trial data to three years in model

The exponential algorithm used to generate the quarterly recurrence rate was then used to extrapolate quarterly recurrences over a 3-year period; i.e.; the submission applied the same values from the first 12 months over a three-year period. The assumption that those rates

would remain constant over 3 years is, in our opinion, unjustified; this has not yet been evaluated in any clinical study and is likely to provide a bias in favour of imiquimod.

6.1.2 Conclusion

In summary, the CE analysis used in the submission is inadequate to demonstrate that imiquimod offers more of a given health outcome than the main comparators largely due to a lack of reliable data on relevant health outcomes, a lack of demonstrated superiority over comparator therapies and inadequate study of the durability of the treatment response.

6.2 Cost minimisation

The previous comments on the efficacy of imiquimod verses its active comparators (see above) fail to demonstrate a superiority of imiquimod for SK over 5-FU or cryotherapy in both the acute and long-term settings. At best, imiquimod may be classified as non-inferior to its main comparators. Therefore, it is our opinion that the only appropriate economic analysis is a cost-minimisation analysis (part III Section D of PBAC procedural guidelines). This analysis applies "when the proposed drug is demonstrated to be no worse therapeutically (in terms of effectiveness and safety) than other drugs at the same or a lower price".

The following analysis is based on the costs of treating SK, consistent within TGA approved prescriber information, comparing Imiquimod, 5-FU and cryotherapy.

Medical, procedure and drug costs

Type	**Natural unit of measurement**	**Source**	**Unit cost**
Medical costs			
Professional attendances	GP visit, level B	MBS A.1 (23)	$32.80
	Consultant physician initial visit	MBS A.4 (110)	$136.30
	Consultant physician subsequent visit	MBS A.6 (116)	$68.20
Procedure costs			
Pathology	Biopsy	MBS 72813	$72.15
Procedures	Cryotherapy	MBS 30192	$35.75
Drug costs			
imiquimod	12 sachets	2546B	$158.97
5-FU	1 tube	RPBS 4222F	$45.56
Cyrotherapy (more than 10 lesions)			$35.75

MBS Medicare Benefits Schedule; PBS Pharmaceutical Benefits Scheme

The equi-effective dose between imiquimod and 5-FU from the clinical studies performed so far would be 1 sachet 3 times a week for 4 weeks (1-2 cycles) for imiquimod verses 1 application twice a day for 4 weeks for 5-FU. 12 imiquimod sachets provide a 4-week course of treatment (3 times per week). The H2H trial demonstrated that 19.2% of patients had SK lesions cleared after one cycle of 4 weeks and the remaining 80.8% after 2 cycles of 4 weeks. The weighted average dispensed drug cost of imiquimod is therefore equal to: \$158.97 + 0.808 x \$158.97 = \$287.42. In the comparison of imiquimod verses placebo, the weighted price of imiquimod is \$158.97 + 0.66 x \$158.97 = \$265 (66% of patients needed 2 cycles of 4 weeks imiquimod.)

6.2.1 Costs for imiquimod

Weighted costs (taking into account GPs and specialists costs) were used by iNova in the submission (page 112). This was based on the results from the Foresearch research, who found that treatment of SK in older persons was managed by GPs in 81.2% of cases and by specialists in 18.8% of cases. Therefore, in the same way we detail thereafter the costs (medical + drug) of the GPs, the specialists and the weighted costs (81.2% GPs, 18.8%).

		vs. 5-FU/cryotherapy		**vs. placebo**	
Parameter	**Unit cost**	**Number**	**Costs**	**Number**	**Costs**
GP visits	\$32.80	3	\$98.40	3	\$98.40
Drug costs	\$158.97	1.808	\$287.42	1.667	\$265.00
Total GP			**\$385.82**		**\$363.40**
GP initial diagnostic visit	\$32.80	1	\$32.80	1	\$32.80
Specialist initial	\$136.30	1	\$136.30	1	\$136.30
Specialist follow-up	\$68.20	2	\$136.40	2	\$136.40
Drug costs	\$158.97	1.808	\$287.42	1.667	\$265.00
Total Specialist			**\$592.92**		**\$570.50**
Weighted costs (81.2% GPs, 18.8% specialist)			**\$424.75**		**\$402.34**

Costs for the comparators (5-FU, cryotherapy and placebo)

		5-FU		Cryotherapy		Placebo	
Parameter	**Unit cost**	**n**	**Cost**	**n**	**Cost**	**n**	**Cost**
GP visits	$32.80	3	$65.60	1	$65.60	3	$65.60
Cryotherapy	$35.75			1	$35.75		
Drug costs	$45.56	1	$45.56				
Total GP			**$111.16**		**$101.35**		**$65.6**
GP initial diagnosis visit	$32.80	1	$32.80	1	$32.80	1	$32.80
Spec initial	$136.30	1	$136.30	1	$136.30	1	$136.30
Spec follow-up	$68.20	2	$136.40	2	$136.40	2	$136.40
Cryotherapy	$35.75			1	$35.75		
Drug costs	$45.56	1	$45.56				
Total Specialist			**$351.06**		**$273.05**		**$305.50**
Weighted costs (81.2% GPs, 18.8% specialists)			**$156.26**		**$133.63**		**$110.70**

Summary of total costs:

imiquimod	5-FU	cryotherapy
$424.75	**$156.26**	**$133.63**

Imiquimod is currently approved in Australia to treat a surface covering up to 25 cm^2 (e.g., 5x5cm) of skin on the face or scalp whereas 5-FU is restricted to 500cm^2 (e.g., 23x23 cm) area. The above calculation assumes that treating the entire face as a field would have to be performed by sections of 25 cm^2 according to the current TGA-approved prescriber information, noting that no data on retreatment or treating areas in excess of 50cm^2 with

imiquimod is available and safety concerns regarding a higher surface area of treatment have been raised. The number of sachets needed to sequentially treat the whole face (up to 500 cm^2) would then be equal to 500cm^2 divided by 25 cm^2= 20 sachets ($264.95). This would have to be multiplied by 12 for each cycle of treatment ($3179.40).

One sachet of imiquimod (250mg) can cover up to 386cm^2 of skin (20). Even if the surface limitation was not observed in clinical practice and imiquimod was used 'off-label', the costs of treating the entire face would then still be highly in favour of 5-FU. A tube of 5-FU contains 20g of cream, which is usually sufficient for an entire course of treatment.

6.3 Conclusion

The superiority of imiquimod over its active comparators 5-FU and cryotherapy has not been established and at best it can be considered a non-inferior treatment for SK. Accordingly, we have conducted a cost-minimization analysis. This analysis shows that imiquimod is significantly more expensive that the two relevant comparators, 5-FU and cryotherapy.

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Appendix 1

Expert Statistician Review of the "H2H Study", published as *Krawtchenko, et al*, Br J Dermatol 157; Suppl 2: 34-40; 2007.

This clinical trial has flaws in design and analysis, which make it difficult to justify the authors' conclusions. The most serious of these are listed below.

1. Changes in the reported primary outcome variables

The Protocol (Original Issue) and the Clinical Study Report both declare the primary outcome variables to be the levels of 'different oncogenes before and after three different treatments' (p19 and p34 respectively). Genes p53, p16, ras and 5 new epithelial oncogene candidates are mentioned in the Protocol (p3), but results for only p53 and p16 are reported in the Clinical Study Report (p13). Results for the other 6 original primary outcome genes were apparently not available. This absence of *any* information regarding 6 of the 8 primary outcome variables is, of itself, sufficient to question the authors' conclusions.

In the associated paper (British J Dermatology 2007), the 'primary criterion in the evaluation of efficacy was the complete clearance at TOC (test of cure)'. This was one of the secondary endpoints of the original Protocol and of the Study Report, yet it has been reported in the paper as a primary outcome variable.

2. Original number of primary outcome variables and sample size implications

It is highly unusual to have more than 2 or possibly 3 primary outcome variables in a randomised trial. Whenever there is more than one primary outcome variable, issues of multiple comparisons and the appropriate adjustment of p-values and sample size need to be considered.

The authors have included sample size statements in both the Protocol (pp 46-47) and Clinical Study Report (pp 22-23). However these are inadequate. There is no clear statement of the null hypotheses, nor of the precise nature of the alternatives being investigated, nor of the power required.

Furthermore the authors' attempt at incorporating results from multiple genes in their sample size calculations does not appear to be appropriate, although it is impossible to tell just what was intended under the headings 'Statistical Analysis with one candidate (gene?) each' etc. Certainly the *sample size should have increased, not decreased*, as more genes were considered as primary outcomes. This is because each additional gene increased the number of multiple comparisons to be undertaken.

Even with a single primary outcome of the proportion responding positively to just one gene being considered, the study lacks power. Over 30 subjects per treatment are required to achieve 80% power of detecting a difference ≥0.2 in Treatment A vs Treatment B proportions. The exact sample size will depend on the actual proportions being considered. Indeed it may be considerable larger than 30 per group. For example, a sample size of 97 per treatment group is required to achieve 80% power of detecting a significant difference between rates of 0.4 for Treatment A and 0.6 for Treatment B (chi-squared test with a 5% two-sided significance level). The sample size used in this study was just 25 in each of 3 treatment groups.

Since the authors appear to be interested in the efficacy of IMIQ versus *each* of Cryosurgery and 5-FU, their sample size estimates and analysis plan should have reflected this and the necessary adjustment for multiple comparisons.

3. Analysis and Conclusions

The authors often reported significant p-values from tests of homogeneity of distributions *across all three treatment groups*. For example, see the first two sentences of the *Results* in the Summary section of the Br J Dermatology paper (p.34) where p=0.03 for each of two chi-squared tests of 3x2 tables. They then went on to interpret this significant test of heterogeneity as evidence of efficacy of IMIQ versus each of the other treatments. In fact, there was *no* statistically significant difference between IMIQ and 5-FU in the examples above. The p-values for IMIQ vs 5-FU are p=0.2 for initial clinical clearance rate of (22/26) vs (23/24), and p=0.6 for histological clearance rate of (19/26) versus (16/24), and these p-values are unadjusted for multiple comparisons.

In the same *Results* section of the Summary, neither was there was a statistically significant difference between the sustained clearance rates of individually cleared lesions using IMIQ (19/26) or 5-FU (13/24), p=0.16. Indeed the only statistically

significant differences between IMIQ and 5-FU (unadjusted for multiple comparisons) reported in this section were for sustained clearance of the total treatment field and for the *unblinded* consultant assessed cosmetic outcomes. Evidence for the latter would have been far stronger had the assessing consultant been blinded as to the original treatment received.

Appendix 2: DOCUMENTS REVIEWED

iNova Submission

- Submission to the Pharmaceutical Benefits Committee for listing ALDARA (imiquimod) 5% Cream (12 x 250mg sachets) to treat Solar (Actinic) Keratosis to July 2008 PBAC
    - Volume 1: Main submission and Attachments
    - Volume 2: Attachments
    - Volume 3: References

- Supporting Material provided by iNova
    - Correspondence with TGA and ADEC in 2005 about imiquimod (red folder)
    - CD
        - *11th IMIQ PSUR US Final - 2006 to Mar 07*
            - 11th imiquimod Periodic Safety Update Report 27 February 2006 to 26 March 2007, prepared by Graceway Pharmaceuticals
            - Electronic copy – hard copy summary also provided
        - *1487 – IMIQ Final Published Report 16 June 2005*
            - Study to Assess Safety and Efficacy of imiquimod 5% Cream Applied Once Daily 3 Days per Week in 1 or 2 Courses of Treatment of Actinic Keratoses on the Head Sponsor**:** 3M Pharmaceuticals Study Initiation Date**:** 11 December 2003 Study Completion Date**:** 11 November 2004
            - Electronic copy – hard copy summary also provided
        - *Final Report – 1459-IMIQ Phase III study*
            - Study to Assess Safety and Efficacy of imiquimod 5% Cream Applied Once Daily 3 Days per Week in 1 or 2 Cycles for Treatment of Actinic Keratoses on the Head Sponsor**:** 3M Pharmaceuticals Study Number**:** 1459-IMIQ Name of Study Drug: Aldara™ (imiquimod) Cream, 5% Phase: II Study Initiation Date: **1**1 April 2002 Study Completion Date: 26 November 2002
            - Electronic copy – hard copy summary also provided
        - *FINAL SUBMISSION imiquimod PBAC SK 4 March 2008*
            - Final submission by sponsor to PBAC – electronic copy
        - *FINAL Risk Sharing SK incidence & financials (V2) 3 Mar 08*
            - Final submission by sponsor to PBAC – electronic copy
        - *PBAC SK imiquimod Markov Model 5-FU Comparator V2*
            - Final submission by sponsor to PBAC – electronic copy
        - *PBAC SK imiquimod Markov Model Cryotherapy Comparator V2*
            - Final submission by sponsor to PBAC – electronic copy
        - *PBAC SK imiquimod Markov Model Placebo Comparator V2*

        - Final submission by sponsor to PBAC – electronic copy
    - *PBAC SK incidence and financials v2*
        - Final submission by sponsor to PBAC – electronic copy
    - *US Submission – 1473 IMIQ Final Published Report*
        - Study to Assess Safety and Efficacy of imiquimod 5% Cream Applied Once Daily 3 Days per Week in 1 or 2 Courses of Treatment of Actinic Keratoses on the Head Sponsor 3M Pharmaceuticals Study Number 1473-IMIQ Name of Study Drug imiquimod Date Report Issued 07 February 2005
        - Electronic copy – hard copy summary also provided

Documentation involved in PBAC deliberations

- Commentary on iNova submission
    - Commentary prepared by PBAC Secretariat
- Supporting documents – these are
    - iNova letter of application and executive summary
    - Extracts from the August 2005 ADEC meeting
    - Approved Product Information
    - PBS Usage Statistics
- iNova pre-sub committee response
- Restrictions Working Group (RWG) advice
- Economics Sub Committee (ESC) advice
- Drug Utilisation Sub Committee (DUSC) advice
- iNova pre PBAC advice
- Item 6.5 imiquimod (Aldara™) – presentation by iNova at meeting
- Lareb November 2007 – imiquimod and severe skin disorders (tabled by PBAC member at meeting)
- PBAC advice to Sponsor and short minutes

Additional documentation:

- PBAC minutes