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Article accepted on 25/12/2007

**A**cute radiation dermatitis (RD) is a common side effect of radiotherapy in many forms of cancer (e.g. head and neck, breast and low pelvic carcinomas). The intensity of the reaction depends on the radiotherapy fraction schedules, the total dose, the treated skin area, and also individual variations [1]. The appearance of the skin is often described as resembling severe sunburn (erythema) with peeling (dry desquamation). The reaction may become more severe with varying degrees of epidermal loss (moist desquamation) and, very rarely, necrosis [2]. Trans-epidermal water loss (TEWL) escalates with the progression of these symptoms [3]. Although relatively short lived, skin reactions are uncomfortable and itchy, can be painful and are sometimes dose-limiting [4]. Overall, however, there is no gold-standard approach in the prevention and management of radiation dermatitis; practice seems to be varied across countries and between centres in each country. Clinical studies of varying quality have been carried out to assess the efficacy of a range of treatments. These include simply washing with water and mild soap, use of aqueous cream, aloe vera, topical corticosteroids of varying potency, gentian violet, sucralfate cream and hyaluronic acid cream. Reviews of these studies concluded that only the last two preparations reduce the sever-

## A double-blind, randomised, vehicle-controlled clinical study to evaluate the efficacy of MAS065D in limiting the effects of radiation on the skin: interim analysis

Our aim was to assess the efficacy of MAS065D, a non-steroidal water-in-oil cream, in preventing and limiting skin reactions caused by radiation therapy (RT). 40 women treated with conservative breast cancer surgery followed by radiotherapy, were randomised to receive MAS065D (22 pts) or vehicle (18 pts). Radiotherapy was delivered in 20 fractions: 2.25 Gy to the whole breast plus a concomitant boost of 0.25 Gy to the tumour bed up to a total dose of 50 Gy. Evaluations of skin toxicity, erythema, and subjective symptoms were carried out weekly and 3 weeks after treatment completion. A statistically significant difference between vehicle and MAS065D groups was recorded regarding the maximum severity of skin toxicity ( $p < 0.0001$ ), burning within the radiation field ( $p = 0.039$ ) and desquamation ( $p = 0.02$ ), in favour of the latter. We conclude that MAS065D may be considered a safe and effective treatment in the prevention and minimization of skin reactions and associated symptoms.

**Key words:** breast, MAS065D, radiation-induced dermatitis, skin care

ity of skin reactions experienced by patients [5-7]. However, a recent clinical trial compared the use of either aqueous or sucralfate cream with no cream, to establish whether either of these creams could reduce acute skin toxicity during radiotherapy (RT) [8]. It was concluded that neither of the creams prevented radiation skin reactions. Although hydrocortisone cream can provide some symptom relief, steroid creams may mask superficial infection and should be used with caution.

MAS065D (Sinclair Pharmaceuticals Ltd, Godalming, UK) is a non-steroidal medical device registered in the US and EU for the symptomatic treatment of RD. MAS065D is a water-in-oil cream with barrier-forming, hydrating and anti-inflammatory properties that can minimize the side effects of RT on the skin. Here we report the results of a randomised, double-blind, vehicle-controlled clinical study, that evaluated the efficacy of MAS065D in minimizing acute skin reactions and associated symptoms during and after RT for breast cancer.

## Materials and methods

### Study population

Following signature of the informed consent approved by the relevant Ethic Committee (EC), 40 adult women diag-

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nosed with breast cancer, scheduled to receive post-operative radiotherapy, were enrolled in the study. Patients had to observe a washout period of 7 days and refrain from using other topical medications for the entire study period; patients with tumour involvement of the skin were excluded from the study; pregnant and lactating women were also excluded, as were women with known allergies to any of the ingredients present in MAS065D, with a history of substance or alcohol abuse, or any other physiological condition that could, in the investigator's opinion, adversely affect patients' adherence to the protocol.

### Study design

This randomised, double-blind, vehicle-controlled, clinical study was conducted at the European Institute of Oncology (IEO), in Milan. The clinical volume for radiotherapy was to the breast with a field size of at least 12 × 12 cm. RT was delivered daily to the whole breast with tangential fields (2.25 Gy/fraction) and concomitantly to the surgical bed in the same session (0.25 Gy/fraction via variously-angled photon beams) in 20 fractions over 4 weeks, using a 6 MV linear accelerator. Patients were examined at the baseline and at consecutive weekly intervals during RT and 3 weeks after its completion.

### Treatments

Patients were randomised to receive tubes of study medication or vehicle. The randomization was generated by computer and both patients and investigators remained blind to it throughout the study. The randomisation codes were only opened at the time of statistical analysis. Vehicle was an emollient base cream similar in colour and consistency to MAS065D, but without the key ingredients. Patients were instructed to apply the study cream on the irradiated area three times daily, starting on the first day of irradiation and continuing until 3 weeks after completion of RT. The use of other topical medications for the treatment of RD was not permitted during the study.

### Study endpoints

The primary efficacy endpoint was the maximum degree of radiation dermatitis experienced during RT and the follow-up period. Skin reaction was visually assessed and recorded with reference to erythema, desquamation, oedema, moist desquamation and ulceration, using the skin toxicity criteria of the National Cancer Institute (NCI) [9]. Secondary endpoints of the study were the patient's evaluation of itch, pain and burning within the radiation field, assessed with a 0-10 cm visual analogue scale (VAS), where 0 corresponded to "none", and 10 to the "worst severity possible". Patient fatigue, the severity of symptoms from the patient's perspective, and compliance with study medication were also investigated.

Evaluations were carried out at baseline, at weekly intervals for 28 days of RT, and 3 weeks after completion of RT.

### Statistical methods

All study endpoints were summarized appropriately by variable; categorical data by counts and percentages and continuous variables by mean, standard deviation, median, minimum, maximum and number of patients. Baseline characteristics of the two groups of patients were compared by Student's t-test or Chi-square test, as appropriate. Differences in the maximum degree of RD between treatment

arms were assessed using the Wilcoxon (Mann-Whitney) Ranks-sum test. For clinical symptoms, severity of symptoms from the patient's perspective, and compliance with study medication the Wilcoxon (Mann-Whitney) Ranks-sum test or the Chi-square test were applied.

The analysis was performed as an ITT (Intention To Treat) analysis and missing values were substituted by the Last Observation Carried Forward (LOCF) method.

All significant tests were two-sided and performed at the 5% significance level.

## Results

### Study patients

40 Caucasian female patients, with a mean age of 57.26 years, were enrolled in the study between June 2004 and May 2005: 22 (55%) were randomised to MAS065D and 18 (45%) to vehicle. Thirty-five patients (87.5%) completed the study. One patient (4.5%) in the MAS065D and 4 patients (22.2%) in the vehicle group were withdrawn from the study, at the investigator's decision, due to a worsening of the skin reaction, resulting in a 1 point increase on the NCI scale for skin toxicity.

### Baseline characteristics

Baseline characteristics are summarized in *table 1*. The Karnofsky performance score, tobacco use, breast size, breast condition and skin pigment, were recorded at baseline for each patient. Breast size was "medium" in 50% of the patients, and skin colouring was "white" or "light brown" in about 90%. 24 patients (60%) reported never having smoked; of these 11 (27.5%) were randomised to MAS065D, and 13 (35.8%) to the vehicle; 3 patients in each group reported having quit smoking more than 6 months before surgery, while 8 (20%) patients in the MAS065D and 2 (5%) in the vehicle group were smokers. Skin condition at baseline was "well healed" for all but 1 patient, for whom this was not specified. No statistically significant difference was found between the groups as for the aforementioned baseline characteristics.

### Efficacy

#### Primary endpoint – Maximum degree of radiation dermatitis (NCI grading index)

A statistically significant difference ( $p < 0.0001$ ) between the two groups was found for the maximum degree of RD: 20 (91%) patients in the MAS065D group reported a grade 0 or 1 (faint erythema or dry desquamation) on the NCI skin toxicity scale, compared with 16 (89%) patients treated with vehicle, who reported a grade higher or equal to 2 (moderate to brisk erythema). The only 2 cases that reached a grade 3 were recorded in the vehicle group, during the follow-up visit. The most significant differences between the two groups were recorded after three weeks of treatment (*table 2*).

#### Secondary endpoints – burning, itching, pain within radiation field (VAS 0-10 cm)

A statistically significant difference ( $p = 0.039$ ) was registered for burning within the radiation field, in favour of MAS065D. The mean value ( $\pm$  SD) registered for the increase in burning sensation was 1.27 ( $\pm$  2.14) in patients treated with vehicle, compared with 0.13 ( $\pm$  1.32) in pa-

**Table 1.** Patients' characteristics

	MAS065D	Vehicle	MAS065D vs vehicle p-value*
<b>N of patients</b>	22	18	
<b>Ethnic origin</b>			
Caucasian	22 (100%)	18 (100%)	-
<b>Age</b>			
Mean	59	55	0.28
Range	43.5-76.9	33.1-75.4	
<b>Karnofsky performance Score</b>			
100	22 (100%)	18 (100%)	-
<b>Skin colouring</b>			
White	7 (31.8%)	11 (61.1%)	0.164
Light brown	12 (54.5%)	5 (27.7%)	
Brown	3 (13.6%)	2 (11.1%)	
<b>Affected breast</b>			
Right	11 (50.0%)	11 (61.1%)	0.537
Left	11 (50.0%)	7 (38.8%)	
<b>Condition of the breast</b>			
Well healed	21 (95.4%)	18 (100%)	1.00
Not specified	1 (4.5%)	-	
<b>Tobacco use</b>			
Never used	11 (50%)	13 (72.2%)	0.182
Yes quit > 6 months	3 (13.6%)	3 (16.6%)	
Yes currently	8 (36.3%)	2 (11.1%)	
<b>Breast size</b>			
Small	7 (31.8%)	5 (27.7%)	0.151
Medium	13 (59.0%)	7 (38.8%)	
Large	2 (9.0%)	6 (33.3%)	

\* *t*-test or chi-square test or Fisher exact test, as appropriate.

tients treated with MAS065D. Although better results were evident in the MAS065D group with respect to pain [ $0.4 (\pm 1.76)$  vs  $0.9 (\pm 1.86)$ ] and itch [ $0.8 (\pm 1.99)$  vs  $1.05 (\pm 2.01)$ ], no statistically significant differences between the two groups were recorded for these symptoms (*table 3*; median = 0, for all the parameters).

**Secondary endpoints – fatigue, severity of symptoms from the patient's perspective and compliance with study medication**  
As regards the symptoms assessed by the patients, a significant difference between treatments was observed for desquamation during the fourth-week visit of the study (*figure 1*): only 13.5% (3 of 22) of patients reported mild to moderate desquamation, compared with 50% (9 of 18) in

**Table 2.** Maximum degree of radiation dermatitis (NCI grading index). MAS065D vs vehicle – Wilcoxon Rank-Sums test:  $p < 0.0001$ 

NCI grade	MAS065D	Vehicle
0	1 (4.5%)	-
1	19 (86.3%)	2 (11.1%)
2	2 (9.0%)	14 (77.7%)
3	-	2 (11.1%)
≥ 4	-	-

the vehicle group. (Chi square test  $p = 0.02$ ). By contrast, no statistically significant difference between the two arms was observed for dryness, itching, pain or difficulties in wearing underclothing.

Both study creams were well tolerated, for their cosmetic acceptability, with no statistical differences between groups.

### Safety

No adverse events were observed or reported in either group.

## Discussion

Despite the common occurrence of radiation-induced skin toxicity, there have been very few trials that have formally evaluated the usefulness of topical therapy and, to date, there is no universally accepted standard approach. It would therefore be of interest to investigate the role of new compounds that could reduce the incidence and severity of acute skin reactions caused by ionising radiation, thus improving patients' quality of life and compliance to treatment constraints.

Although limited by the small number of patients, this study registered a statistically significant difference between vehicle and MAS065D groups regarding the maximum severity of skin toxicity ( $p < 0.0001$ ), symptoms of burning within the radiation field ( $p = 0.039$ ) and desquamation ( $p = 0.02$ ). Baseline characteristics were well balanced, although a higher proportion of women with fair skin was allocated to the vehicle group. Although the relationship between skin type and the response to exposure to ultraviolet light is well known, the potential prognostic factor of skin phenotype for radiation-induced dermatitis is uncertain and to date there are no studies that show a systematic correlation. Other factors presumed to have an impact on the severity of radiation-induced dermatitis, such as breast size and smoking, failed to reach statistical significance in our study, probably due to the small cohort of patients.

This interim analysis showed that MAS065D can have a beneficial role in the management of patients undergoing RT for breast cancer. In this study, the topical application of MAS065D from the first day of RT until 2 weeks after its completion was associated with a significant reduction in the severity of erythema ( $p < 0.0001$ ) and a significant reduction in burning sensation ( $p = 0.039$ ), two conspicuous and widely-encountered symptoms of radiation dermatitis. No adverse events were observed or reported and none of the patients randomized to MAS065D was required to stop RT as a consequence of the effects of radiation dermatitis. No significant differences were observed concerning pain, itching and dryness. Notwithstanding this, patients expressed an overall appreciative opinion of the effectiveness of MAS065D.

MAS065D is a water-in-oil formulation containing hyaluronic acid (HA), shea butter, glycyrrhetic acid (GrA), *Vitis vinifera* and telmesteine, which are believed to contribute, synergistically and independently, to the minimization of radiation induced skin reactions. HA is a major component of the extracellular matrix of the skin. It has demonstrated remarkable hygroscopic properties which are relevant to wound healing [10]. HA is also the most pow-

**Table 3.** Degree of pain, itching and burning in the irradiated territory. VAS - 0 (no symptom) to 10 (worst possible symptom)

	Treatment	Visit/Changes	Mean VAS score	Std Dev
<b>PAIN</b> (P = 0.43)	<b>MAS065D</b> (N = 22)	Baseline	0.59	1.368
		Week 4	1.00	1.511
		Changes vs baseline	0.40	1.763
	<b>Vehicle</b> (n = 18)	Baseline	0.55	1.199
		Week 4	1.50	2.255
		Changes vs baseline	0.94	1.862
<b>ITCHING</b> (P = 0.96)	<b>MAS065D</b> (N = 22)	Baseline	0.27	0.935
		Week 4	1.04	1.703
		Changes vs baseline	0.77	1.998
	<b>Vehicle</b> (n = 18)	Baseline	0.16	0.514
		Week 4	1.22	2.129
		Changes vs baseline	1.05	2.013
<b>BURNING</b> (p = 0.039)	<b>MAS065D</b> (N = 22)	Baseline	0.22	0.751
		Week 4	0.36	1.135
		Changes vs baseline	0.13	1.320
	<b>Vehicle</b> (n = 18)	Baseline	0	0
		Week 4	1.27	2.136
		Changes vs baseline	1.27	2.136

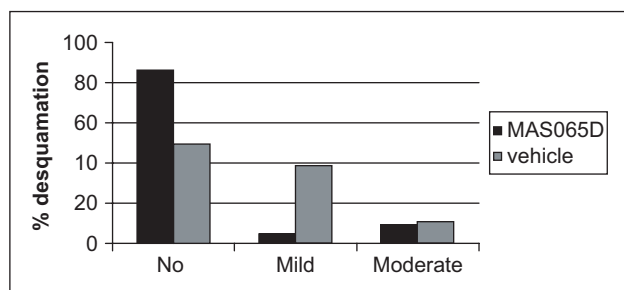
erful moisturizing agent known, being able to attract and retain 1,000 times its weight in water. Shea butter is an excellent source of saturated fatty acids, mono-unsaturated fatty acids and linoleic acid and resembles sebum in its composition. It is these fatty acids that help restore skin barrier function, by supporting the elasticity and turgidity of the skin [11]. GrA has demonstrated the ability to inhibit 11 $\beta$ -hydroxysteroid dehydrogenase, an enzyme responsible for metabolizing hydrocortisone. Inhibition of this enzyme results in an accumulation of endogenous hydrocortisone, a natural steroid with anti-inflammatory properties [12, 13]. The anti-inflammatory action of GrA is reinforced by the presence of bisabolol (chamomile extract) [14]. *Vitis vinifera* extract in the formulation exerts a natural antioxidant activity, a property that may be very helpful against radiation-induced skin damage [15, 16]. MAS065D also contains telmesteine, which has shown anti-elastase and anti-collagenase activity *in vitro* [17]. Given the results of this interim analysis, and those of a recently published randomised, double-blind pilot clinical study [18], MAS065D can be regarded as one of the available treat-

ment regimens effective in the prevention of radiation skin reactions and the promotion of symptomatic relief. ■

**Acknowledgments.** Sponsor: Sinclair Pharmaceuticals Ltd, Godalming Business Centre, Woolsack way, Godalming, GU7 1XW Surrey, UK. We thank Dr. Antonio Colantoni for the statistical analysis of data. Conflicts of interest: none declared.

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**Figure 1.** Effect of MAS065D on desquamation. At the fourth-week visit a significant difference between MAS065D and vehicle was recorded for desquamation: only 13.5% (3 of 22) of patients reported mild to moderate desquamation, compared with 50% (9 of 18) in the vehicle group (Chi square test  $p = 0.02$ ).

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