

# Sustained Clearance of Superficial Basal Cell Carcinomas Treated With Imiquimod Cream 5%: Results of a Prospective 5-Year Study

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*We conducted a prospective, multicenter, phase 3, open-label study to assess long-term sustained clearance of superficial basal cell carcinomas (sBCCs) treated with imiquimod cream 5%. A biopsy-confirmed tumor (area  $\geq 0.5$  cm<sup>2</sup> and diameter  $\leq 2.0$  cm) was treated once daily 7 times per week for 6 weeks. Participants with initial clinical clearance at 12 weeks posttreatment were followed for 60 months. Tumor recurrence, serious adverse events (AEs), local skin reactions (LSRs), and skin quality assessments (SQAs) were measured. The initial clearance rate was 94.1% (159/169). Estimated sustained clearance (proportion of participants*

*who achieved initial clearance at the 12-week posttreatment visit and remained clinically clear at each time point during the long-term follow-up period; N=157) was 85.4% at 60 months (life-table method: 95% confidence interval [CI], 79.3%-91.6%). The overall estimate of treatment success was 80.4% at 60 months (N=169; 95% CI, 74.4%-86.4%). Of 20 recurrent tumors, 14 (70%) occurred within the first 24 months of follow-up. Local skin reactions and application site reactions, the AEs reported by the most participants, occurred predominantly during the treatment period and resolved posttreatment. Compared to baseline, investigator-assessed SQA scores for the target tumor site improved for skin surface abnormalities and hyperpigmentation, and worsened for hypopigmentation. For low-risk sBCCs, daily application of imiquimod for 6 weeks had high initial and 5-year sustained clearance rates.*

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**N**onmelanoma skin cancers are the most frequently occurring malignancies in the white population, with basal cell carcinomas (BCCs) representing approximately 80% of cases.<sup>1,2</sup> The male age-standardized incidence rates for BCC have been reported to range from 159 to 407, 46 to 128, and 145 to 2055 cases per 100,000 for the United States, Europe, and Australia, respectively; rates reported for females were approximately 10% to 50% lower.<sup>3</sup> Exposure to UV radiation is considered a causative factor for developing BCCs, resulting in formation of pyrimidine dimers

and abnormalities in protein p53 function; disturbing the patched sonic hedgehog pathway; and inducing local and systemic immunosuppression.<sup>4-6</sup> Basal cell carcinomas seldom metastasize or cause death, but they can cause morbidity through local invasion. Therefore, treatment is warranted, preferably eradicating the tumor in a cosmetically acceptable manner.<sup>7-9</sup> Treatment methods vary among countries, but surgical excision and electrodesiccation with curettage generally are the more commonly used treatments. Alternatives include imiquimod, cryotherapy, photodynamic therapy, Mohs micrographic surgery, and radiation therapy, with the latter two typically used in more complicated tumors.<sup>7-9</sup>

Imiquimod is a toll-like receptor 7 agonist that is approved by the US Food and Drug Administration (FDA) in a cream formulation with a 5% concentration for superficial BCC (sBCC) in immunocompetent adults; it also is approved for use in Europe, Canada, and Australia. Toll-like receptors recognize pathogen-associated molecular patterns, resulting in activation of both the innate and acquired immune systems.<sup>10</sup> Topical application of imiquimod results in local induction of IFN- $\alpha$  and other cytokines as well as influx of immune cells such as natural killer cells and T lymphocytes.<sup>11</sup> In vehicle-controlled phase 3 studies of treatment with imiquimod cream 5% for 6 weeks, the composite clearance rates (clinical and histologic) at 12 weeks posttreatment were 75% for 5 times per week dosing and 73% to 77% for 7 times per week dosing.<sup>12,13</sup>

The ultimate goal of sBCC treatment is to have initial clearance of the tumor with an adequate cosmetic outcome as well as no recurrence in the future. Thus long-term follow-up is required to evaluate for sustained tumor clearance. The vehicle-controlled studies of imiquimod for the treatment of BCC included evaluation of histologic clearance, which required excision of the tumor site after treatment.<sup>12,13</sup> As a result, assessment for subsequent recurrences after successful treatment with imiquimod was not possible. This prospective clinical study was specifically designed to evaluate the long-term efficacy of imiquimod cream 5% as treatment of sBCC when applied once daily 7 times per week for 6 weeks. Efficacy was determined by evaluating clinical clearance of a target tumor 12 weeks following treatment and monitoring for recurrences during a 5-year follow-up period. The initial clearance rate and interim 2-year follow-up results from this study have been reported elsewhere<sup>14</sup>; herein we report the final 5-year follow-up results.

## Materials and Methods

The study methods have been previously described.<sup>14</sup> This prospective, multicenter, phase 3, open-label study was conducted in Australia (13 centers) and New Zealand (5 centers). Study protocol, informed consent, and recruitment materials were approved by independent ethics committees as per applicable national and local requirements. Written informed consent was obtained from each participant. Participants were 18 years or older with 1 primary (ie, not previously treated) biopsy-confirmed sBCC located on the limbs, trunk, neck, or head with a minimum area of 0.5 cm<sup>2</sup> and a maximum diameter of 2.0 cm. The study design included 3 phases: a 6-week treatment period, a 12-week posttreatment period, and a 60-month long-term follow-up period. Participants self-applied sufficient imiquimod cream 5% to cover the target tumor once daily 7 times per week for 6 weeks. Initial clearance of the target tumor was clinically assessed by the investigator at 12 weeks posttreatment. Participants who had initial clearance (defined as the proportion of participants with no clinical evidence of sBCC at the target tumor site at the 12-week posttreatment visit) then entered a long-term follow-up period with assessments at months 3, 6, 12, 24, 36, 48, and 60 after the 12-week posttreatment visit. During the long-term follow-up period, participants were evaluated for clinical recurrence of the target tumor, adverse events (AEs) that were serious, defined local skin reactions (LSRs), and skin quality (skin quality assessments [SQAs]). The sustained clearance rate was defined as the proportion of participants who achieved initial clearance at the 12-week posttreatment visit and remained clinically clear at each time point during the long-term follow-up period. A protocol amendment allowed for biopsy of a clinically diagnosed recurrence of the target tumor. In response to a request from the FDA, the planned analyses were amended to include calculation of the sustained clearance rates using the life-table method in addition to the originally planned Kaplan-Meier method, as well as an overall estimate of treatment success, which was calculated by multiplying the initial clearance rate by the sustained clearance rate at each time point during the long-term follow-up period.

## Results

*Study Population and Disposition*—Interim data from the study, including participant demographics, treatment safety, initial clearance, and sustained clearance rates up to 24 months, have been previously reported.<sup>14</sup> The first participant was enrolled on March 27, 2001, and the last participant completed the 60-month long-term follow-up visit on

**Estimated Sustained Clearance Rate and Overall Estimate of Treatment Success for 60-Month Long-term Follow-up Period<sup>a</sup>**

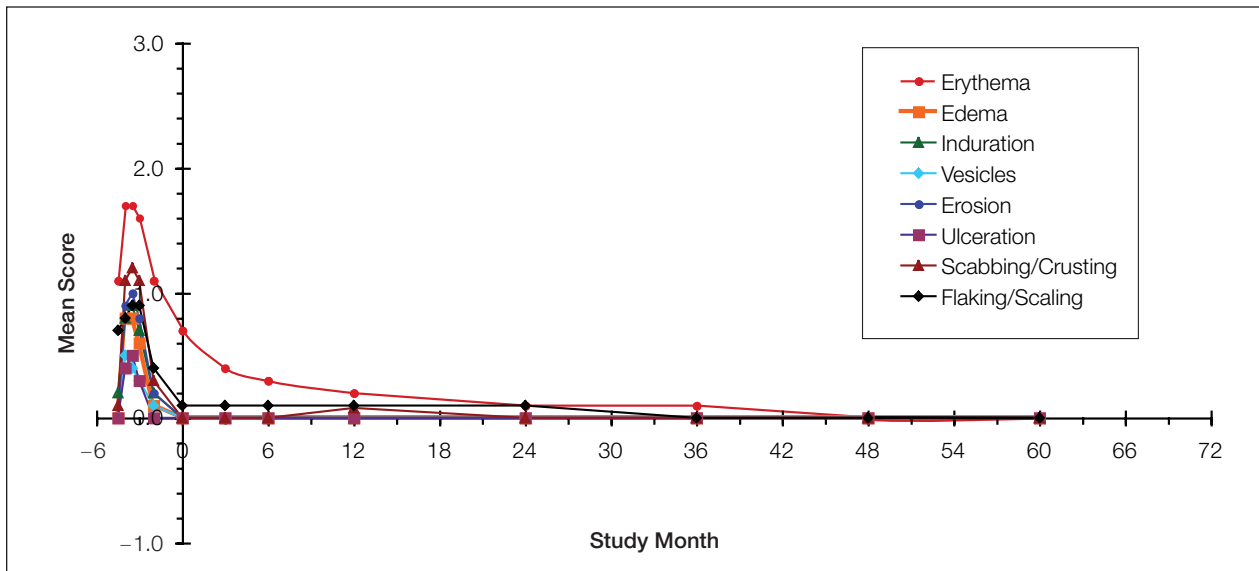
Visit	Participants in Follow-up, n	sBCC Recurrence, n	Discontinued Without sBCC, n	Life Table Sustained Clearance Rate (95% CI) <sup>b</sup> (N=157)	SE of Life Table Rate	Overall Estimate of Treatment Success <sup>c</sup> (N=169)
12 weeks posttreatment	157	NA	NA	1 (1-1)	0	0.941
Month 3	155	1	1	0.994 (0.981-1)	0.0064	0.935
Month 6	152	1	2	0.987 (0.970-1)	0.0090	0.929
Month 12	146	4	2	0.961 (0.930-0.992)	0.1056	0.904
Month 24	134	8	4	0.908 (0.862-0.958)	0.0235	0.854
Month 36	132	1	1	0.901 (0.853-0.949)	0.0243	0.848
Month 48	127	3	2	0.880 (0.828-0.932)	0.0265	0.828
Month 60	119	2	6	0.854 (0.793-0.916)	0.0314	0.804

Abbreviations: sBCC, superficial basal cell carcinoma; CI, confidence interval; SE, standard error; NA, not applicable.

<sup>a</sup>Days in long-term follow-up were calculated from the date of the 12-week posttreatment visit and assigned per the following: month 3 (days 0-119); month 6 (days 120-210); month 12 (days 211-420); month 24 (days 421-784); month 36 (days 785-1148); month 48 (days 1149-1526); month 60 (days > 1526).

<sup>b</sup>Estimate for sustained clearance rate included those participants who achieved initial clearance at the 12-week posttreatment visit and remained clinically clear at each time point during the long-term follow-up period (N=157).

<sup>c</sup>Overall estimate of treatment success was calculated by multiplying the initial clearance rate (94.1%) for all participants enrolled (N=169) by the sustained clearance rate at each time point during the long-term follow-up period.



**Figure 1.** Mean local skin reaction scores (0=none; 1=mild; 2=moderate; 3=severe) during the treatment period, posttreatment period, and long-term follow-up period. The study month displayed is relative to the 12-week posttreatment visit (month 0), as this visit was the beginning of the 60-month follow-up to evaluate sustained clearance. The months displayed before month 0 include the treatment period (6 weeks of treatment and 12 weeks prior to determining initial tumor clearance).

April 20, 2007. Of 241 individuals screened, 169 entered the treatment period, 168 entered the posttreatment period, 157 entered the long-term follow-up period, and 119 completed the study.

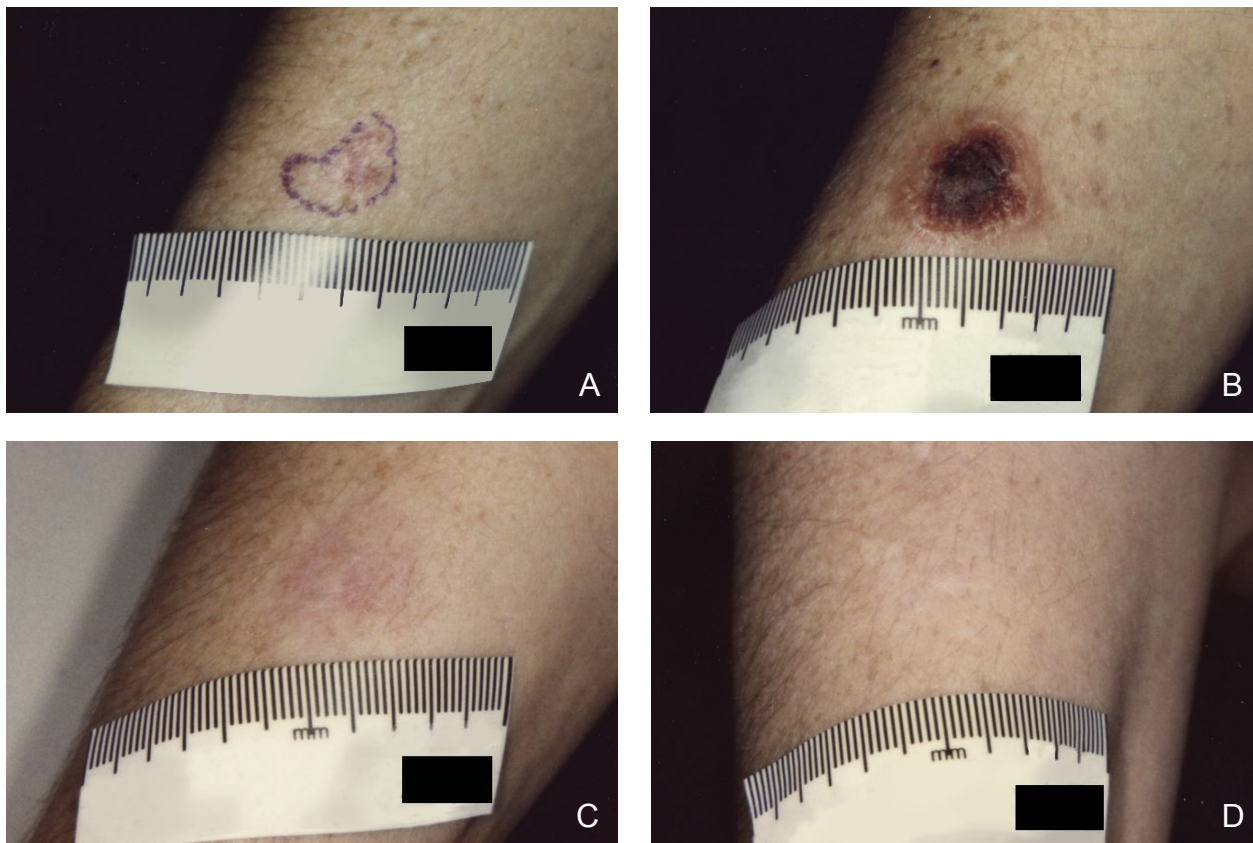
**Efficacy**—By clinical assessment, the initial clearance rate at the 12-week posttreatment visit was 94.1% (159/169).<sup>14</sup> Of 157 participants who entered the long-term follow-up period, 20 had a clinical recurrence of their target sBCC, occurring within the first 24 months for 14 participants. On biopsy, 16 of the clinical recurrences were confirmed as sBCC, 1 was not, and 3 were not biopsied. The estimates for sustained clearance were nearly identical at the follow-up visits by the life-table and Kaplan-Meier methods, except at the 60-month visit when the sustained clearance rate was 85.4% (95% confidence interval [CI], 79.3%-91.6%) and 86.7% (95% CI, 81.2%-92.1%), respectively. For all participants enrolled in the study (N=169), the 60-month overall estimate of treatment success (achieving initial clearance and remaining clear) was 80.4% (95% CI, 74.4%-86.4%)(Table).

**Safety**—During the study, 23 participants reported serious AEs; 5 participants died. All serious AEs were considered by the investigators as being probably not related or not related to the study drug. During the treatment, posttreatment, and long-term follow-up periods, 2, 1, and 8 participants discontinued, respectively, for LSRs or AEs. Application site reactions were the AEs reported by

the most participants. Most LSRs occurred mainly during the treatment period and were almost completely resolved by the 12-week posttreatment visit, except erythema, which was almost completely resolved by the 24-month visit (Figure 1). Compared to baseline, SQA scores for the target tumor at the 60-month visit worsened with respect to hypopigmentation ( $P<.0001$ , Wilcoxon signed rank test, 2-tailed), while scores improved for skin surface abnormalities (rough/dry/scaly) ( $P<.0001$ ) and hyperpigmentation ( $P=.0041$ ). Although 50% of participants (60/120 with SQA data) had an increase in hypopigmentation score compared to baseline, most had an increase of only one grade. Of the participants, 43%, 99%, 83%, 98%, 85%, and 88% had no hypopigmentation, hyperpigmentation, scarring, skin surface abnormalities, mottled/irregular pigmentation, or atrophy at the target site, respectively. Figure 2 depicts the tumor site of a representative participant at initiation, during treatment, at the 12-week posttreatment visit, and at month 60.

### Comment

In this open-label study of low-risk sBCC treated with imiquimod once daily 7 times per week for 6 weeks, the initial clinical clearance rate was 94.1% (intention to treat), which was slightly higher than the composite clearance rates (73%–77%) or histologic clearance rates (79%–88%) reported in



**Figure 2.** Tumor site of a participant at study initiation (A). At 2 weeks of treatment, the investigator assessed local skin reaction scores of mild erythema, edema, erosion, ulceration, and flaking/scaling, and moderate scabbing/crusting and induration (B). At the 12-week posttreatment visit, skin quality assessment scores included mild hypopigmentation and atrophy (C). Skin quality assessment scores at the 60-month visit included mild mottled/irregular pigmentation, mild scarring, and moderate hypopigmentation (D).

vehicle-controlled studies<sup>12,13</sup> but comparable to the clinical clearance rate (90%) in a similar open-label, long-term, follow-up study with application once daily 5 times per week for 6 weeks, the FDA-approved dosing regimen.<sup>15</sup> Three of 10 participants were counted as initial treatment failures because they were lost to follow-up. Among participants who achieved initial clearance, a high proportion remained clear of tumor at the 60-month visit, with estimated sustained clearance rates of 85.4% and 86.7% by life-table and Kaplan-Meier methods, respectively. These estimates were almost identical to those reported in the study with 5 times per week dosing, which were 87% and 85%, respectively.<sup>16</sup> In this study, the majority of recurrences (70%) occurred at or before the 24-month follow-up visit, while in the study with 5 times per week dosing, the majority of recurrences occurred before the 12-month visit.<sup>16</sup> The differences observed may be a consequence of the small number of recurrences and the study visit intervals, but overall the timing is

consistent with prior observations reported with other treatment modalities.<sup>17</sup>

Direct comparative data of imiquimod versus other treatment modalities from prospective clinical studies in the treatment of sBCCs are currently lacking. Comparisons with the published literature are limited in that reported rates frequently reflect retrospective rather than prospective experience, represent the treatment experience of a single institution, involve multiple or different BCC subtypes, and utilize different methodologies for calculating rates. Surgical excision generally is regarded as the standard therapy for BCC. Acknowledging the difference between clinical versus histologic assessments, the initial clearance rates after treatment of sBCC with imiquimod are comparable to conventional surgery. Incomplete excision rates, mostly based on retrospective data, have been reported to range from 5% to 25%; a rate of 11% was reported based on prospective experience with 1241 tumors at a single institution.<sup>18</sup> Some of these

cases of incomplete excision may subsequently clear without further treatment or have no residual tumor detected on reexcision, but reexcision generally is recommended in such cases.<sup>7-9</sup> Some of the variation in incomplete excision rates may reflect the size of predetermined surgical margins utilized; the probability of tumor-positive margins after excision of a BCC up to 10 mm in diameter has been reported to be as high as 30% with a margin of 2 mm, 16% with a margin of 3 mm, and 5% with a margin of 5 mm.<sup>19</sup> The larger surgical defect associated with increased margins may, however, result in less satisfactory cosmetic outcome for the patient.

The 5-year sustained clearance rates after treatment of sBCC with imiquimod appear somewhat lower than those reported for conventional surgery. In a literature review, Rowe et al<sup>17</sup> reported 5-year recurrence rates of 10% by the life-table method. Subsequent to that review, 5-year recurrence rates of 5% and 1.7% for patients treated with surgical excision were reported by Silverman et al<sup>20</sup> and Werlinger et al,<sup>21</sup> respectively. However, it should be noted that the references cited by Rowe et al<sup>17</sup> had recurrence rates ranging from 1.2% to 23.4%, and Silverman et al<sup>20</sup> and Werlinger et al<sup>21</sup> reported retrospective experience from single settings (a skin cancer unit) and a private practice group, respectively.

There are limited data on sBCC recurrences from prospective, randomized, clinical studies directly comparing different therapies. Bassett-Seguín et al<sup>22</sup> reported on the 5-year follow-up of sBCC treated with photodynamic therapy using topical methyl aminolevulinate (up to 3 sessions) versus cryotherapy (up to 2 sessions of 2 freeze-thaw cycles). Initial tumor clearance rates for photodynamic therapy and cryotherapy after the last treatment were 87.7% (100/114) and 88.6% (93/105), respectively, and 5-year recurrence rates were 22% and 20%, respectively.<sup>22</sup> While one cannot simply subtract recurrence rates from 100% to obtain sustained clearance rates (or vice versa), the reported rates are comparable to those observed in our study. Our study also did not include a comparison to surgical excision; a study of recurrences of sBCC after treatment with imiquimod versus surgical excision is ongoing in the United Kingdom.<sup>23</sup>

The study reported herein and the study reported by Gollnick et al<sup>16</sup> represent the experience from multicenter prospective clinical studies. Other factors besides anticipated initial and sustained clearance rates influence the selection of treatment of BCC, including patient health, primary versus recurrent tumor, histologic tumor subtype, tumor size and location, reliability of patient compliance

and follow-up, and even patient concerns regarding cosmetic outcomes. With respect to changes in SQA parameters, the improvement in skin surface abnormalities and slight worsening of hypopigmentation scores could be explained by skin remodeling related in part to tumor resolution but also postinflammatory changes. The “younger” skin with less pigmentation appears hypopigmented relative to the background of more darkly pigmented surrounding skin with prior chronic photodamage. The increase in hypopigmentation score, which is determined by investigator scoring, may not be relevant to the participant; for example, 22.2% of participants had an increase in hypopigmentation score at 12 weeks posttreatment, but no participants reported hypopigmentation as an AE during treatment or at the 12-week posttreatment visit. Overall, at the 60-month follow-up, cosmetic outcome appeared to be very good as reflected by more than 80% of participants without hyperpigmentation, scarring, skin surface abnormalities, mottled/irregular pigmentation, or atrophy at the former target tumor site by investigator assessment.

## Conclusion

While surgical excision remains the standard for the treatment of high-risk BCC, imiquimod represents a reasonable alternative for low-risk tumors with respect to initial clearance and long-term sustained clearance rates as well as cosmetic outcome.

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