Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Bosentan

Proprietary Product Name: Tracleer

Sponsor: Actelion Pharmaceuticals Australia Pty

September 2012

TGA Health Safety Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission ____ 4

Submission details ____ 4

Product background ____ 4

Regulatory Status ____ 5

II. Quality findings ____ 5

III. Nonclinical findings ____ 5

IV. Clinical findings ____ 6

Introduction ____ 6

Pharmacokinetics/Pharmacodynamics ____ 6

Efficacy ____ 6

Safety ____ 19

Clinical summary and conclusions ____ 23

V. Pharmacovigilance findings ____ 24

Risk management plan ____ 24

VI. Overall conclusion and risk/benefit assessment ____ 26

Quality ____ 27

Nonclinical ____ 27

Clinical ____ 27

Risk management plan ____ 28

Risk-benefit analysis ____ 29

Outcome ____ 34

I. Introduction to product submission

Submission details

Type of Submission	Major Variation (New Indication)
Decision:	Rejected
Date of Decision:	21 December 2011
Active ingredient(s):	Bosentan
Product Name(s):	Tracleer
Sponsor's Name and Address:	Actelion Pharmaceuticals Australia, 13b Narabang Way, Belrose NSW 2085
Dose form(s):	Tablets
Strength(s):	62.5 mg and 125 mg
Container(s):	High density polyethylene bottle enclosed in outer carton.
Pack size(s):	60's
Approved Therapeutic use:	Not applicable
Route(s) of administration:	Oral (PO)
Dosage:	See *Product background* below.
ARTG Number (s)	Not applicable

Product background

Bosentan is an antagonist of endothelin receptors (a non-selective endothelin-1A and 1B antagonist) and was originally developed to treat the vasculopathy associated with pulmonary arterial hypertension (PAH). The histopathological changes of obliterative vasculopathy observed in pulmonary arteries of patients with PAH have also been found in digital arteries. This suggests that therapies which target the changes observed in the pulmonary vessels may also improve digital vascular function. Clinical observations by investigators during trials investigating bosentan for the treatment of PAH suggested improvement in the digital ulcers of patients with scleroderma (systemic sclerosis).

Digital ulcer disease occurs in approximately 35 – 60% of patients with systemic sclerosis. Endothelin-1, a protein produced by endothelial cells, is a potent vasoconstrictor which is thought to play a role in its pathogenesis.

The drug is currently registered for the treatment of pulmonary arterial hypertension (PAH) due to various causes, including PAH associated with systemic sclerosis[1].

This AusPAR describes the application for an extension of indications to:

> *"The reduction in the number of new digital ulcers in patients with systemic sclerosis with active digital ulcer disease."*

Digital ulcers are a complication of scleroderma which can seriously impact the quality of life of patients with this condition. The ulcers are slow to heal and can be complicated by infection, including osteomyelitis. The ulcers are painful and can lead to chronic analgesic use. An agent which can effectively target this complication of scleroderma would be a useful adjunct to therapy.

The proposed dose for the treatment of digital ulcers is 62.5 mg twice daily for an initial four week period followed by 125 mg twice daily thereafter. This is the same dosage regimen approved for use in PAH. No new dosage forms or strengths are proposed.

Bosentan has been designated as an orphan drug in Australia (27 August 2010) for the digital ulcer indication.

Regulatory status

Bosentan was registered with the TGA in 2002. Extension of indication applications have been made in 2005, 2006 and 2007 to increase the number of types of pulmonary hypertension included and the grades of cardiac impairment included in the indication.

Bosentan is registered in the USA, European Union (EU), Canada and numerous other countries for the treatment of PAH,.

An indication for the treatment of digital ulcers is approved in the EU (7 June 2007) and Switzerland (6 July 2007). The digital ulcer indication registered in the EU and some other countries is "reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease" in an adult population.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

[1] Tracleer is indicated for the treatment of:
- Idiopathic pulmonary arterial hypertension
- Familial pulmonary arterial hypertension
- Pulmonary arterial hypertension associated with scleroderma
- Pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology.
- In patients with WHO function class II, III or IV symptoms.

IV. Clinical findings

Introduction

The clinical submission consisted of the final study reports of two Phase III studies AC-052-401 (RAPIDS-1) and AC-052-331 (RAPIDS-2).

The trials appear to have been conducted in accordance with good clinical practice.

Pharmacokinetics/Pharmacodynamics

There were no new data submitted.

Efficacy

The submission includes two pivotal efficacy trials, designated RAPIDS-1 and RAPIDS-2

Pivotal efficacy studies

RAPIDS-1

Study design, objectives, locations and dates

RAPIDS-1 comprised two phases. The first was a 16-week multi-centre, double blind, randomised placebo controlled study. This was followed by an optional 12 week open label extension phase which patients could enter if the investigator felt it could be of benefit.

Patients were randomised 2:1 bosentan:placebo. 122 patients were enrolled, with 79 being treated with bosentan and 43 as placebo.

The primary objective was to investigate the effect of bosentan therapy on the number of new ulcers appearing during the 16-week randomised phase.

The secondary objective was to evaluate the rate of healing in patients with existing ulcers and the quality of life of patients.

The trial was conducted between October 2001 and September 2002 in centres in Canada, Europe, UK and the USA.

Inclusion and exclusion criteria

Eligible patients were adults with Reynaud's syndrome and systemic sclerosis who had a history of digital ischemic ulcers within the year preceding participation in RAPIDS-1. Patients could be included with existing ulcers but patients with ulcers due to extrusion of calcification, as can occur with the CREST syndrome, were not included.

Significant exclusion criteria included

- severe organ failure,
- treatment with parenteral prostanoids within 3 months prior to the trial,
- use of systemic antibiotics for infection of digital ulcers within 2 weeks prior to the trial
- treatment with glibenclamide, cyclosporine A and/or tacrolimus at enrolment or where such treatment was expected during the trial.

Note that co-administration of glibenclamide or cyclosporine A with bosentan is contraindicated. Tacrolimus and bosentan are to be co-administered with caution due to potential pharmacokinetic interaction.

Study treatments

Patients on active treatment during the double blind phase received bosentan 62.5 mg twice a day (bid) for 4 weeks followed by bosentan 125mg bid for the remaining 12 weeks.

Patient's usual treatment for digital ulcers (Calcium Channel Blockers, ACE inhibitors, Angiotensin II receptor antagonists, antiplatelet therapy or vasodilators) was to have remained constant for 1 month before the study commenced. In the event that digital ulcers worsened patients continued bosentan but were allowed to add medications *other than parenteral prostanoids.*

During the open label-phase patients were recommenced on 62.5mg bid and titrated to 125mg bid after 4 weeks for the remaining period of the open label phase.

Efficacy variables and outcomes

The main efficacy variables were:

- Number of digital ulcers: The total number of ulcers was counted on each hand distal to the proximal inter-phalangeal joint. The size of each lesion was recorded.
- Healing of ulcers: Partial healing was defined as the presence of <50% of the total digital ulcer surface area present at baseline. Complete healing was defined as visual resolution of the ulcer.

These were measured at baseline and the Weeks 4, 8, 12 and16 visits of the randomised phase of the trial. Measurements were continued in patients who entered the open label phase at baseline and visits on Weeks 4, 8 and 12.

The primary efficacy outcome was the number of ulcers present at each assessment visit.

Other efficacy outcomes included:

- The Scleroderma Health Assessment Questionnaire (SHAQ) was completed at the end of Week 16 of the randomised phase or at discontinuation from the trial. Patients were instructed to qualitatively rate their capacity to perform a function (dressing, grooming etc) over the previous 7 days on a 4-point scale from 0, "without any difficulty", to 3, "unable to do". Patients are also asked whether they use aids or devices to help with particular activities or if they usually required assistance from another person for certain activities. The available answers can be averaged to form a disability index (DI), which is a continuous variable between 0 (no disability) and 3 (severe disability).
- Six Visual Analog Scale questions which form part of the SHAQ were completed at each visit. These assess the degree of pain and limitation from digital ulcers and are described in Table 1.

Table 1. Six Visual Analog Scale questions

- Pain scale: "How much pain have you had because of your Raynaud's and finger ulcers in the past week?"
- Vascular scale: "In the past week, how much has your Raynaud's interfered with your daily activities?"
- Ulcer scale: "In the past week, how much have your finger ulcers interfered with your daily activities?"
- GI scale: "In the past week, how much have your intestinal problems interfered with your daily activities?"
- Lung scale: "In the past week, how much have your breathing problems interfered with your daily activities?"
- Scleroderma disease scale: "Overall, considering how much pain and limitations in your daily life and other changes in your body and life, how severe would you rate your disease today?"

Six Visual Analog Scale Questions from SHAQ

Patients were asked to score each symptom between 0 and 100 marked on a 15 cm continuous visual analog scale (VAS) where 0 was none and 100 was the most severe. The VAS was read by the investigator to the nearest 0.2 cm from the end of the VAS to the point indicated by the patient, converting each score into a length in centimetres from 0 (none) to 15 (most severe).

Randomisation and blinding methods

Patients were screened no longer than 2 weeks prior to randomisation, at which consent was obtained and baseline data collected. Eligible patients were randomised at the second visit in a 2:1 ratio between bosentan and placebo arms. Treatment was dispensed in identical containers and with placebo of the same size, colour and shape as active treatment.

Patients were evenly recruited among the participating centres.

Patients who completed the 16 week double blind phase of the trial could enter the 12 week open label phase provided the investigator believer treatment could be beneficial.

Analysis populations

All 122 patients enrolled in the study were included in the safety analysis.

The Intent-to-Treat (ITT) population for the primary endpoint comprised 121 patients, excluding one bosentan treated patient who had no post-baseline treatments due to discontinuing.

The ITT population for the purposes of ulcer healing consisted of 52 bosentan and 24 placebo treated patients respectively who had at least one digital ulcer at baseline.

Statistical methods

The trial has relatively small numbers of patients and involves discrete data such as the number of ulcers at a particular time-point.

The sample size was planned for a 2:1 randomisation of at least 60 bosentan treated and 30 placebo treated patients. This would achieve a power of 80% to detect a difference in the number of ulcers at p=0.05 assuming that at least 20% of bosentan-treated and 50% of placebo-treated patients developed new ulcers. The trial enrolled more than the minimum number of required subjects and about 40% of patients developed new ulcers in each treatment arm, and so the trial was adequately powered.

All efficacy parameters were all tested using the ITT population. The initial test of significance of difference between active and placebo treatment was performed using a Mann-Whitney-Wilcoxon (MWW) rank sum test.

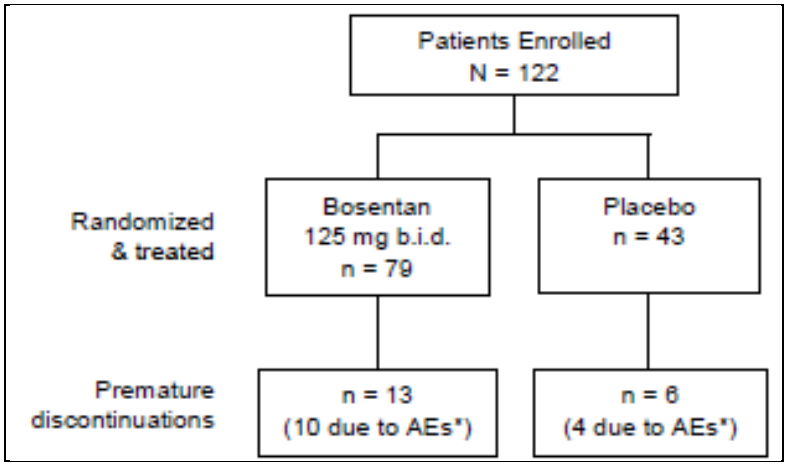
Post hoc it was concluded that the MWW test was not appropriate and data was analysed using a permutation test. This is an exact non-parametric test in which the difference between treatments is calculated for every possible combination of the patients in the trial in groups the same size as the treatment arms. If the observed difference occurs in a high proportion of these combinations then there is a high probability that the treatment and placebo groups are part of the same population and the difference is not significant. If the observed difference occurs rarely (<1% for p=0.01 for example) then the two arms are different populations and the test is significant.

Participant flow

Double blind phase

The following figure describes the disposition of the patients during the double blind phase.

Figure 1. Disposition of patients during the double blind phase of the study.

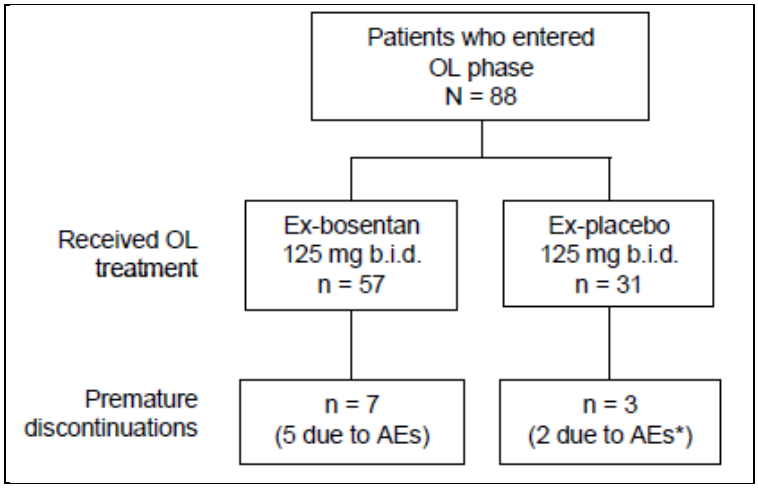


Some 122 patients were enrolled and randomised. There was no apparent imbalance in discontinuations between the placebo and treatment arms throughout the trial.

Open label phase

The following figure describes the disposition of the patients during the open label phase.

Figure 2. Disposition of patients during the open label phase of the study.



A fairly high proportion of patients continued into the open label (OL) phase of the trial.

Major protocol violations/deviations

There were no major protocol violations.

Baseline data

The baseline characteristics of the patients were balanced for age, sex, weight and trial location.

With regard to the primary endpoint the baseline characteristics are described in Table 2.

Table 2. Baseline characteristics

Number of digital ulcers at baseline	Bosentan arm (n=79)	Placebo arm (n=43)
0	26	19
At least 1	53	24
Mean number of ulcers at baseline	2.2	1.9

Baseline characteristics of ITT population including patients with no ulcer at baseline

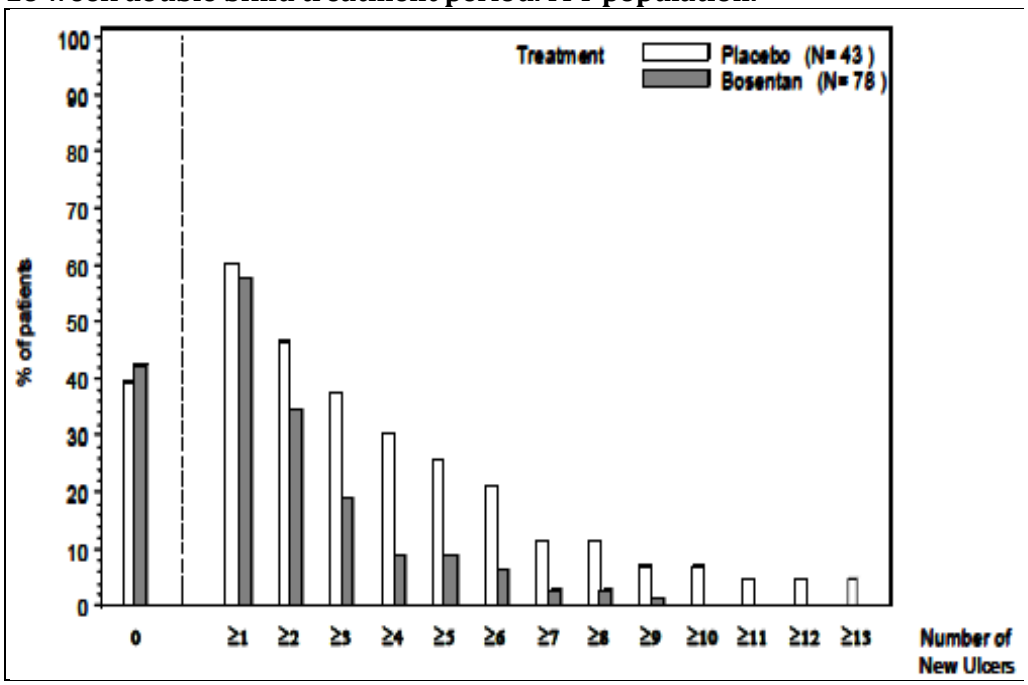
Among patients with ulcers at baseline, the mean total surface area of the ulcers was 93.8mm^2 for the bosentan arm and 90.9mm^2 for the placebo arm.

Results for the primary efficacy outcome

Placebo controlled phase. Numbers of new ulcers

In ITT population the mean number of digital ulcers which occurred during the double blind phase was lower in bosentan treated patients (1.4) than in those on placebo (2.7). This was not statistically significant using the Mann-Whitney U-test originally intended, but was significant using the permutation and Poisson regression tests. The evaluator notes that these latter tests are reasonable to establish significance but there is no estimate of confidence intervals (those in table 9, section 10 of this report are from the U-test). What is established by this test is that the difference in the mean effects of the active and placebo treatments is greater than zero.

Figure 3. Proportion of patients with a given number of new digital ulcers during the 16 week double blind treatment period. ITT population.



Over the 16 weeks, 60.5% of bosentan treated and 57.7% of the placebo treated patients experienced new ulcers and this difference was not statistically significant at p=0.05. The

difference in the proportion of patients who developed new ulcers was greater between bosentan and placebo when only those with an ulcer at baseline were considered (83.3% on placebo versus 67.3% on bosentan, respectively) but also not statistically significant at p=0.05.

The time to the onset of the first and second new ulcer was not significantly different between bosentan and placebo (p=0.56 and 0.07, respectively). The time to onset of the third and fourth new ulcers was statistically significantly longer in bosentan treated patients than placebo (p=0.0431 and p<0.01, respectively).

This pattern was similar in the sub-population of 52 bosentan-treated and 24 placebo-treated, patients who had ulcers at baseline. The time to onset of the first, second and third new ulcers is not significant, while the time to onset of the 4th ulcer was significant (p=0.0133).

Healing of ulcers

There was no significant difference in the proportion of patients who experienced complete ulcer healing on bosentan (20.8%) or placebo (19.2%). Similarly there was no significant difference in the rate of partial ulcer healing, defined by <50% of the ulcer surface area present at baseline, in the bosentan (57.7%) or placebo (58.3%) groups.

Results for other efficacy outcomes

The following table (Table 3) summarises the SHAQ results.

Table 3. Scleroderma Health Assessment Questionnaire (SHAQ)

VAS variable	Change from Difference from baseline at Week 16 (Bosentan)/cm	Change from Difference from baseline at Week 16 (placebo)/cm	p-value of Difference between Treatments/cm
Pain	-1.2	-1.6	0.52
Raynauds interference with daily activity	-1.2	-1.2	0.61
Ulcers interference with daily activity	-0.7	-0.9	0.39
Gastro-intestinal disease	0.6	0.5	0.95
Lung Disease	-0.2	-0.1	0.92
Severity of disease	-0.1	-0.9	0.23

These VAS scores are measured on a 15 cm tape measured to the nearest 0.2cm.

Table 4. Summary of change from baseline to Week 16 in selected SHAQ components assessing hand functionality. ITT population.

SHAQ component	Placebo (mean ± SD) n = 41	Bosentan (mean ± SD) n = 76	p-value (Mann-Whitney U-test)
Dressing and grooming	0.20 ± 0.81	-0.09 ± 0.73	0.0176
Hygiene	0.27 ± 0.92	-0.09 ± 0.59	0.0263
Grip	0.15 ± 0.76	-0.09 ± 0.68	0.1555
Hand functionality*	0.20 ± 0.58	-0.09 ± 0.47	0.0041

* Hand functionality is a composite of the three components (dressing, hygiene, and grip).

There were reductions (improvements) in hand-function elements of the SHAQ in bosentan treated and worsening in hand-function elements in the placebo treated groups. The study investigators have noted that this suggests hand function was improved with bosentan treatment, presumably as a result of a decrease in ulcer burden. The evaluator notes that this is plausible but speculative. The majority of patients in the ITT population experienced 2 or fewer new ulcers with no difference between placebo or bosentan treatment.

It is notable that there was no significant difference in pain from baseline. Therefore any putative increase in hand function does not appear to arise from an improvement in this clinically important symptom.

The sponsor has not indicated a minimal clinically significant difference for particular components of the SHAQ. However, the evaluator feels that it is not possible to interpret a single significant result among several insignificantly different tests of overall disability.

RAPIDS-2

Study design, objectives, locations and dates

RAPIDS-2 was a randomised, placebo controlled trial of bosentan over 24 weeks to 36 weeks. There was an eight week follow up period after the last dose of study medication.

Patients who completed the 24-36 week double blind phase and 8-week followup and who still had digital ulcers could enter an open label trial, AC-052-333. An interim report of AC-052-333 has been presented in this application. Efficacy has not been evaluated in the interim report and it is discussed in the safety evaluation. The duration of open label treatment had not been set at the time of the interim report.

Patients in RAPIDS-2 were randomised 1:1 to either active or placebo treatment.

The primary objective of the study was to evaluate the effect of bosentan on the healing of existing digital ulcers and incidence of new digital ulcers in patients with scleroderma.

A secondary objective was to assess the effect of bosentan on hand-function and pain from digital ulcers.

RAPIDS-2 was undertaken in a number of centres in the US, Canada, UK and Europe.

Inclusion and exclusion criteria

The inclusion criteria were similar to RAPIDS-1 except that patients were required to have *at least one* digital ulcer at baseline that was at least one week old at randomisation but no more than 3 months old at randomisation.

One of the ulcers present at baseline had to qualify as a Cardinal Ulcer (CU), which was at least 2 mm in size, de-epithelialised and not-infected or associated with calcinosis. The CU was required to be on the volar aspect of the finger, not in a crease, and be located distal to the proximal interphalangeal joint. If several ulcers were present which could qualify as a

CU, then the investigator would chose either the largest ulcer or the one which bothered the patient the most.

An exclusion criteria in RAPID-2 not specified in RAPIDS-1 was severe Pulmonary Arterial Hypertension Grades III and IV.

Study treatments

Patients were commenced on placebo or bosentan 62.5 mg bid. The active treatment arm was up-titrated to bosentan 125 mg bid from Week 4. Patients could, however, be down-titrated to 62.5 mg bid during the trial at any time for reasons of intolerability and potentially returned to 125 mg bid thereafter.

Patients whose CU healed at Week 16 or later were treated for another 12 weeks (maximum of 36 weeks) to assess whether the primary outcome of maintaining 12 weeks of healing was achieved.

Efficacy variables and outcomes

The main efficacy variables were:

- The total number of new digital ulcers in each patient.
- Healing of the CU: Complete healing was defined as re-epithelialisation of the ulcer regardless of residual pain. The status of each ulcer was rated as 'U' – unhealed, 'H' – healed, or 'I'- intermediate healing. Scabbed ulcers were rated as 'I' as epithelialisation could not be assessed with a scab present.

The primary efficacy outcomes were:

- The number of new digital ulcers in each patient over 24 weeks of treatment.
- The time to complete healing of the CU in patients in whom CU healing was maintained for at least 12 weeks.

Other efficacy outcomes included:

- The proportion of patients without a new digital ulcer over 24 weeks.
- The proportion of patients who did not develop any new digital ulcers after the first 4 weeks of treatment up to Week 24.
- The proportion of patients with complete healing of all digital ulcers at Week 24.
- Change from baseline to Week 24 in the total number of digital ulcers.
- Change from baseline to Weeks 12 and 24 in hand pain assessed by VAS on a sore of 1-100 measured to the nearest 0.2 cm on a 15 cm strip and recorded as a score from 0 to 15.
- Change from baseline to Weeks 12 and 24 in hand disability (dressing/grooming/grip and hygiene components of the SHAQ.

(These are described in more detail under the description of the RAPIDS-1 trial)

With the exception of the VAS and SHAQ assessed at Weeks 12 and 24, efficacy endpoints were measured at Weeks 4, 8, 12, 16, 20, 24, 38, 32 and 36.

Randomisation and blinding methods

Patients were screened no longer than 2 weeks prior to randomisation, at which time consent was obtained and baseline data collected. Eligible patients were randomised at the second visit in a 1:1 ratio between bosentan and placebo arms. Treatment was dispensed in identical containers and with placebo of the same size, colour and shape as active treatment.

Patients were evenly recruited among the participating centres.

Analysis populations

There were four analysis populations:

1. **All randomised population**: included all randomised patients regardless of whether they received any treatment (n=90 placebo, n=98 bosentan)
2. **All treated population**: included all randomised patients who had received at least one dose of treatment (n=90 placebo, n=98 bosentan)
3. **Safety population**: included all randomised and treated patients who had at least one baseline safety assessment during the study treatment period (n=90 placebo, n=96 bosentan)
4. **Per-protocol set**: All randomised and treated patients compliant with the protocol (n=87 placebo, n=94 bosentan)

Statistical methods

The analyses presented were all performed on the "All-treated" sets . This was not a true ITT population but did not differ significantly from the All Randomised Population.

Significance was tested using Poisson, Wilcoxan Rank-Sum test and a Permutation Test (Pitman Permutation Test).

The sample size was calculated to detect a clinically meaningful difference in the monthly healing rate of the CU of 20% in the placebo treatment arm and 33% in the bosentan treatment arm. The assignment of 90 patients to each treatment arm gives a power of 93% to detect this difference at a p=0.05 level of significance.

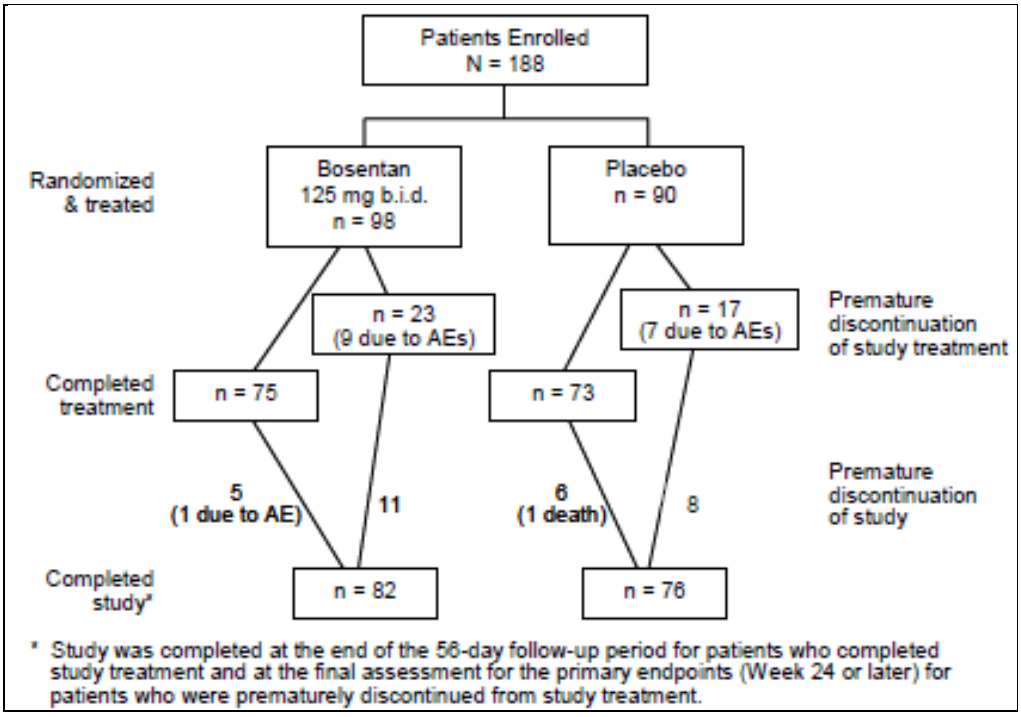
The sample calculation for the number of new ulcers was conducted on the basis of using a permutation test to detect a difference in the number of new ulcers of 40% from 5.4 new ulcers in the placebo group (based on RAPIDS-1) to 3.24 in the bosentan group. It was estimated that the permutation test would have a 93% power to detect this difference at p=0.05.

Participant flow

RAPIDS-2 double blind phase

The disposition of patients in RAPIDS-2 double blind phase is described in Figure 4.

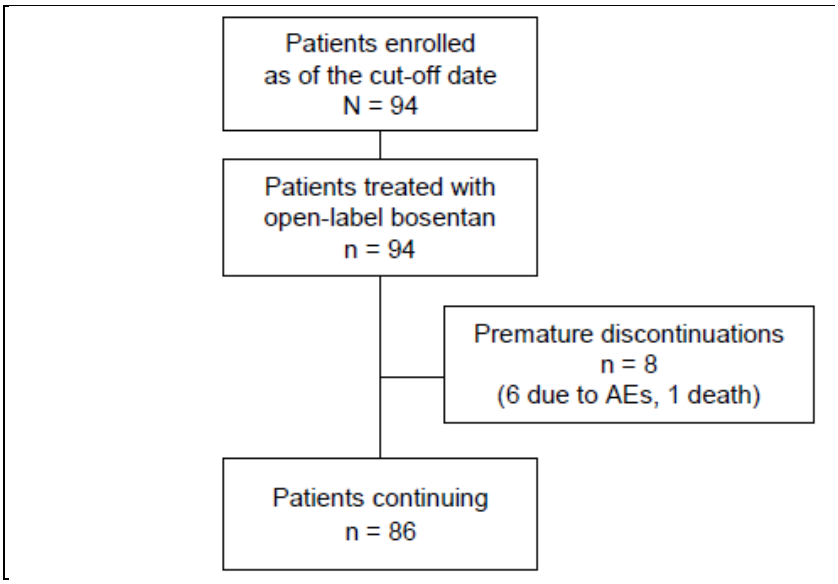
Figure 4. Disposition of patients



Open label phase (AC-052-333)

The disposition of patients is described in Figure 5.

Figure 5. Disposition of patients as of the cut-off date 19 may 2005.



Major protocol violations/deviations

The per-protocol analysis excluded 3 bosentan-randomised and 4 placebo-randomised patients. Two patients were also excluded from the safety analysis due to early withdrawal.

Baseline data

There were no significant biases between treatment groups in baseline demographic data.

Table 5. Baseline data. Number of digital ulcers at baseline.

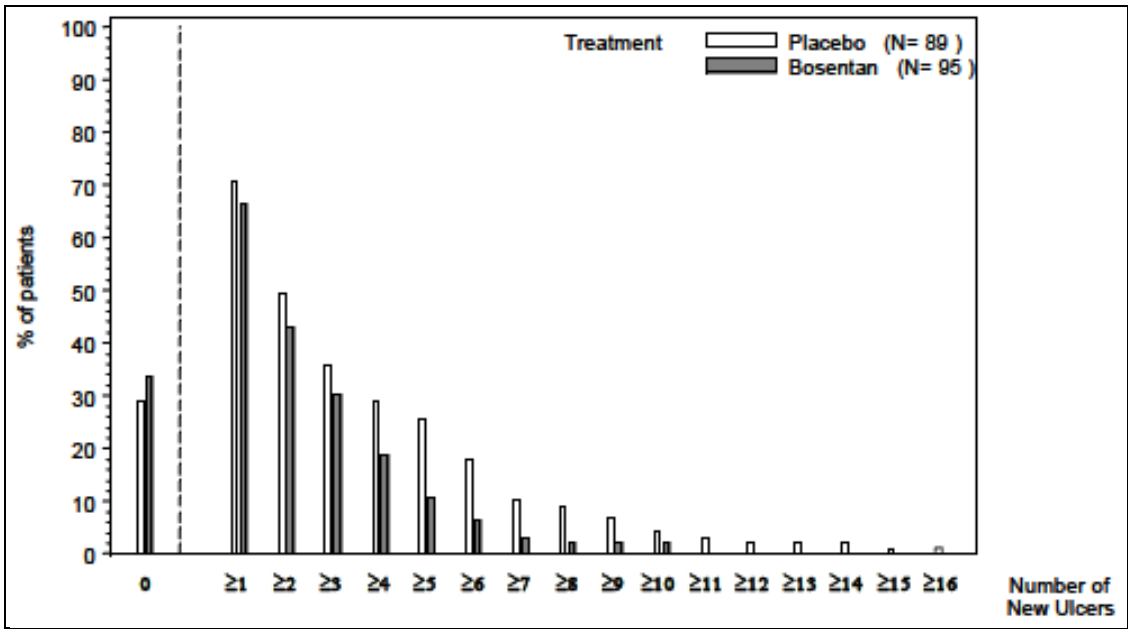
Number of digital ulcers at baseline	Bosentan arm (n=98)	Placebo arm (n=90)
Mean number of ulcers at baseline	3.6	3.7

Results for the primary efficacy outcome

RAPIDS-2 double blind phase. Total number of new ulcers in patients.

The mean number of new ulcers in patients at Week 24 was lower in bosentan treated patient s than those on placebo; 1.9 versus 2.7, respectively. This was not a significant difference on the Wilcoxon test (p=0.17) but was a significant different based on a Posisson test (p=<0.01) and a Permutation test (p=0.0351).

Figure 6. Proportions if patients with a given number of new digital ulcers during the 24 week treatment period. All treated set.



There was no significant difference in the number of patients who developed no new ulcers in the bosentan treated (33.7%) and placebo treated (29.2%) groups, respectively p=0.52. The treatment effect was more marked for patients with larger numbers of new ulcers.

The time to the development of new ulcers was not significantly different between bosentan and placebo treated patients for those with <5 new ulcers but was significant for the fifth new ulcer (p=0.03).

Healing of the Cardinal Ulcer

There was no statistically significant difference in the time to healing of the CU in patients in whom healing was maintained for 12 weeks between the bosentan and placebo treated patients (p=0.63). More than 50% of placebo and bosentan groups had complete healing and there was no significant difference between the groups at p=0.05.

Other exploratory endpoints

There was no significant difference in the proportion of patients with complete healing of all ulcers (baseline and new) at Week 24 between placebo (39.3%) and bosentan (36.8%) treated groups (p=0.76).

The time to complete healing of all ulcers (baseline and new) in patients in whom this happened was not significantly different between treatment groups.

The total number of new digital ulcers over the first 4 weeks of treatment was not significantly different between treatment groups (p=0.54).

Quality of life endpoints

Hand Pain assessed by VAS

Results are summarised in Table 6 below.

Table 6. Hand pain assessed by VAS

Overall Hand Pain	Placebo	Bosentan	P=value of difference
Change to week 12	-17+/-4	-26 +/- 3	0.08
Change to week 24	-24 +/- 4	-26 +/- 3	0.72
Pain of the Cardinal Ulcer			
Change to week 12	-24 +/- 4	-33 +/- 3	0.09
Change to week 24	-30 +/- 4	-32 +/- 3	0.75

The difference in pain was statistically significant using the Permutation test (but not the Wilcoxon test) at Week 12. There was no significant difference in pain assessed by VAS at Week 24.

Scleroderma Health Assessment Questionnaire

Improvements were observed in placebo and bosentan treated patients in the elements of the SHAQ, most of which were not significant.

Table 7. SHAQ: Changes from baseline to Weeks 12 and 24 in hand disability and overall disability index. All treated set.

SHAQ score (mean ± SEM)	Placebo (n = 90)	Bosentan (n = 98)	p-values*
Hand disability†			
n	86	86	
Baseline	1.06 ± 0.08	1.05 ± 0.08	
Change to Week 12	−0.11 ± 0.05	−0.22 ± 0.05	0.1537, 0.1449
Hand disability†			
n	87	86	
Baseline	1.05 ± 0.08	1.05 ± 0.08	
Change to Week 24	−0.13 ± 0.05	−0.17 ± 0.06	0.6234, 0.7547
Overall disability index			
n	86	86	
Baseline	0.93 ± 0.07	0.91 ± 0.07	
Change to Week 12	−0.05 ± 0.03	−0.11 ± 0.04	0.3118, 0.3471
Overall disability index			
n	87	86	
Baseline	0.92 ± 0.07	0.91 ± 0.07	
Change to Week 24	−0.05 ± 0.04	−0.09 ± 0.04	0.5098, 0.4907

* p-values determined by the Pitman permutation and the Wilcoxon exact test, respectively.
† Hand disability is a composite of three components of the SHAQ (dressing/grooming, hygiene, and grip).

SEM=Standard error of the mean.

There was no significant difference between treatments for the SHAQ components which assess hand disability.

Evaluator's conclusions on clinical efficacy

The indication requested on the basis of RAPIDS-1 and RAPIDS-2 is for

"*..the reduction in the number of new digital ulcers in patients with systemic sclerosis with active digital ulcer disease..".*

The data supports bosentan having an effect to reduce the incidence of new digital ulcers in some patients. The small reduction in the mean number of new ulcers observed between bosentan and placebo treatment needs to be interpreted cautiously, however, because it is likely to be driven by a difference in a small proportion of patients who developed large numbers of ulcers on placebo. Both RAPIDS-1 and RAPIDS-2, however, found no significant difference in the number of patients who developed *no new ulcers* between the bosentan and placebo groups. The sponsor has not presented the *statistical significance of the differences* between treatment groups in the proportion of patients developing increasing numbers of ulcers. It appears to the evaluator, however, that the difference in the number of new ulcers in patients taking bosentan compared to placebo is fairly small for low numbers of ulcers (for example 1-2) than for high numbers (for example >4).

The statistical comparison of incremental efficacy which has been presented in RAPIDS-1 and RAPIDS-2 is for the *time* for patients to develop their first, second, third and so on ulcer. The proportion of patients developing >1, >2, >3 ulcers has been presented in these trials but not the significance of the difference between bosentan and placebo. Given that there is no significant difference between bosentan in the time to develop the first-second[d] new ulcers in RAPID-1 and first-fourth new ulcers in RAPIDS-2, the evaluator feels that the question as to whether there was an overall reduction in the number of ulcers in most patients is pertinent. If this is not the case in a significant proportion of patients then what has been observed in these patients in RAPIDS-1 and RAPIDS-2 is a delay in the development of ulcers over the trial, not a net benefit of treatment at the end of the trial.

In this context, the duration of RAPIDS-1 and RAPIDS-2 is a further limitation in interpreting the efficacy data. If treatment only delays the development of ulcers it is not clear whether, after a period, the numbers of ulcers on on placebo and bosentan become more similar. This is particularly the case since bosentan does not appear to increase the healing of extant ulcers. It is therefore not clear how long a clinician should treat a patient for digital ulcers or when to cease therapy.

The clinical issue this data raises is that the clinician cannot know before commencing treatment whether their patient would have developed a high number of ulcers without treatment and therefore will benefit significantly from bosentan. This is an important risk assessment given the potential adverse effects of therapy.

On the basis of the placebo rate in RAPIDS-1, 1:2.5 (39.5%) patients would develop no new ulcers without treatment. In RAPIDS-2, where patients have ulcers at baseline and presumably more active disease, this figure is 1:3.4 (29.2%). The evaluator calculates that the number needed to treat to prevent a patient developing 1-4 ulcers in the RAPIDS-2 data is about 6 and this increases to about 14 to prevent a patient developing at least 7 ulcers.

It is also significant that there is no consistent evidence for a reduction in pain on bosentan as this is an important symptom of ulcers.

The evaluator therefore concludes that bosentan mostly reduces the number of patients developing large numbers of ulcers but, as this only occurs in a proportion of patients in any case, there is a significant number needed to treat to achieve this endpoint. For the

majority of patients who will, on the evidence of the placebo group, develop smaller numbers of ulcers the evidence of efficacy is more marginal. There is, in fact, no difference in the number of patients who develop at least one new ulcer.

Should this application be approved, given the significance of the decision to initiate bosentan therapy in a population who may not other indications for treatment, the evaluator felt that the data from RAPIDS-1 and RAPIDS-2 should be presented in the Australian Product Information (PI) in the form of the tabulated incidence of increasing numbers of ulcers.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- RAPIDS-1
- RAPIDS-2

RAPIDS-1 presented a final report analysing data from the controlled and open label phases of the trial.

RAPIDS-2 presented a final report analysing data from the controlled phase of the trial. These comprise the pivotal safety analysis.

An interim report for the open label phase of RAPIDS-2 was presented separately as trial AC-052-333.This forms a non-pivotal safety analysis.

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by medical examination at each 4 weekly visit.
- Laboratory tests, including Liver Function Tests (LFTs) and Haemoglobin (Hb) were assessed at each 4-weekly visit.

Non-pivotal efficacy studies

Study AC-052-333 was only evaluated for deaths, reported serious adverse events and reported reasons for discontinuations as these occurred or at regular assessment visits. These occurred 4 weekly for the first 2 visits and 8 weekly thereafter. Complete information on the duration of treatment of patients in this trial was not available in the interim report but it states that patients may have been treated for up to 10 months.

Patient exposure

Table 8 describes the overall duration of exposure in the placebo controlled trials.

Table 8. Summary of the overall duration of exposure during placebo controlled trials.

	RAPIDS-1		RAPIDS-2		Pooled studies		PC + OL
	Placebo (n = 43)	Bosentan (n = 79)	Placebo (n = 90)	Bosentan (n = 98)	Placebo (N = 133)	Bosentan (N = 175)	Bosentan (N = 206)
Mean (weeks)	15.3	15.1	24.5	22.7	21.5	19.5	21.8
Std deviation	4.0	4.3	8.1	8.6	8.2	7.8	9.1
Median	16.4	16.3	25.0	24.3	24.1	17.9	24.3
Range	0.9–18.1	0.4–19.1	1.3–38.7	1.4–37.6	0.9–38.7	0.4–37.6	0.4–37.6

PC = placebo controlled, OL = open label, Std = standard.
Reference: Studies AC-052-401, AC-052-331, and the Integrated Summary of Clinical Safety.

Adverse events

All adverse events (irrespective of relationship to study treatment)

Frequent adverse events (AEs) are summarised in Table 9 below.

Table 9. Summary of frequent adverse events, during and up to 1 day after the end of treatment.

Number (%) of patients	Placebo-controlled trials		All bosentan-treated patients (PC + OL)* N = 206
	Placebo N = 133	Bosentan N = 175	
Patients with ≥ 1 AE	116 (87.2%)	154 (88.0%)	180 (87.4%)
Number of different AEs	415	585	745
AE preferred term			
Oedema peripheral	6 (4.5%)	24 (13.7%)	27 (13.1%)
Headache	18 (13.5%)	23 (13.1%)	31 (15.0%)
Diarrhoea	10 (7.5%)	16 (9.1%)	22 (10.7%)
Upper respiratory tract infection	12 (9.0%)	15 (8.6%)	17 (8.3%)
Infected skin ulcer	8 (6.0%)	15 (8.6%)	17 (8.3%)
Arthralgia	13 (9.8%)	14 (8.0%)	19 (9.2%)
AST increased	2 (1.5%)	11 (6.3%)	11 (5.3%)
ALT increased	1 (0.8%)	11 (6.3%)	12 (5.8%)
Pain in extremity	7 (5.3%)	10 (5.7%)	14 (6.8%)
Vomiting	8 (6.0%)	9 (5.1%)	11 (5.3%)
Nausea	—‡	—‡	11 (5.3%)
Other†	107 (80.5%)	147 (84.0%)	170 (82.5%)

* Includes all bosentan-treated patients in AC-052-401 and AC-052-331.
† All AEs with an overall incidence of < 5% with bosentan are pooled under "other."
‡ The incidences of nausea in placebo-controlled trials are included in the pool of "other."
AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, OL = open label, PC = placebo controlled.

The evaluator notes that peripheral oedema and hepatic injury are known potential adverse effects of bosentan therapy.

The most common cause for treatment discontinuation was raised Liver Function Tests, which is a known adverse effect of bosentan.

Treatment-related adverse events (adverse drug reactions)

Pivotal studies

The rates of adverse events were within the expected range of known toxicity of bosentan. These include the incidence of liver function abnormalities and reduced haemoglobin (see *Laboratory tests*)

Deaths and other serious adverse events

Pivotal studies

The following table summarises the AEs in completed trials RAPIDS-1 and RAPIDS-2.

Table 10. Overview of AEs up to 1 calendar day after the end of study treatment in completed trials RAPIDS-1 and RAPIDS-2*.

Number (%) of patients	Placebo-controlled trials		All bosentan-treated patients (PC + OL) †
	Placebo N = 133	Bosentan N = 175	N = 206
Pts with ≥ 1 AE	116 (87.2%)	154 (88.0%)	180 (87.4%)
Pts with ≥ 1 AE (excluding unrelated)	31 (23.3%)	68 (38.9%)	80 (38.8%)
Deaths	1 (< 1%)	1 (< 1%)‡	1 (< 1%)‡
Pts with ≥ 1 SAE	18 (13.5%)	11 (6.3%)	19 (9.2%)
Pts with AE leading to d/c of study treatment	15 (11.3%)	25 (14.3%)	32 (15.5%)
Pts d/c due to abnormal liver function test result	—	10 (5.7%)	11 (5.3%)

* Includes deaths reported up to the end of the follow-up period.
† Includes all bosentan-treated patients in AC-052-401 and AC-052-331.
‡ Death occurred outside the study period (treatment + 56-day follow-up in RAPIDS-2), but the event that resulted in death began on an unknown date and was conservatively considered to have occurred during the study period.
AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, d/c = discontinuation, OL = open label, PC = placebo controlled, pts = patients, SAE = serious adverse event.

One placebo treated patient died of acute respiratory distress syndrome 36 days after completing treatment in RAPID-2. One bosentan patient died of pneumonia 58 days after treatment in RAPIDS-2. This death was outside the reporting period of the trial but has been included because it is not certain when the adverse event started.

One suspected unexpected serious adverse reaction was reported on bosentan. This was an initial episode of diplopia which was later diagnosed as myasthenia gravis after the patient discontinued treatment. This is not considered related to the study drug.

Non-pivotal studies

Study AC-052-333 (RAPIDS-2 open label phase interim report)

One patient died suddenly for unclear reasons after developing breathlessness on Day 42 of this study. Sinusitis had been diagnosed by his physician 3 days before his death and he had been treated with antibiotics. No autopsy was performed. The investigator assessed this event as not being related to study medication.

A further 11 patients had suffered serious adverse events which were not assessed as being related to bosentan treatment.

Discontinuation due to adverse events

Pivotal studies

There were 32 discontinuations among bosentan treated patients, 11 of which were for abnormal liver function tests.

Non pivotal studies

Six patients discontinued treatment; 4 for elevated liver function tests, 1 for headache and 1 for peripheral oedema. The evaluator notes that these are relatively common adverse events reported on bosentan treatment.

Laboratory tests

Liver function and haematology

Pivotal studies

Liver function abnormalities were reported fairly frequently in bosentan treated patients. This is consistent with the known effects of this medication. There was a slightly higher rate of reduced haemoglobin levels in patients treated with bosentan.

Table 11. Incidences of special laboratory abnormalities during the treatment period.

Number (%) of patients	Placebo-controlled trials		All bosentan-treated patients (PC + OL)* N = 206
	Placebo N = 133	Bosentan N = 175	
ALT and/or AST > 3 × ULN	1/129 (0.8%)	19/168 (11.3%)	20/198 (10.1%)
ALT and/or AST > 5 × ULN	0/129 (—)	12/168 (7.1%)	12/198 (6.1%)
ALT and/or AST > 8 × ULN	0/129 (—)	4/168 (2.4%)	4/198 (2.0%)
Hb < 10 g/dL with a ≥ 15% decrease from baseline	4/129 (3.1%)	7/167 (4.2%)	9/197 (4.6%)

* Includes all bosentan-treated patients in AC-052-401 and AC-052-331.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, Hb = haemoglobin, OL = open label, PC = placebo controlled.

Post marketing experience

No new information was submitted.

Evaluator's overall conclusions on clinical safety

RAPIDS-1 and RAPIDS-2 do not significantly increase the known exposure of patients to bosentan, which the sponsor has reported as 26,500 patients, although they do provide a placebo controlled comparison of adverse events. No unexpected adverse events related to drug therapy were reported.

A significant aspect of the safety data in RAPIDS-1 and RAPIDS-2 is that the population in these trials did not have Class II-IV heart failure[2]. This is, therefore, a different population than is included in the existing indication for bosentan in Australia and against which the safety of the drug has been assessed. There is no indication that bosentan was less well tolerated in this population.

Clinical summary and conclusions

Benefit-Risk Assessment

Assessment of benefits

The benefits of bosentan in the proposed usage are:

- A reduction in the number of digital ulcers suffered by a proportion of patients with systemic sclerosis.

Assessment of risks

The risks of bosentan in the proposed usage are:

- The known toxicity of bosentan , particularly in terms of liver function, haemoglobin and potential foetal exposure.

First round assessment of benefit-risk balance

The benefit-risk balance of bosentan, given the proposed usage, was considered favourable.

Recommendation Regarding Authorisation

Scleroderma is a rare condition mostly treated under specialist supervision. Bosentan is not a new medication for this condition, of which digital ulcers are a serious complication which impacts on the quality of life of patients. However, the marginal efficacy expected for bosentan in many patients means that the risk-benefit balance must be informed by more complete information than proposed in the current Australian PI. The evaluator strongly recommends amendment to the draft prescribing information to provide this.

[2] NYHA Classification - The Stages of Heart Failure. In order to determine the best course of of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown in Table 12.

Table 12. Summary of Ongoing Safety Concerns

Important identified risks	• Hepatotoxicity • Teratogenicity
Important potential risks	• Decrease in haemoglobin concentration, thrombocytopenia • Pulmonary oedema associated with veno-occlusive disease (PVOD) • Fluid retention • Interaction with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives) • Neutropenia, leukopenia
Important missing information	• Potential association of bosentan to cases of vasculitis (remains under close monitoring, please see 10th PSUR) • Results of the COMPASS studies (associated use of bosentan and sildenafil)

OPR reviewer comment

The sponsor has stated that the safety profile of bosentan in patients with digital ulcer disease from clinical trials was consistent with that in other indications. Consequently no new adverse events were identified.

The table 'Summary – Ongoing Safety Concerns' of the RMP is inconsistent with the table 'Summary of the EU Risk Management Plan'. Consequently the sponsor should include the Important missing information: 'Long term safety and efficacy in digital ulcer population', 'Long term safety and outcomes in the paediatric population', 'Possible interaction with anti-retroviral compounds' and 'Possible seminiferous tubule atrophy' as ongoing safety concerns. The relevant sections of the RMP should be amended accordingly.

Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance activities to monitor all the specified ongoing safety concerns, except for the Important potential risk: 'Neutropenia, Leukopenia'. The sponsor has provided an assurance that these activities are consistent with the activities outlined in the relevant TGA adopted EU guideline[3].

In addition, the sponsor proposed to further monitor the Important missing information: 'Interaction with sildenafil' via the results of the ongoing COMPASS 2 study (AC-052-414): 'Effects of combination of bosentan and sildenafil versus sildenafil monotherapy on morbidity and mortality in symptomatic patients with pulmonary arterial hypertension'.

[3] 3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03). http://www.tga.gov.au/pdf/euguide/ich571603en.pdf)

This is a multicentre, double blind, randomised, placebo controlled, parallel group, prospective, event driven study. This will be followed by a 12-month, open label, non-controlled extension phase which is anticipated to end in the second quarter of 2013.

Section 2.2: 'Summary of safety concerns and planned pharmacovigilance actions' of the RMP also makes reference to the 'Pregnancy Action Plan' for the Important identified risk: 'Teratogenicity'. It is acknowledged that this plan mainly involves additional risk minimisation activities, although within this plan updated pregnancy reporting forms are sent to every case of reported pregnancy in patients exposed to Tracleer as follow-up.

Section 2.2 also makes reference to a registry within the EU specifically enrolling patients with digital ulcers associated with systemic sclerosis. The registry is a multicentre, prospective program designed to ensure adherence to Summary of Product Characteristics (SmPC) requirements for liver function, pregnancy testing, and the use of adequate contraception in these patients; and to obtain prospectively defined data on disease course in patients with systemic sclerosis (SSc) and digital ulcers treated with Tracleer. All physicians prescribing Tracleer for SSc and digital ulcers are encouraged to participate in this registry, and 6 monthly reports summarising the data collected are being submitted to the European Medicines Agency (EMA)/The Committee for Medicinal Products for Human Use (CHMP) in parallel with the Periodic Safety Update Report (PSUR). The protocol and the data collection form for the registry were agreed with the EMEA/CHMP and the registry started 10 April 2008.

Section 2.2 also makes reference to the sponsor acknowledging a need for additional, prospective data collection the paediatric experience with bosentan. The RMP states that this could best be achieved through the utilisation of ongoing registries that are already collecting data on paediatric patients with pulmonary hypertension, treated or not with Tracleer. The sponsor committed to submit a protocol for consolidated reporting from ongoing registries collecting prospective data on paediatric patients with pulmonary hypertension. The study protocol "Disease characteristics and outcomes of PAH in children and adolescents in real world clinical settings: Systematic review of four prospective, observational registries" in order to collect further data on long-term safety and outcomes in paediatric patients with PAH was submitted to the CHMP in July 2009.

The table 'Summary of the EU Risk Management Plan' of the RMP states that for the Important missing information: 'Possible interaction with anti-retroviral compounds' a drug-drug interaction study between bosentan and the antiretroviral product Kaletra® (lopinavir/ritonavir) in healthy volunteers was completed.

The table also states that for the Important missing information: 'Possible seminiferous tubule atrophy' a multi-centre, open label, single-arm, safety Study (AC-052-402) to investigate the effects of chronic Tracleer treatment on testicular function in male patients with PAH was completed on 6 November 2007.

Risk minimisation activities

Planned actions

Routine risk minimisation activities were proposed to include contraindications, special warning & precaution statements and/or notification of undesirable effects in the Australian PI for all the specified Ongoing Safety Concerns, except for the Important missing information: 'Possible vasculitis'.

Additional risk minimisation activities are also proposed for the Important identified risks: 'Teratogenicity' & 'Hepatotoxicity'. The RMP states that a component of the Tracleer postmarketing surveillance program that remains in operation is the controlled distribution system, which allows the identification of prescribers of Tracleer. New prescribers are approached on an ongoing basis to be given information (Prescriber Kit)

and education on the safety concerns related to the use of Tracleer, and especially on the need for strict adherence to the regular monitoring of liver function tests (LFTs) for the duration of treatment with Tracleer, and the need for monthly pregnancy tests. In addition, the inclusion of the Tracleer Patient Reminder Card in every package of Tracleer facilitates patient awareness of the need for regular blood and pregnancy testing, requirements which are fundamental to ensuring the continued safe use of Tracleer.

Furthermore a "Reminder Letter" was sent in 2008 to all known prescribers in the EU, reminding them of the safety concerns with Tracleer. This reminder letter focused on the contra-indication of Tracleer in pregnancy, the need for reliable contraceptive measures in all women of childbearing potential and the unreliability of hormonal contraceptives when used alone.

In order to evaluate the effectiveness of these proposed measures the RMP states that all reports of pregnancies in patients exposed to Tracleer are carefully followed up, specifically described and analysed in upcoming PSURs. The sponsor provides an assurance that every effort to proactively obtain information from the reporter (especially with regard to contraceptive use/failure and outcome of pregnancy) through data clarification forms or by telephone contact on a number of separate occasions and by sending the updated pregnancy reporting form in every case.

Excerpt from the Summary of OPR evaluator's recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted RMP is applicable without modification in Australia unless so qualified:

- In principle there was no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified Ongoing Safety Concerns.
- The sponsor was requested to state whether the registry within the EU specifically enrolling patients with digital ulcers associated with systemic sclerosis will be expanded to Australia or provide justification for not doing so.
- The sponsor's proposed Risk Minimisation Plan (RiMP) appeared to be reasonable. However, the Australian sponsor should definitively state whether the proposed additional risk minimisation activities will be conducted in Australia in accordance with Australian specific registration details.
- The data from spontaneous ADRs are unlikely to be sufficient in measuring the effectiveness of the proposed additional risk minimisation activities. This is due to the under reporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. Consequently the sponsor should plan appropriate alternative methods to assess the effectiveness of these additional risk minimisation activities as a measure to reduce risk.
- In regard to the proposed routine risk minimisation activities, various revisions of the draft PI and draft consumer medicine information document were recommended to the Delegate.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacokinetics (PK) / Pharmacodynamics (PD)

There were no new PK or PD data in the application.

Efficacy

The submission is based on the results of two randomised, double blind, placebo controlled trials (RAPIDS-1 and RAPIDS-2). These two studies have been published[4].

The *RAPIDS-1* study enrolled systemic sclerosis patients with a history of digital ulcers in the preceding 12 months. Patients *without* active ulcers could therefore be enrolled. Subjects were randomised (2:1) to receive bosentan or placebo for a treatment period of 16 weeks. Patients could continue on any current oral vasodilator drugs. The trial enrolled a total of 122 patients.

The primary endpoint was the number of *new* ulcers occurring during the treatment period. Results are shown in the clinical evaluation report (CER). Bosentan treatment was associated with a reduction in the mean number of new ulcers (1.4 versus 2.7). There were two pre specified statistical tests of this result; the Mann-Whitney-Wilcoxon two-sample test which did not indicate statistical significance (p=0.1748) and a Poisson regression test which did indicate statistical significance (p=0.0083). The sponsor also conducted a post hoc analysis using a permutation test which was also statistically significant (p=0.0042).

There was no difference in the proportion of patients who experienced complete healing of existing ulcers (20.8% versus 19.2%).

The study also included a quality of life assessment (SHAQ). Results indicated there were generally no significant benefits associated with bosentan treatment (see CER). Specific components in the SHAQ related to hand function (dressing/grooming, hygiene, grip) suggested some improvement with bosentan. In a post hoc analysis these components were combined into a single score of 'hand functionality' and significant difference in favour of bosentan was found (CER).

The *RAPIDS-2* study enrolled systemic sclerosis patients with at least one digital ulcer at baseline. One of the ulcers present in each patient had to be designated as the 'cardinal' ulcer (see CER). Subjects were randomised (1:1) to receive bosentan or placebo for a treatment period of 24 weeks. Patients could continue on any current oral vasodilator drugs. The trial enrolled a total of 188 patients.

There were two primary endpoints:

- the mean number of *new* ulcers occurring during the treatment period; and

[4] Korn J.H. et al, (2004). Digital Ulcers in Systemic Sclerosis Prevention by Treatment With Bosentan, an Oral Endothelin Receptor Antagonist. Arthritis & Rheumatism 50 (12): 3985–3993 and Matucci-Cerinic M et al (2011). Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double blind, placebo controlled trial. Ann Rheum Dis 70:32–38.

- the time to healing of the CU.

Results for mean number of new ulcers are shown in the CER. Bosentan treatment was associated with a reduction in the mean number of new ulcers (1.9 versus 2.7). The pre specified statistical test for this endpoint was the Pitman permutation test and the result was statistically significant (p=0.0351).

As in the RAPIDS-1 trial, there was no difference in the proportion of patients who developed at least 1 new ulcer (66.3% with bosentan versus 70.8% with placebo) and the benefit of bosentan appeared to be confined to a reduction in the proportion of patients who developed multiple ulcers (see CER).

There was no significant difference between groups in the time to healing of the cardinal ulcer (CER).

In this study there were no benefits demonstrated on the SHAQ measures of quality of life, including overall hand pain, pain from the cardinal ulcer, overall disability or hand disability (CER).

Safety

In the two placebo controlled studies, a total of 175 subjects received bosentan for a mean duration of 19.5 weeks. The submission also included safety data from an open extension study to the RAPIDS-2 trial in which patients previously assigned to placebo could receive bosentan. Including these subjects, a total of 201 subjects received the drug for a mean of 21.8 weeks.

As shown in the CER, in the placebo controlled trials, bosentan treatment was not associated with an increase in the overall incidence of adverse events (88.0% with bosentan versus 87.2% with placebo) or serious adverse events (6.3% with bosentan versus 13.5% with placebo). There was a slight excess in the bosentan group in patients discontinuing treatment due to adverse events (14.3% versus 11.3%). There was no increase in patient deaths.

Compared to placebo, bosentan treatment was associated with increased incidence of:

- Peripheral oedema -13.7 % versus 4.5 %;
- ALT and/or AST increased (3xULN) - 11.3 % versus 0.8 %;
- Diarrhoea - 9.1 % versus 7.5 %;
- Infected skin ulcer - 8.6 % versus 6.0 %;
- Haemoglobin decreased (< 100 g/) - 4.2 % versus 3.1 %;

Peripheral oedema, abnormal LFTs and decreased haemoglobin have previously been documented with bosentan.

The evaluator concluded that no unexpected adverse events related to bosentan were identified by the new studies.

Risk management plan

Following review by the OPR and revisions by the sponsor, the sponsor's risk management plan has been found to be acceptable by the TGA's OPR.

Risk-benefit analysis

Delegate considerations

Assessment of benefits versus risks

The efficacy benefit of bosentan in the management of digital ulcers appears modest. It did not result in improved healing of existing ulcers and did not stop the development of some new ulceration. The severity of new ulceration, in terms of numbers of new ulcers, was decreased. The two trials suggest that, on average, it will prevent the development of approximately one new ulcer. There was no improvement in pain. There was a suggestion of improved hand function in the RAPIDS-1 study but this was not confirmed by the RAPIDS-2 study.

No new safety issues were raised with use of the drug in the new population. Overall adverse events were not markedly increased in the bosentan treated group.

Overall, the Delegate considered that the benefit-risk ratio was borderline. However, if the view of the Advisory Committee on Prescription Medicines (ACPM) was that the efficacy benefit is clinically significant, the Delegate would propose to approve the application.

The Delegate proposed to approve the application subject to the Committee's advice on whether the demonstrated efficacy benefit is clinically significant. The advice of the Committee was requested.

Response from sponsor

The Delegate requested the advice of the ACPM committee on whether the demonstrated efficacy benefit seen in the current application is clinically significant. Specifically, the Delegate has stated:

"The efficacy benefit of bosentan in the management of digital ulcers appears modest. It did not result in improved healing of existing ulcers and did not stop the development of some new ulceration. The severity of new ulceration, in terms of numbers of new ulcers, was decreased. The two trials suggest that, on average, it will prevent the development of approximately one new ulcer. There was no improvement in pain. There was a suggestion of improved hand function in the RAPIDS-1 study but this was not confirmed by the RAPIDS-2 study. No new safety issues were raised with use of the drug in the new population. Overall adverse events were not markedly increased in the Bosentan treated group. Overall, the Delegate considered that the benefit-risk ratio is borderline. However, if the Committee's view was that the efficacy benefit is clinically significant, the Delegate would propose to approve the application."

In this regard, the sponsor wished to apprise the Committee of the following:

Background and morbidity of Digital Ulcers

Bosentan (Tracleer®) is an oral, dual endothelin (ET-1)-receptor antagonist that competes with the binding of ET-1 to both ET_A and ET_B receptors and thereby interferes with the deleterious effects of ET-1. It has demonstrated efficacy in patients with pulmonary arterial hypertension (PAH) of various aetiologies and has been approved in Australia (and elsewhere) for the treatment of WHO functional class II, III and IV PAH to improve symptoms and exercise capacity, based mainly on studies performed in patients with idiopathic PAH, PAH secondary to systemic sclerosis (SSc) or associated congenital heart disease.

The histopathological changes of obliterative vasculopathy with intimal proliferation characteristic of SSc have been observed in both small pulmonary arteries and digital arteries, suggesting that therapies that target the vasculopathy of SSc should improve both

pulmonary and digital vascular function in afflicted patients. Clinical observations by investigators during bosentan trials in PAH suggested improvement not only in PAH symptomatology but also in ischaemic digital ulcers (DU) in several SSc patients. Based on this clinical evidence, mechanistic rationale, and preclinical support, a program was developed to evaluate the use of bosentan in SSc patients with ischaemic DU.

Digital ulcers are painful, slow to heal (3 to 15 months) and can be complicated by secondary infections (superficial infection in 50% of cases, osteomyelitis in 1%).

Recurring DU can be a major source of disability. Few therapies have shown an effect on the evolution of DU. Calcium channel blockers have shown some benefit in the prevention and amelioration of Raynaud's phenomenon, and intravenous and oral prostacyclin analogues have inconsistently shown some benefit in the treatment of DU. Thus, pharmacological therapy that would affect the natural course of DU and especially prevent the development of new ulcers is needed.

Digital ulcers are estimated to develop in around 50% to 60% of SSc patients at some time in the course of the disease. Approximately 10–25% of SSc patients are likely to have DU at any one time. Since SSc is a chronic, currently incurable disorder, the majority of afflicted patients will experience repeated episodes of DU[5].

DU impose a significant burden on patients by impacting their daily life and ability to work.[6] This impact was also shown for patients enrolled in the DUO Registry[7], an ongoing, international, multi-center, observational study to assess outcomes in patients with past or present DU disease associated with SSc which is maintained at the request of, and reported to, the EMA.

More than 2,000 patients have been enrolled in the DUO Registry and at the last reporting date approximately 1,400 had data on at least part of the functional assessment questionnaires, including data on work impairment, daily activity impairment and help needed (paid and unpaid). These findings showed a clear relationship between the number of DU and the proportion of patients impaired in their daily activities in the preceding month (37.1%, 53.1%, 63.1% for patients with 0, 1 to 2, ≥ 3 DU, respectively) and ability to work in the preceding month (31.9%, 40.7%, 47.9% for patients with 0, 1 to 2, ≥ 3 DU, respectively). A similar relationship was seen between the number of DU and hours of paid and unpaid help needed in the last month (2.3, 8.2, 10.1 hours of paid help for patients with 0, 1 to 2, ≥ 3 DU, respectively, and 17.4, 33.4, 62.5 hours of unpaid help for patients with 0, 1 to 2, ≥ 3 DU, respectively). Thus, a reduction of the number of new DU would reduce the overall symptom-generating disease burden, and is therefore clinically meaningful to the patient.

DU may also cause serious complications. Infection, ischaemia, pain and gangrene are such important complications of DU and, apart from suffering, lead to frequent pharmacological and surgical interventions, and to repeated hospitalisations[5]. In the DUO Registry, the number of DU was associated with the occurrence of DU complications during the follow-up period (hospitalisation for DUs, gangrene, [auto] amputation, debridement, tissue infection requiring systemic antibiotics, osteomyelitis and critical digital ischemia [0.695, 1.448, 2.223 cumulative events per patient-year for patients with 0, 1 to 2, ≥ 3 DUs, respectively]).

[5] Hachulla E, Clerson P, Launay D et al. (2007). Natural history of ischemic digital ulcers in systemic sclerosis. Single-center retrospective longitudinal study. J *Rheumatol* 2007;34:2423-30

[6] Berezne A, Seror R, Morell-Dubois S et al. (2011). Impact of systemic sclerosis on occupational and preofessional activity with attention to patients with digital ulcers. *Arthritis Care & Research* 63:277-285

[7] Hunsche E, Denton CP, Krieg T et al. (2010). Work and daily activity impairment in patients with digital ulcers (DUs) – results from the DUO Registry. Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 13th Annual European Congress, Prague, Czech Republic, 6–9 November, 2010.

All these complications, although affecting a low absolute number of patients within the rare disorder of SSc, contribute to serious suffering for the individual and have as their basis the DU. Given that every DU, in and of itself, might be a potential substrate for those serious complications, a reduction in the cumulative number of new DU is clinically relevant.

Clinical evidence for bosentan in patients with SSc and DU

To determine the efficacy and safety of bosentan in patients with ischaemic DU secondary to SSc, the clinical development program consisted of two multicentre, randomised, double blind, placebo controlled, parallel-group trials (RAPIDS-1 and RAPIDS-2) conducted in a total of 312 patients at 56 centres in Europe and North America.

The first study (RAPIDS-1) consisted of a 16-week double blind treatment phase (N = 122), followed by an optional 12 week open label treatment phase (N = 88) for patients who completed the double blind phase and could receive possible benefit from continuing in the study.

The second study (RAPIDS-2, N = 190) consisted of a 24 to 36 week double blind treatment period and an 8 week post treatment follow-up period.

RAPIDS-1 and RAPIDS-2 represent the largest prospectively collected database in the orphan disorder of DU with SSc. The studies were designed with the common aim to show an effect of bosentan to reduce the development of new DU. The study population was chosen to represent a target population of patients with high propensity for developing new DU, thought to be those with ongoing DU or with a recent history of DU, that is, patients with active DU disease secondary to SSc. In both studies, bosentan treatment resulted in a significant reduction in the number of new DU versus placebo ($p = 0.0042$

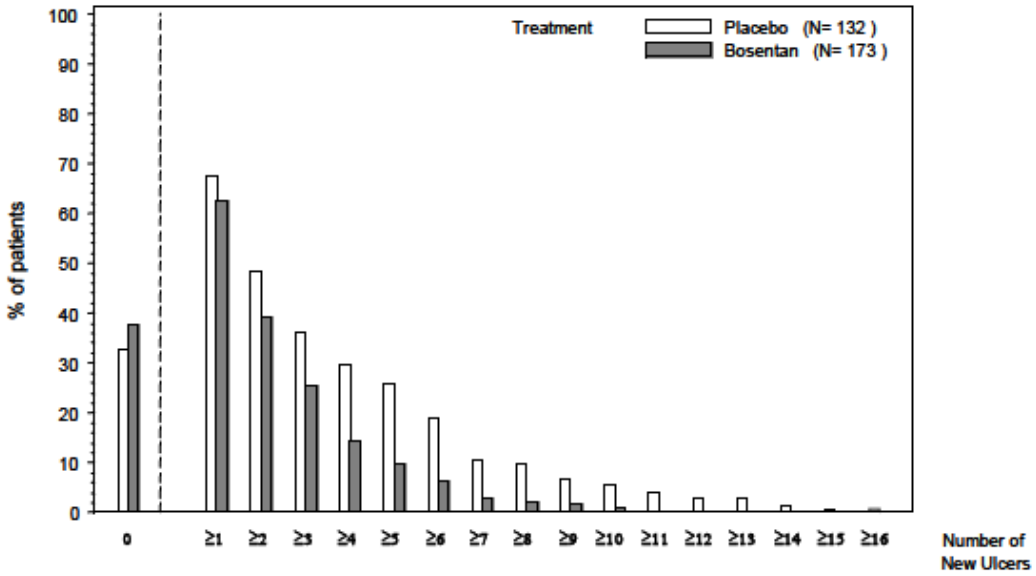
in RAPIDS-1 and non-corrected $p = 0.0351$ in RAPIDS-2), and the effect size of 30–50% reduction in the mean number of new DU in the primary analysis in the two studies (37% in the pooled dataset) is in line with what was considered clinically relevant in discussions with EU Health Authorities.

The inclusion of a healing endpoint in RAPIDS-2 was requested by the FDA despite there being no pharmacological rationale to expect any healing effect of bosentan. The biology of wound healing is complex and includes microvascular angiogenesis, restoration of tissue hydrostatics and other factors. Endothelin is not known to be participatory in wound healing biology other than potential effects on afferent vasomotion and there is little scientific basis to expect benefit on wound healing from endothelin-receptor antagonism. The observation from RAPIDS-2 that bosentan treatment did not confer benefit for healing of established digital ulcers was therefore not unexpected, and is important information for prescribers, hence its inclusion in the proposed Australian PI.

The Delegate highlighted that bosentan treatment did not stop the development of some new ulceration. In this regard, it is important to understand that the potential benefit of bosentan in DU with SSc was thought to be related not to vasodilation *per se*, which is not prominent in systemic blood vessels, but, rather, to an effect on the underlying processes of fibrosis and vascular remodelling. This effect would not be of immediate onset, as is also shown by the experience with bosentan in the structurally similar vasculopathy of pulmonary arterial hypertension. The incidence of patients with/without new DU was nonetheless evaluated in both trials (secondary endpoint in RAPIDS-1, exploratory endpoint in RAPIDS-2). In both studies there was a clear effect on the proportion of patients forming multiple new DU (9.0% on bosentan versus 25.6% on placebo in RAPIDS-1, and 10.5% on bosentan versus 25.8% on placebo in RAPIDS-2, developed more than five new DU) but a small difference between active treatment and placebo in the proportion of patients with no new DUs (42% on bosentan versus 40% on placebo in RAPIDS-1, and 34% on bosentan versus 29% in RAPIDS-2).

As alluded to by the Delegate, the effect of bosentan to reduce the number of new DU was more apparent in patients with higher DU disease activity [whether defined by the presence of multiple DU at baseline, high ulcer VAS scale score or Raynaud VAS scale score at baseline, or need for immunosuppressive therapy as an indicator of the severity of the underlying SSc process]. Patients on bosentan were less likely to have a large number of new digital ulcers (Figure 7) and took longer to develop each successive new digital ulcer than did those on placebo.

Figure 7. The proportion of patients in pooled data with a given number of new digital ulcers up to study endpoint. ITT data set.



* Study endpoint was Week 16 for AC-052-401 and Week 24 for AC-052-331.

The Delegate pointed out that there was no improvement in pain. The sponsor acknowledged the intrinsic benefit of pain reduction and that an effect on hand pain was not consistently demonstrated in trials RAPIDS-1 and RAPIDS-2. However, the sponsor considers that overall hand pain in patients with SSc is probably too multi-factorial to be a sensitive outcome measure to detect a treatment effect of pharmacological intervention against DU.

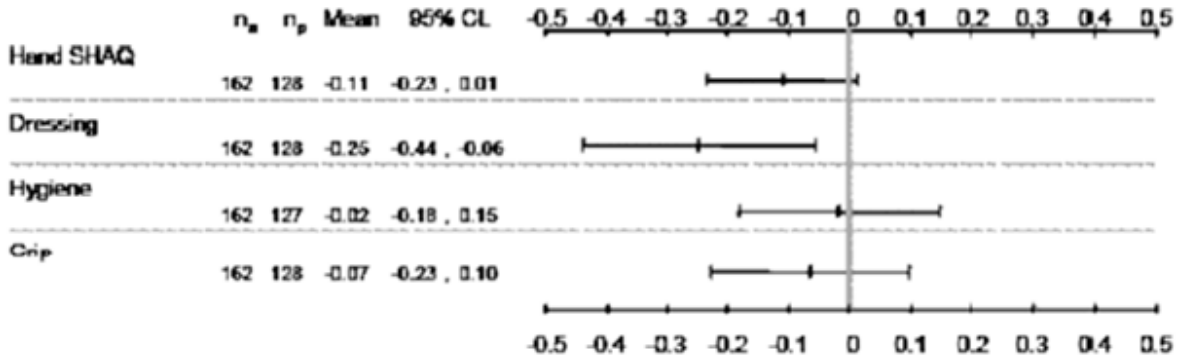
Hand pain in SSc could be related to DU but also to protrusive calcinosis, crusts and fissures of a dry and sclerotic skin, underlying ischaemic pain related to diffuse narrowing of the vascular lumen of the hand and finger arteries, pain related to finger arthropathy, terminal tuft bone resorption, bone infection, hand retraction, tendinitis, fibrosis, and entrapment of the tendon sheaths. The patients were requested to report specifically the overall hand pain related to DU but it remained difficult for them to discriminate this from other types of hand pain. For those patients who did not have DU at Week 24, there was a wide span of pain levels reported in both groups, further suggesting that hand pain does not appear to be a sensitive measure for pharmacological intervention against DU disease.

Moreover, hand pain associated specifically with DU may be more related to ulcer localisation than to total ulcer number or area of open sores. Thus, fingertip ulcers are considered to be especially relevant for hand functionality in patients with SSc and DU but may not be sufficiently reflected in the overall hand pain VAS.

In this context, it is relevant to re-emphasise the effect of treatment with bosentan on the hand functionality components of the Scleroderma Health Questionnaire (SHAQ) VAS and, especially, the effect on the domain considered most reflective of fingertip function, that is, dressing, for which a consistent response to treatment with bosentan was seen in both trials and in pooled data (Figure 8). The sponsor considered this an important, supportive

observation that the reduction in number of new DU does translate into clinical benefit for the patient.

Figure 8. SHAQ: Placebo corrected changes from baseline to study endpoint in hand disability and component scores in trials RAPIDS-1 and RAPIDS-2. Pooled ITT data set.



*Study endpoint was Week 16 for AC-052-401 and Week 24 for AC-052-331. CL=Confidence Limits.

Conclusion

Active DU are associated with significant morbidity and impact on daily life, as well as potentially serious complications, and currently available, non-approved, therapies are unsatisfactory. RAPIDS-1 and RAPIDS-2 are the first trials to show a reproducible treatment effect in DU secondary to SSc, and by reducing the number of new DU, bosentan is the first oral treatment to show a benefit in patients with this rare disorder.

The magnitude of the treatment effect with bosentan (30% to 50% reduction in new digital ulcers), demonstrated in two adequate and well-controlled trials, is considered clinically significant.

Clinical benefit was obtained using the dose regimen proven efficacious in PAH, and similar vascular pathology is seen in pulmonary and digital arteries in SSc. The trigger for the development of digital ulcers remains unclear and those who have multiple and chronic digital ulcers are especially burdened. The finding that bosentan can provide a greater preventive effect in patients with a high ulcer burden than in those with milder disease provides a treatment that can reduce the occurrence and delay the onset of multiple digital ulcers, even in severely afflicted patients. As previously endorsed by Health Authorities, this effect is considered clinically important *per se*, and its clinical is also reflected by positive effects on components of hand functionality that are especially reflective of fingertip function, important for the patient's daily activities.

Given the difficulty and time needed to heal established digital ulcers and the potential loss of finger tissue, the prevention of new ulcers can reduce the overall ulcer burden and have a meaningful effect on symptoms, ability to use the hands, and the quality of life for these patients.

Importantly, the findings also provide clear evidence that treatment with bosentan does not confer benefit for healing of established digital ulcers, as would be expected from its pharmacological mode of action. This is also important information for prescribers and patients. In clinical practice, the benefit for the patient in the proposed indication can only be decided on an individual basis, and by the experienced treating physician and the patient together. Initiation of treatment with bosentan should be considered only in patients with active DU disease and should be continued only in those who show a relevant response to treatment. The need for continued therapy should be re-evaluated on a regular basis.

The risks with bosentan are well delineated through experience from clinical trials, focused post-marketing surveillance and spontaneous adverse event reporting.

The sponsor noted that the Clinical Evaluator and Delegate (and EU CHMP) agreed with the sponsor's conclusions that the safety profile of bosentan in trials RAPIDS-1 and RAPIDS-2 was consistent with that demonstrated in the currently approved therapeutic indication. The safety profile of bosentan has been shown to be manageable in clinical practice, but requires active and continuous adherence to risk minimisation measures, especially as regards monitoring of liver function and maintenance of adequate contraception in women of childbearing potential.

In summary, the sponsor firmly believed that the multiple and consistent efficacy findings in the RAPIDS-1 and RAPIDS-2 studies are clinically significant in the context of a positive benefit/risk assessment.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

- The ACPM considered this product to have a negative benefit-risk profile for the proposed indication, for the following reasons:
  - The submitted data did not demonstrate clinically significant efficacy for the appropriate quantitative or quality of life end points. Specifically, there was no evidence of a decrease in the proportion of patients developing some new ulcers, in healing time, infection rates or pain. The reduction in the number of new ulcers was not considered clinically significant.
  - While overall, adverse events were not markedly increased in the study group, this agent is a very efficacious antihypertensive agent and therefore presents significant safety risks that require careful monitoring.
  - Overall the clinical benefit was not sufficient to outweigh the adverse effects of the drug in the proposed population group.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of bosentan (Tracleer) tablets (62.5 mg and 125 mg) for oral administration for the indication:

> *The reduction in the number of new digital ulcers in patients with systemic sclerosis with active digital ulcer disease.*

The Delegate's findings with regard to quality, safety and efficacy were as follows:

Quality

1. The quality of the product had been satisfactorily established previously. There were no proposed changes to the quality of the product.

Efficacy

1. The two pivotal studies submitted with the application demonstrated statistically significant improvements in the number of new digital ulcers developing in patients.

   Evidence: Data from the sponsor's application.

2. The two pivotal studies submitted with the application did not demonstrate statistically significant improvements in:
   - The proportion of patients developing some new digital ulceration;

- Healing of existing digital ulcers;
- Pain;
- Infections in digital ulcers;
- Overall quality of life measures.

Evidence: Data from the sponsor's application.

3. The two pivotal studies submitted with the application did not consistently demonstrate statistically significant improvements in hand function.

   Evidence: Data from the sponsor's application.

4. The reduction in numbers of new digital ulcers was not clinically significant.

   Evidence: The ACPM advice.

Safety

1. Use of bosentan was associated with an increase in some adverse events compared to placebo, including:
   - Peripheral oedema;
   - Abnormal liver function tests.

   Evidence: Data from the sponsor's application and the Request for ACPM Advice'.

2. Use of bosentan was associated with an increase in the proportion of patients withdrawing from treatment due to adverse events compared to placebo.

   Evidence: Data from the sponsor's application and the Request for ACPM Advice'.

3. The types of adverse events associated with bosentan in the two pivotal studies were consistent with those observed with the drug in previously evaluated clinical trials.

   Evidence: Data from the sponsor's application and the Request for ACPM Advice'.

Efficacy and safety

1. Independent expert opinion indicated that the efficacy benefits obtained with bosentan were outweighed by the adverse effects of the drug.

   Evidence: The ACPM Advice.

Reasons for the decision

Given the independent expert advice provided by the ACPM, the Delegate concluded that, for the proposed new indication:

- Efficacy had not been satisfactorily established; and
- The efficacy benefits were outweighed by the drug's adverse events and that therefore the drug had an unfavourable balance of benefits and risks.

The Delegate therefore decided to reject the sponsor's application.

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