Product Name: Tracleer
Procedure No: EMEA/H/C/000401/II/0029

SCIENTIFIC DISCUSSION

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1. Introduction

Tracleer (bosentan) is an endothelin receptor (ET_A and ET_B) antagonist and thus competes with the binding of ET-1 and other ET peptides to both ET_A and ET_B receptors. Bosentan decreases both pulmonary and systemic vascular resistance resulting in increased cardiac output without increasing heart rate.
In February 2002, the CPMP recommended the granting of a Marketing Authorisation for the medicinal product TRACLEER 62.5 mg and 125 mg film-coated tablet.
The approved indication is:
Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in:

- *primary (idiopathic and familial) PAH*
- *PAH secondary to scleroderma without significant interstitial pulmonary disease.*
- *PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology*

The Marketing Authorisation Holder (MAH) applied to extend the indication to reduce the number of new ischemic digital ulcers in patients with systemic sclerosis and active digital ulcer disease based on results from two pivotal studies (RAPIDS-1 and RAPIDS-2).
In addition, an update to sections 4.2 (posology and method of administration), 4.4 (special warnings and special precautions for use), 4.8 of the SPC (undesirable effects) to describe the incidences of aminotransferase elevation and haemoglobin concentration changes seen in the proposed patient population in these studies and section 5.1 (pharmacodynamic properties) has been proposed to describe the clinical findings from the two pivotal studies.

The proposed posology is that Tracleer treatment should be initiated at a dose of 62.5mg twice daily for 4 weeks and then increased to the maintenance dose of 125mg twice daily.

2. Clinical aspects

2.1 Introduction

Systemic sclerosis (SSc) is a multisystem disorder of unknown etiology involving autoimmune mechanisms, which contribute to vascular damage, mainly to small arteries and arterioles, and excessive accumulation of collagen and other extracellular matrix components in skin and internal organs. The disease is characterised by progressive vascular damage (Raynaud's phenomenon and digital ulcers, hypertensive renal failure, cardiomyopathy, pulmonary hypertension) and organ fibrosis (skin thickening, pulmonary fibrosis, gastrointestinal dysmotility, myocardial fibrosis).
There are two types of skin involvement: limited cutaneous systemic sclerosis with skin thickening confined to the distal extremities and diffuse cutaneous systemic sclerosis with skin thickening involving the entire extremity frequently associated with visceral organ involvements.
Current management of SSc focuses on the organ manifestations of the disease, since no therapy has been shown to improve the overall course of SSc in blinded placebo-controlled trials. A common manifestation of the small-vessel vasculopathy in SSc is Raynaud's phenomenon, defined as episodic vasoconstriction of small arteries in the fingers. In some patients, ischemic ulcers develop on finger tips and in nail folds. Digital ulcers may develop together with other systemic manifestations of SSc (notably PAH and pulmonary fibrosis) or appear in patients with skin involvement only.

The MAH has performed a review of the available, published literature relating to digital ulcers (DU) in patients with systemic sclerosis (SSc) and their complications, and has in addition explored one US health care database and three hospital databases from the US and Europe. The review can be summarised as follows :

Estimation of the frequency of DU complications and therapeutic interventions is difficult due to several limitations inherent to the nature of the data available, but the consistency in the range of

estimates from the different sources of information provides some confidence in the reliability of the findings :

- A DU infection is estimated to occur annually in between 3 to 8% of DU patients, based on reported DU infections and incidence of antibiotic therapy for DU. Osteomyelitis of a phalanx is expected to occur annually in around 0.5% of these DU patients. The annual rate of DU patients hospitalised for antibiotic therapy is estimated to be 1% for those who have persistent or recurrent DU.
- Critical finger ischaemia is estimated to occur annually in 2 to 3% of DU patients.
- The annual incidence of SSc patients with DU having digital gangrene is estimated to be around 2–3% overall, with a range of 1 to 6%.
- The rate of DU patients hospitalised for their DU condition is estimated to be in the range of 5 to 10% per year. The frequency of hospital admissions is higher in SSc patients with persistent DU than in SSc patients without DU.
- The rate of DU patients hospitalised for the prevention or treatment of DU complications with parenteral prostanoids is estimated to be about 5% per year.
- Ten percent of DU patients may require chronic administration of opioids and dependency has been reported in up to 40% of these patients.
- The rate of DU patients that have to undergo sympathectomy is estimated to be in the range of 0.5 to 1% per year.
- Finger amputation may occur annually in between 0.5 and 1.5% of DU patients referred to hospital as in- or outpatients. In addition, auto-amputation, which is preferred as a conservative approach, may occur in up to 4% of DU patients every year.
- Arthrodesis to facilitate healing of ulcers overlying inter-phalangeal joints and to prevent sepsis is required in about 0.5% of DU patients per year.
- Additional morbidity is associated with the therapeutic means themselves, such as opioids, parenteral prostanoids, or digital sympathectomy. Furthermore these strategies do not prevent subsequent digital amputations due to the progressive nature of the obstructive vasculopathy.

In conclusion, 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.

A medication that can reduce the number of new DU during periods of disease activity could be of added value for the patient.

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 ulcers can be a major source of disability, interfering with the capacity to work and the activities of daily life that depend on hand function. Digital ulcers can also lead to the chronic use of analgesics and antibiotics, and sometimes to hospitalisation and surgery (including digital amputation). Few therapies have shown an effect on the evolution of digital ulcers. Results of studies suggest that intermittent intravenous iloprostol improves healing of digital ulcers and prevents episodes of digital ischaemia.

2.2. Overview of the clinical development programme

The clinical development to determine efficacy and safety of bosentan in patients with ischaemic digital ulcers secondary to SSc consisted of two similar multicentre (Studies AC-052-401and AC-052-331), randomised double-blind, placebo-controlled, parallel-group studies and were conducted in a total of 312 patients.

The first study (AC-052-401/RAPIDS-1) consisted of a 16-week double-blind treatment phase (N = 122), followed by an optional 12-week open-label phase.
The **primary endpoint** was the **number of new digital ischemic ulcers** during the 16-week double-blind treatment period.

The second study (AC-052-331/RAPIDS-2) consisted of a 24- to 36-week double-blind treatment period (N = 190) and an 8 week post-treatment follow-up period.
The **Co-primary endpoint** is defined as **total number of new digital ulcers per patient** up to Week 24 and **time to complete healing of the cardinal ulcer (CU)** up to Week 24 in patients whose CU healing was maintained 12 weeks.

Patients in the two double-blind, placebo-controlled studies had the opportunity to continue in following extension studies of RAPIDS-1 and RAPIDS-2. An interim report from the open label extension study AC052-333 is provided as additional information.
The table 1 below gives an overview of the therapeutic studies conducted in patients with digital ulcers secondary to systemic sclerosis.

Table 1 : Overview of the therapeutic studies in patients with digital ulcers secondary to systemic sclerosis

Protocol (Report no.)	Study objectives (Study design)	Study treatment*	Treatment duration	No. of patients enrolled
AC-052-401 RAPIDS-1 (D-05.149)	Efficacy and safety (DB)	Bosentan 62.5/125 mg b.i.d.	DB: 16 weeks	Bosentan 79
		Placebo		Placebo 43
	Long-term safety and efficacy (OL)	Bosentan 62.5/125 mg b.i.d.	OL: 12 weeks	Ex-bosentan 57
				Ex-placebo 31
AC-052-331 RAPIDS-2 (D-05.150)	Efficacy and safety (DB)	Bosentan 62.5/125 mg b.i.d.	24 weeks or up to 36 weeks for patients with healing of the CU after Week 12	Bosentan 100†
		Placebo		Placebo 90
AC-052-333 (Interim Report D-05.151)	Long-term safety and efficacy (OL extension of AC-052-331)	Bosentan 62.5/125 mg b.i.d.	Ongoing (data cut-off: 19 May 2005)	Enrolled as of cut-off 94

* 62.5/125 mg = forced titration after 4 weeks treatment.

† Two patients from one center that did not follow Good Clinical Practice regarding data recording were excluded from all analyses.

b.i.d. = twice daily, CU = cardinal ulcer, DB = double-blind phase, OL = open-label phase.

A total of 312 patients with a history of active ischemic digital ulcers secondary to SSc were enrolled in these two placebo controlled studies. Because digital ulcers associated with SSc may be precipitated by cold temperature, these studies were initiated during the coldest months of the year.
Most patients in both groups were female (76.7% and 82.0% in bosentan and placebo groups, respectively) and Caucasian (92.0% and 84.2%, respectively), with mean ages of 50.9 and 49.8 years, respectively.

No new clinical pharmacology studies were conducted for the programme in digital ulcers.

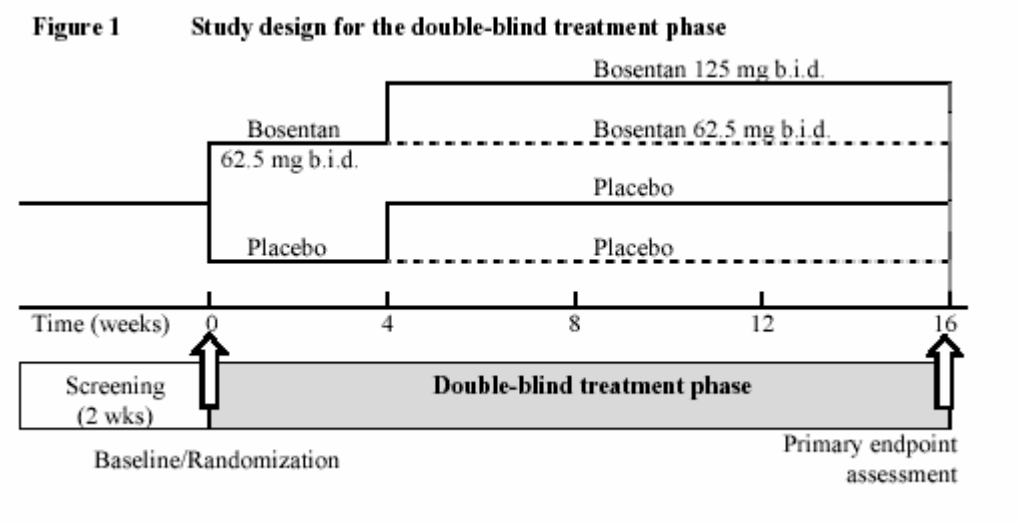
In addition, no specific dose finding study was considered necessary by the Applicant for the indication of digital ulcers in patients with SSc.
The dose regimen (initial dose of 62.5 mg b.i.d. for 4 weeks followed by up-titration to the target dose of 125 mg b.i.d.) proposed by the Applicant for the claimed indication is only based on benefit risk assessment of pulmonary arterial hypertension (PAH) patients. The safety profile of bosentan, the potential for birth defects and particularly hepatotoxicity, were not assessed for other dosage regimen in the proposed indication. Lower bosentan doses may have been effective and have better safety profile.

2.3 Study AC-052-401- RAPIDS-1

a) Methodology-study design
The primary objective of study AC-052-401/ RAPIDS-1 was to show a preventive effect of bosentan on the number of new ischemic digital ulcers occurring over the 16-week double-blind treatment

period. The study consisted of a 16-week double blind treatment phase, followed by an optional 12-week open label treatment phase for patients who completed the double blind phase and could receive possible benefit from continuing in the study.

Figure 1 Study design for the double-blind treatment phase



The patient population had history of documented digital ischemic ulcers (deep denuded areas of skin at least 1 mm wide with full epidermal loss) due to systemic sclerosis within the past year. Evolving digital ulcers, scars due to digital ulcers, and/or a history of gangrene/amputation were permitted. Efforts were to be made, however, not to include patients with digital ulcers due to extrusion of a calcification, particularly for patients with CREST syndrome defined as Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, and Telangiectasia (syndrome).

Eligible patients had also Raynaud's phenomenon and a diagnosis of either limited or diffuse systemic sclerosis using the American College of Rheumatology criteria (one major or two minor – see below). Patients with limited systemic sclerosis must have had Raynaud's phenomenon and at least 2 of the following: calcinosis, esophageal dysfunction, sclerodactyly, or telangiectasia.

Major	Proximal scleroderma	Tightness, thickening, and non-pitting induration changes proximal to the metacarpophalangeal or metatarsophalangeal joints, affecting other parts of the extremities, face, neck, or trunk.
Minor	Sclerodactyly	Tightness, thickening, and non-pitting induration changes distal to metacarpophalangeal or metatarsophalangeal joints, limited to fingers and toes
	Digital pitting scar	Depressed areas at tip of digit as a result of digital ischemia
	Bibasilar pulmonary fibrosis	Bilateral reticular pattern of linear or lineonodular densities that are most pronounced in basilar portions of the lungs on standard chest roentgenogram

Patients with either a history of ischaemic digital ulcers within the previous year, or with active digital ulcers at baseline were randomised, therefore they may have or may not have digital ulcer at baseline. However, almost all included patients had mainly skin manifestations of SSc.

- Primary and secondary endpoints:

The *primary endpoint* was *the number of new digital ischemic ulcers during the 16-week* double-blind treatment period.

Patients were evaluated on an outpatient basis at baseline and Weeks 4, 8, 12, and 16 or at premature withdrawal and at optional visits for patients with new digital ulcers occurring between scheduled visits. Patients in the EU were also evaluated 2 weeks after dose up-titration.

The *secondary endpoints* are listed below:

- Evaluations of digital ulcers:
  - Percentage of patients with new digital ulcers from baseline to week 16.
  - Time from baseline to onset of new digital ulcers.
  - Change in ulcer surface area over time.
  - Percentage of patients with complete or partial healing of digital ulcers during the 16-week study period.
  - Time from baseline to complete healing of digital ulcers.

- Quality of life as assessed by:
  - Vascular visual analogue scale to evaluate pain and Raynauds phenomenon
  - Disability index of the scleroderma health assessment questionnaire
  - Time to failure of therapy and reasons for failure of therapy.

- Safety and tolerability
  - clinical findings
  - vital signs
  - laboratory assessments
  - recording of adverse events

- Visual analog scale (VAS) for pain and Raynaud's phenomenon
  The vascular VAS assessment for scleroderma encompassing the six VAS of the Scleroderma Health Assessment Questionnaire (SHAQ) was to be completed at each visit except for the screening visit. Patients were instructed to respond to a question for each scale : pain scale, vascular scale, ulcer scale, GI scale, lung scale and scleroderma disease scale.

- Scleroderma Health Assessment Questionnaire
  The SHAQ was to be completed at baseline, at the end of the double-blind phase of the study (Week 16 or at premature withdrawal), and at the end of the open-label phase of the study. Patients were instructed to rate their capacity to perform selected activities of daily living within the previous 7 days. Missing values were considered missing, rather than zero, in the calculation.

- Study treatment

During the double-blind treatment phase, patients were randomized in a 2:1 ratio to one of two treatments:

- Bosentan 62.5 mg b.i.d. for the first 4 weeks, followed by up-titration to bosentan 125 mg b.i.d. for 12 weeks
- Placebo for 16 weeks

During the open-label treatment phase, all patients were to receive bosentan 62.5 mg b.i.d. for the first 4 weeks followed by bosentan 125 mg b.i.d. for 8 weeks without unblinding treatment during the double-blind phase.

Down-titration to or maintenance at 62.5 mg b.i.d. was available at any time for reasons of intolerability.

- Statistical Methods

The sample size was estimated conservatively assuming that the between-treatment comparison would be made using a Mann-Whitney-Wilcoxon two-sample test under the assumptions of a two-sided probability of 0.05, a power of 80%, and an expected distribution of patients with 0, 1, 2, or 3 new digital ulcers in the bosentan and placebo groups.
The protocol and analysis plan stipulate that the primary endpoint was to be analyzed on the intent-to-treat (ITT) population using a Mann-Whitney-Wilcoxon two-sample test ($\alpha = 0.05$, $\beta = 0.20$, main analysis) and using the Poisson regression with adjustment for overdispersion.

The analysis plan for the double-blind phase included several changes (protocol amendments) described in the protocol:

1) An all-randomized population was included, and the definition of the ITT population was altered to include only those patients who had a valid post baseline assessment of new digital ulcers. A second analysis of the primary endpoint was planned using the Poisson regression.

2) After completion of the double-blind treatment phase, several alternative analyses of efficacy variables to further explore the robustness of results were suggested during meetings with regulatory authorities.
It was concluded that neither the Mann-Whitney-Wilcoxon rank sum test specified in the protocol nor the Poisson regression added in the analysis plan was the most appropriate test, given the nature of the data. Consequently a post hoc analysis was performed, data were additionally analyzed using the permutation test with stratification by randomization block, in order to address deficiencies in both prespecified analyses.
This post hoc analysis could be acceptable as the permutation test demonstrated that the bosentan treatment effect was statistically significant as well as the Poisson regression

3) An additional analysis population was defined in order to appropriately analyze secondary endpoint based on digital ulcer healing.
Healing could only be assessed in patients who had digital ulcers present at baseline. In addition to parameters based on healing, all other efficacy parameters based on digital ulcers were also analyzed on this population for exploratory purposes, although this was not foreseen in the analysis plan

According to analysis plan all patients who prematurely discontinue treatment due to treatment failure as well as patients who are lost to follow up were assigned "worst rating". Failure to treatment occurred in placebo group and analysis plan was respected

b) Efficacy results

122 patients were randomized in a 2:1 ratio (79 bosentan and 43 placebo) at 17 centers in Europe and North America.

Nineteen patients were prematurely discontinued from the study during the double-blind phase (13 on bosentan and 6 on placebo), most often because of an adverse event.

- Summary of baseline information

In this study, all patients were supposed to have Raynaud's phenomenon but only 48.1% and 48.8%, respectively in bosentan and placebo groups were recorded to suffer from it at baseline.
The Raynaud's phenomenon is generally defined as episodic attacks of vasoconstriction of the small arteries precipitated by cold or emotional stress, occurs in over 90% of patients with systemic sclerosis.

In view of the high risk population included, defined as documented digital ischemic ulcers within the past year, patients entering in the study were allowed to continue treatment with oral vasodilatating drugs and other oral medications for Raynaud syndrome, including ACE inhibitors and calcium channel blockers.
Possible drug treatments for digital ulcers include oral vasodilators (calcium channel blockers, serotonin antagonists, angiotensin converting enzyme [ACE] inhibitors and intravenous (i.v.) prostaglandins.
However, only 36.7% and 48.8% patients, respectively to bosentan and placebo had selective calcium channel blocker treatment at baseline, and only 14.0% of patients and 17.7% of bosentan group had ACE-inhibitors as previous/concomitant treatments at baseline.

There is no clear data on digital ulcer management (topical treatments, surgery, grafting, local infection) in bosentan vs placebo group and a possible difference in DU management might represent a major bias on efficacy assessment (healing).

It is considered that the two groups are not comparable for several criteria at baseline. Several baseline data suggest milder skin involvement (as regards digital ulcers) in bosentan group as compared to placebo :

a) In both treatment groups, more patients were classified as having limited than diffuse skin disease, but limited systemic sclerosis occurred in a larger proportion of patients on bosentan than on placebo.

b) The times from diagnosis of systemic sclerosis and of digital ulcers were greater in the bosentan group than in the placebo group; 64.5(placebo) vs 98(bosentan) months. In addition, total number of digital ulcers per patient, ulcers interference with daily activity, Raynaud interference with daily activity and pain, were less important in bosentan group.

The impact of these factors on primary endpoint is addressed later in the discussion part.

- Main efficacy results of RAPIDS 1 study

	Placebo	**Bosentan**	**Test**	**p**
At Baseline At least one digital ulcers per patient [n (%)] Total number of digital ulcers per patient Mean (sd)	N=43 24(55.8%) 2.2 (2.9)	N=79 53(67.1%) 1.9 (2.1)		
At 16 weeks ITT population **(1)** Total of new ulcers per patient: mean (sd)	N=43 **2.7**(3.5)	N=78 **1.4.(**1.9)	Mann-Whitney U-test, Poisson regression permutation test	p = 0.1748 p = 0.0083 p = 0.0042
ITT population **(2)** Total of new ulcers per patient: mean (sd)	N=43 2.7(3.4)	N=78 1.4.(1.9)	Mann-Whitney U-test, Poisson regression permutation test	p = 0.1748 p = 0.0094 p = 0.0047
ITT population **(3)** Total of new ulcers per patient: mean (sd)	N=43 2.3(2.9)	N=78 1.4.(1.9)	Mann-Whitney U-test, Poisson regression permutation test	p = 0.2240 p = 0.0507 p = 0.0176
At least one new digital ulcers per patient [n (%)] **At 16 weeks(4)**	N=43 26(60.5%)	N=78 45(57.7%)		

(1) missing values were replaced using the worst" rating
(2) missing values were replaced using the trend carried forward method : Trend carried forward was based on the assumption that each patient would have developed new digital ulcers during the missing time period in the same manner as during the observed time period.
(3) missing values were replaced using the last observed value carried forward
(4)exact fisher test non provided by the MAH(p=0.85 (StatXact version6)

Patients to be included may have or may not have digital ulcer at base line. 67.1% of patients in bosentan group and 55.8% in the placebo had digital ulcers at baseline.

1) Overall ITT population (number of new digital ischemic ulcers during the 16-week) :
Overall ITT population including both patients with and without digital ulcers showed that patients on bosentan had fewer new digital ulcers than did those on placebo, means 1.4 vs 2.7, respectively, but the difference did not reach significance in the analysis based on ranks (Mann-Whitney U-test, p = 0.1748).
However, using the Poisson regression with correction for overdispersion, the treatment difference obtained in the ITT population was statistically significant (p = 0.0083). The more general permutation test with stratification by randomization blocks showed that the mean number of new digital ulcers was significantly less with bosentan than with placebo (p = 0.0042).

*2) Subgroup population of patients **with digital ulcers at baseline** (number of new digital ischemic ulcers during the 16-week):*
A separate analysis was performed with patients with digital ulcers at baseline. This subgroup was thought to be at greater risk for the development of new ulcers. This analysis, patients with digital ulcers at baseline, showed differences on efficacy results according to methodologies used for substitution of missing variables (LOCF, Trend carried). The predetermined method of handling missing values assigned the "worst" rating to patients who were discontinued due to treatment failure or were lost to follow up. For all other cases, missing values were replaced by trend carried forward, using carry forward of the last observed post-baseline value with correction for the missing time period.

Summary of additional analyses of the primary endpoint, patients in the ITT population with digital ulcers at baseline		
	Method for replacing missing values*	
	Trend carried forward	**Last observed value carried forward**
Number of new DU (mean ± SD)		
Bosentan (n = 52)	1.8 ± 2.2	1.8 ± 2.2
Placebo (n = 24)	3.6 ± 3.3	2.8 ± 2.5
p-value for treatment difference determined from:		
Mann-Whitney U-test	0.0344	0.0690
Poisson regression	0.0075	0.0778
Permutation test, stratified by randomization block	0.0391	0.1305

***** No "worst" rating applied.
DU = digital ulcers, ITT = intent to treat, SD = standard deviation.

The difference observed, 3.6 new ulcers in the placebo group vs 1.8 new ulcers in the bosentan group (p=0.0391; mean difference,1.8 new ulcers) is statistically significant only when "Trend carried forward" methodology is applied but is not statistically significant when LOCF methodology is used (1.8 new ulcers in bosentan group vs 2.8 new ulcer in placebo group, (p=0.135 ; mean difference, 1new ulcer).

In addition, if mean numbers of ulcers at baseline for the whole population are 1.9 for bosentan group and 2.2 for placebo group (0.3 mean difference), mean number of new ulcer for patients with digital ulcers at baseline can be approximately estimated at 2.8 new ulcers for bosentan group and 3.9 for placebo group, with then a mean difference of 1.1 new ulcers.
Consequently, the effect observed with the subgroup population of patients **with digital ulcers at baseline** is less important and varies then not from 0.3 to 1.8 but only from 1.1 to 1.8 new ulcers.

Summary of new digital ulcers during the 16-week double-blind treatment period by number of digital ulcers at baseline (altered substitution methods), ITT population

New ischemic digital ulcers during the 16-week study period, **using carry forward in place of worst substitution**			New ischemic digital ulcers during the 16-week study period, **using last value in place of worst substitution**	
	Placebo N=43	Bosentan N=78	Placebo N=43	Bosentan N=78
Number of new digital ulcers Patients with 0 ulcers at baseline				
n	19	26	19	26
Mean	1.5	0.6	1.5	0.6
Standard deviation	3.3	0.9	3.3	0.9
95% CL of mean	-0.0 , 3.1	0.3 , 1.0	-0.0 , 3.1	0.2 , 0.9
Median	0.0	0.0	0.0	0.0
95% CL of median	0.0 , 2.0	0.0 , 1.0	0.0 , 2.0	0.0 , 1.0
Min , Max	0.0, 13	.0 0.0 , 3.0	0.0, 13.0	0.0 , 3.0
Number of new digital ulcers Patients with 1-3 ulcers at baseline				
N	13	37	13	37
Mean	2.2	1.5	2.2	1.5
Standard deviation	2.0	1.8	2.0	1.8
95% CL of mean	1.0 , 3.4	0.9 , 2.1	1.0 , 3.4	0.8 , 2.1
Median	2.0	1.0	2.0	1.0
95% CL of median	0.0 , 6.0	0.0 , 2.0	1.0 , 6.0	0.5 , 2.0
Min , Max	0.0 , 6.0	0.0 , 8.0	0.0 , 6.0	0.0 , 8.0
Number of new digital ulcers Patients with 4 or more ulcers at baseline				
N	11	15	11	15
Mean	**5.1**	**2.7**	**3.5**	**2.7**
Standard deviation	3.9	2.7	3.0	2.7
95% CL of mean	2.5 , 7.8	1.2 , 4.2	1.5 , 5.5	1.2 , 4.2
Median	5.0	2.0	2.0	2.0
95% CL of median	1.0 , 9.7	1.0 , 5.0	1.0 , 8.0	1.0 , 5.0
Min , Max	0.0 , 11.2	0.0 , 9.0	0.0 , 8.0	0.0 , 9.0

CL=confidence limits.

The method for replacing missing values might have affected results particularly when missing values were replaced by "trend carried forward", using carry forward of the last observed post baseline value with time adjustment based on the number of new digital ulcers per unit time over the period observed. This could favour the arm in which withdrawals occur early (first month).
For 3 placebo-treated patient, and for 6 bosentan-treated patient, substituted value was "0" new ulcers. Four patients withdrew within first month in the bosentan arm (last assessment dated on D15, D22 and D29 (2 patients) while only one (D 29) withdrew in the placebo group and were considered as having no ulcers for the missing time period.

Even if the unbalanced 2:1 randomisation is taken into account, the difference could have favoured bosentan arm.
In conclusion, the Rapids 1 efficacy results are questionable particularly considering that groups are not comparable at baseline for several criteria and also when handling of missing data could have been in favour of bosentan group. Moreover, the secondary endpoint, vascular visual analogue scale assessment for pain, is not either convincing. Patients were instructed to mark on a continuous 15-cm scale, where 0 was none and 100 was the most severe. The visual analogue scale for pain at baseline was at 6.5 for both groups.

As secondary endpoint, pain decrease would have indicated a simple clinical benefit for the patient. the mean difference observed respectively –1.2 in placebo group and –1.6 in bosentan group is not statistically significant and not clinically relevant and which further establish that a clinical benefit, if any, would be slight.

The company provided an additional analysis of subgroups of patients with 0, 1-3 or with 4 or more ulcers at baseline.

No difference was observed for subgroups of patients with 0 or 1-3 ulcers at baseline independently of the methodology used. Preventive effect of bosentan seems to be of clinical interest only in a subgroup of patients having more than 4 digital ulcers at baseline, but differences were observed between bosentan and placebo groups depending on the methodologies used for missing variables (LOCF, Trend carried).

Decrease in number of new digital ulcers in patients with 4 or more ulcers at baseline were significant only when missing values were replaced using the trend carried forward method (5.1 vs 2.7, mean difference 2.4), but not when using the last observed value carried forward (3.5 vs 2.7., mean difference 0.8) (see table above). This sub category of the subgroup population corresponds to only 15 patients with bosentan treated group and 11 patients treated with placebo.

Several concerns were raised during the assessment regarding handling of missing data, robustness of the effect and its clinical relevance. They are addressed later in the discussion section of this report.

- Secondary endpoints

Quality of life was assessed by vascular visual analogue scale to evaluate pain and Raynauds phenomenon.

Visual analogue scale for pain
As secondary endpoint, pain decrease would have indicated a simple clinical benefit for the patient. The mean difference observed, respectively –1.2 in placebo group and –1.6 in bosentan group, is not statistically significant and not clinically relevant and which further establish that a clinical benefit, if any, would be slight.

In order to assess specific effects of digital ulcers on hand functionality, a hand disability index was introduced that comprised the dressing, hygiene, and grip scores of the *Scleroderma Health Assessment Questionnaire (SHAQ)*.

Summary of the change from baseline to Week 16 in selected SHAQ components assessing hand functionality, ITT set

SHAQ component (mean ± SD)	**Placebo (n = 41)**	**Bosentan (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).
ITT = intent to treat, SD = standard deviation, SHAQ = Scleroderma Health Assessment Questionnaire.

The composite of SHAQ components related to hand functionality showed an improvement in favour of bosentan group compared with those on placebo (p = 0.0041; Table above).

c) Safety results

The most frequently reported adverse event was headache,(17.7% and 16.3%, respectively). Clinically relevant marked elevations in liver aminotransferases (> 3 × upper limit of normal) were more frequent among bosentan- than placebo-treated patients (14.1% vs 0%), and an abnormal liver function test result was the main reason for discontinuation of bosentan therapy (5 patients vs none on placebo among the 12.7% and 9.3%, respectively, who were discontinued due to an adverse event). A small mean decrease in blood pressure (-3.0 mmHg systolic, -2.6 mmHg diastolic) was similar to that observed with placebo (-3.9 and -3.1 mmHg, respectively), and there was no relevant change in pulse rate. The small mean decrease in blood pressure observed at Week 4 either remained stable or returned towards baseline with continued treatment and was not associated with events of hypotension or postural hypotension.

The elevations in liver aminotransferases were asymptomatic, and had incidence, severity, and timing similar to what has been reported in other indications. LAT decreased with treatment discontinuation, interruption, and/or dose reduction.

No deaths on bosentan and placebo occurred during the double-blind phase. However, a patient subsequently died from severe pulmonary hypertension on 77 days after discontinuation of bosentan ie beyond the 28-day follow-up period. The investigator assessed the death as unrelated to bosentan treatment.

The SAEs that occurred during double-blind treatment or within 28 days after the end of treatment are summarized in table below. Five patients in total experienced an SAE, comprising 2.5% of patients on bosentan and 7.0% on placebo. Of the two patients on bosentan, one experienced ventricular tachycardia, and the other experienced dyspnea, aspiration pneumonia, ventricular tachycardia, and palpitations. In both patients, the events were likely related to the underlying disease (pulmonary arterial hypertension and cardiac condition, respectively).

Summary of serious adverse events during or within 28 days after the end of double-blind treatment, safety population

Body system / Adverse event	**Placebo** N=43 No.(%)	**Bosentan** N=79 No. (%)
All body systems		
Total pts with at least one SAE	3 (7.0%)	2 (2.5%)
Total number of SAEs	5	5
ventricular tachycardia	-	2 (2.5%)
dyspnoea	-	1 (1.3%)
palpitations	-	1 (1.3%)
pneumonia aspiration	-	1 (1.3%)
dyspnoea exacerbated	1 (2.3%)	-
oesophagitis	1 (2.3%)	-
peripheral ischaemia	1 (2.3%)	-
pulmonary oedema	1 (2.3%)	-
vomiting	1 (2.3%)	-

The preferred term 'DISEASE PROGRESSION' was associated to each of the symptoms/diagnosis terms reported together with it.SAE = serious adverse event, pts = patients.

Fourteen patients (12.7% of patients on bosentan and 9.3% on placebo) were prematurely discontinued from double-blind treatment because of an adverse event. Five patients on bosentan were discontinued due to an abnormal liver function test (including increased ALT and/or AST and increased transaminases), and two patients on bosentan were discontinued due to gastro-esophageal reflux disease.

2.4 Study AC-052-331- RAPIDS-2

a) Methodology – Study design

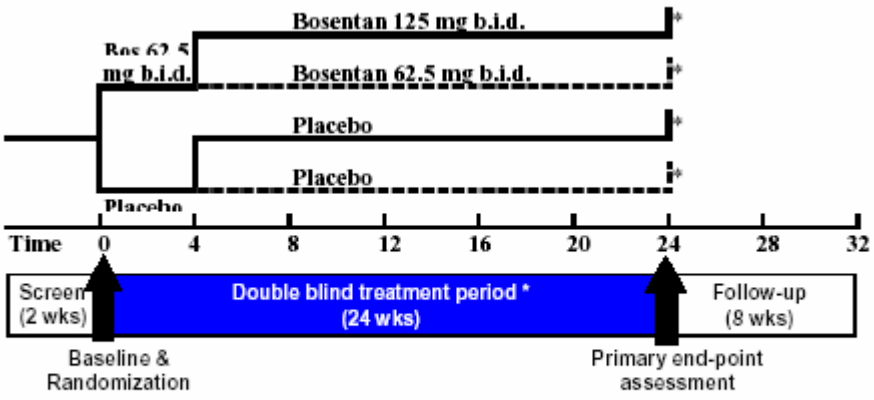
In this study, the primary objectives were to evaluate the effect of bosentan both on prevention and on healing of ischemic digital ulcers in patients with SSc suffering from active ischemic digital ulcers.

The following *definitions* have been used for the study:

Digital ulcer**:** A digital ulcer was defined as a painful area with visually discernable depth and a loss of continuity of epithelial coverage, which could be denuded or covered by a scab or necrotic tissue. If denudation was not clearly visible, loss of epithelialization, epidermis, and dermis was to be determined by the investigator. If the area was denuded, the ulcer was pronounced active. If denudation could not be judged because of the presence of a scab or necrotic tissue, the ulcer was pronounced indeterminate. This definition did not include fissures, paronychia, extrusion of calcium, or ulcers over the metacarpophalangeal joints or elbows. Only digital ulcers from the proximal interphalangeal joints distally were to be assessed.

Cardinal ulcer**:** A CU was defined as a digital ulcer distal to the proximal interphalangeal joint, volar to the equator of the finger, and not localized in the proximal or distal interphalangeal creases, which was vascular in origin, painful, possibly triggered by trauma, and was without bone infection or calcinosis. It was to be at least 2 mm in size and de-epithelialized with clear 'depth' (loss of epidermis and dermis). The CU was to be selected by the investigator based on the clinical judgment that it could both heal and be evaluated for healing. If several digital ulcers were qualified, the CU could be either the largest or the most painful ulcer, or the ulcer that disturbed the patient the most (within the definition of the CU). For each patient, only one digital ulcer was to be identified by the investigator as the CU. Patients with SSc felt to be at high risk for digital ulcers were to be identified duringthe screening period but were not eligible for enrolment until a CU developed. The status of each digital lesion was to be rated as "U", a current digital ulcer according to the definition, "H", a completely healed digital ulcer, or "I", an ulcer with indeterminate status between a current digital ulcer by definition and a completely healed ulcer.

Figure 1 Overall study design



* The treatment period could be extended for an additional 4, 8, or 12 weeks for patients whose cardinal ulcer healed at Week 16, 20, or 24, respectively. In such case, healing maintenance was assessed at the end of treatment.

Patients who completed RAPIDS-2 and still had digital ulcers or who developed a digital ulcer after the end of the follow up period could continue treatment in AC-052-333.

- Study population

Eligible patients were:

- Patients with SSc according to the classification criteria of the American College of Rheumatology as defined by the presence of one major or two minor criteria (see definition in RAPIDS-1 study).
- SSc patients with at least one DU at baseline qualifying as a CU
  CU occurred < 3 months and > 1 week prior to randomization The subset of patients with SSc felt to be at high risk for Dus will be identified in the screening period but will not be eligible for enrolment until a CU has developed.

Patients with severe PAH (World Health Organization class III and IV) were excluded from the study as well as those receiving antibiotics or inhaled oral or parenteral prostanoids for infected ulcers.

- Primary and secondary endpoints:

The *primary endpoints* were as follows: (Co-primary endpoints):

- *New digital ulcers:* Total number of new digital ulcers that were observed by the investigator at planned visits up to Week 24
- *Time to complete healing:* Time to complete healing of the CU up to Week 24 in patients whose CU healing was maintained for 12 weeks

The co-primary objective of both prevention and healing was requested by FDA based on the need for healing in the treatment of the disease. In order to evaluate the treatment effect on healing, a baseline

CU that might be amenable to healing during the time frame of the study was defined during meetings with the Steering Committee. The maintenance of a healing effect for 12 weeks of continued treatment was considered appropriate to the assessment of healing by the FDA.

As a consequence, all patients were to have active digital ulcers at baseline, and the investigator was to identify at baseline a CU of recent onset that was considered amenable to healing and which could be evaluated for healing during the study.
It should be noted that in RAPIDS-2 "prevention" and "treatment" designs are mixed although the designs are not similar:
In the "prevention trial", the primary endpoint is "no new ulcer". In the healing trial, the primary endpoint is complete healing. These endpoints address different questions and should be analysed separately. However, taken into account this multiplicity, an alpha spending correction rule has been applied.

The *Secondary efficacy endpoints* were as follows:

- Prevention endpoints:
  - Proportion of patients without a new digital ulcer up to Week 24
  - Proportion of patients who do not develop any new digital ulcers after the first 4 weeks of treatment up to Week 24.

- Healing endpoints:
  - Proportion of patients with complete healing of all digital ulcers (baseline and new) at Week 24
  - Time to complete healing of each of the baseline digital ulcers up to Week 24.

- Overall evaluation of digital ulcers:
  - Change from baseline to Week 24 in the total number of observed digital ulcers

- Quality-of-life endpoints:
  - Change from baseline to Weeks 12 and 24 in hand disability index (composite of dressing/grooming, grip, and hygiene components of the SHAQ)
  - Change from baseline to Weeks 12 and 24 in overall hand pain as assessed by a VAS

- <u>Study treatment</u>

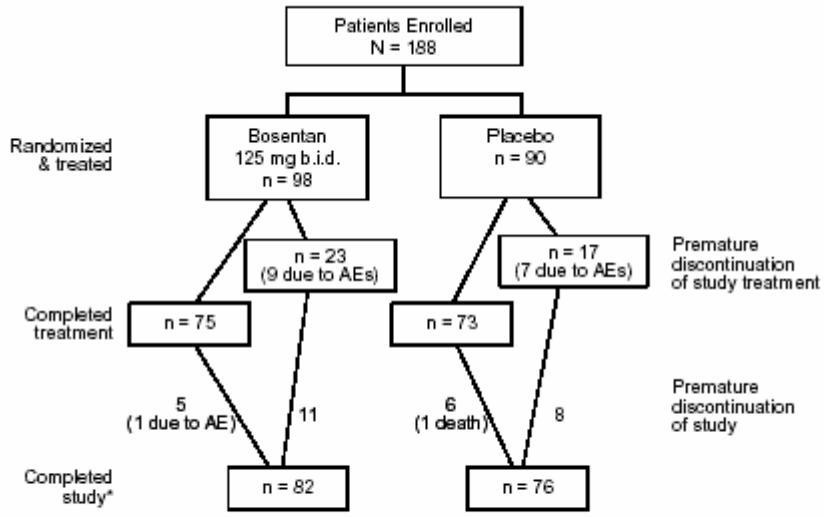
Patients were randomized to either bosentan or placebo with an initial dose of bosentan 62.5 mg twice daily (b.i.d.) for the first 4 weeks and a target dose of bosentan 125 mg b.i.d. for the rest of the 24- to 36-week treatment period.

Down-titration to or maintenance at 62.5 mg b.i.d. was available at any time for reasons of intolerability with possible subsequent up-titration to the target dose.

b) Rapids 2 study Efficacy results

A total of 190 patients were randomized to bosentan (n = 100) and placebo (n = 90) in 42 centers in Europe and North America. Two patients from were excluded from the study analyses because the center failed to comply with GCP guidelines regarding study documentation and the data were considered unreliable. 188 patients remained in the study (98 bosentan, 90 placebo).
The disposition of patients is presented in the figure below:

Figure 3 Disposition of patients



* Study was completed at the end of the 56-day follow-up period for patients who completed study treatment and at the final assessment for the primary endpoints (Week 24 or later) for patients who were prematurely discontinued from study treatment.

AE = adverse event.

- Summary of baseline information

The placebo group had a larger proportion of patients who were current smokers (21.6% vs 12.8% in the bosentan group). It appears that standard management care has not been taken into account in this study design. Smoking is one of the factors known to be associated with severity of disease. Patients with systemic sclerosis (SSc) are at high risk for digital vascular complications. Moreover groups at baseline is not well matched. The Applicant addressed all the aspects of baseline imbalances during review, and a discussion appears later in this assessment.

Patients entering in the study were allowed to continue treatment, however, only 52.0% and 55.6% patients, respectively to bosentan and placebo had selective calcium channel blocker treatment at baseline, and only 14.4% of placebo groups and 16.3% of bosentan group had ACE-inhibitors as previous/concomitant treatments at baseline.
Moreover, it should be noted that around 2% of patients used nasal preparation with vasoactive effect.

Concomitant treatments at baseline were not comparable between bosentan and placebo groups. Antibacterials for systemic use, psychotropic agents with vasoactive effect, antiseptics and emollients were more important in bosentan group than in placebo group. On the other hand smokers, immunosuppressive agents, opioids and other analgesics were more important in the placebo group.

- Main efficacy results of RAPIDS 2 study : primary endpoints

	Placebo	**Bosentan**	Test	**p**
At Baseline(4) number of digital ulcers per patient Mean (sd)	 N=90 3.6(3.3)	 N=98 3.7 (4.4)		
Patients with complete healing of the cardinal digital ulcer up to 24 weeks (time to complete healing)	N=90 50	N=98 49	Log-rank test (*)	P=0.6327
During the 24 weeks Treated population (1) Number of new digital ulcers per patient(sd)	 N=89 2.7 (3.3)	 N=95 1.9(2.2)	 Pitman permutation Wilcoxon exact Poisson	 p = 0.0351 p = 0.1791 p = 0.0001
Treated population (2) Number of new digital ulcers per patient(sd)	N=90 2.2(2.6)	N=98 1.9.(2.1)	Pitman permutation Wilcoxon exact	p = 0.3452 p = 0.5695
Treated population (3) Number of new digital ulcers per patient(sd)	N=90 4.2 (5.5)	N=98 5.3 (6.4)	Pitman permutation Wilcoxon exact	p = 0.2359 p = 0.4286
Treated population (4) Number of new digital ulcers per patient(sd)	N=90 1.9 (2.7)	N=98 1.4 (1.9)	Pitman permutation Wilcoxon exact	p = 0.0875 p = 0.2126
During the 24 weeks Patients with at least one ulcer n (%)	N=89 63 (70.8%)	N=95 63 (66.3%)	Fisher test	P=0.5298

(*)cox model : Hazard ratio 0.909 and 95% CL (0.613 , 1.348)
(1) missing values were replaced using the "trend" method : Trend carried forward was based on the assumption that each patient would have developed new digital ulcers during the missing time period in the same manner as during the observed time period
(2) substitution method : Intergroup cross
(3) substitution method : Worst observed outcome
(4) substitution method: Best observed outcome

In RAPIDS-2 trial two endpoints were investigated, one for prevention and one for treatment. No effect on healing was observed with bosentan compared with placebo, including in the time to complete healing of the CU.
During 24 weeks of double-blind treatment, patients on bosentan had fewer new digital ulcers than did those on placebo (1.9 vs 2.7 new digital ulcers).
However, in order to keep the alpha risk at 0.05 for the whole trial, a multiplicity correction must be applied. This correction would necessarily make the only positive conclusion (prevention) no longer significant.
In Rapids-2, the difference between groups is not statistically significant (p=0.0351) even after adjustment for ulcers at baseline (p=0.0497).

The difference between groups at baseline of mean number of new ulcer for patients with digital ulcers at baseline was approximately estimated at 1.1 new ulcers. According to methodologies used for substitution of missing variables (LOCF, Trend carried) the difference between groups was 1 or 1.8 new ulcers. The effect observed was considered by the rapporteur to be not significant and the results questionable in term of robustness. The issue of robustness was discussed at length in the Oral Explanation (see later in this report) and the CHMP concluded that indeed the treatment effects were robust.

- Secondary endpoints results

Exploratory subgroup analyses were performed by the number of digital ulcers at baseline and number of ulcers at baseline (<= 3 or > 3 digital ulcers).

Number of digital ulcers: Change from baseline to Week 24 by number of digital ulcers at baseline, all-treated set

	Placebo N=90	Bosentan N=98
Change in total number of digital ulcers patients with baseline DUs <=3		
n	60	59
Mean	**-0.5**	**-0.6**
Standard deviation	2.2	1.6
Standard error	0.3	0.2
95% CL of mean	-1.1 , 0.1	-1.0 , -0.2
Median	-1.0	-1.0
95% CL of median	-1.0 , -1.0	-1.0 , 0.0
Min , Max	-3.0 , 9.2	-3.0 , 6.1
Change in total number of digital ulcers patients with baseline DUs >3		
n	29	36
Mean	**-3.6**	**-3.4**
Standard deviation	4.9	4.3
Standard error	0.9	0.7
95% CL of mean	-5.4 , -1.7	-4.8 , -1.9
Median	-4.0	-3.5
95% CL of median	-5.0 , -2.0	-4.0 , -3.0
Min , Max	-13.0 , 6.7	-19.0 , 7.0

Proportion of patients without new digital ulcers after the first 4 weeks and up to Week 24 by number of digital ulcers at baseline, all-treated set

	Placebo N=90	Bosentan N=98
Patients with baseline DUs <=3		
n	56	57
Patients without new DUs	23 (41.1%)	23 (40.4%)
95% confidence limits	28.1%, 55.0%	27.6%, 54.2%
Treatment effect:		
Relative risk		0.98
95% confidence limits		0.63, 1.53
Patients with baseline DUs >3		
n	29	35
Patients without new DUs	7 (24.1%)	8 (22.9%)
95% confidence limits	10.3%, 43.5%	10.4%, 40.1%
Treatment effect:		
Relative risk		0.95
95% confidence limits		0.39, 2.30

The company provided an additional post hoc analysis of subgroups of patients with less or > 3 digital ulcers at baseline
This sub category of the subgroup (patient with digital ulcers at baseline) showed same trend than those observed in subgroup analysis of RAPIDS-1 study.

VAS: Changes from baseline to Weeks 12 and 24 in overall hand pain, all-treated set

As secondary endpoint, pain decrease would have indicated a simple clinical benefit for the patient. The mean difference observed respectively –24 in placebo group and –26 in bosentan group is not statistically significant and not clinically relevant and which further establish that a clinical benefit, if any, would be slight.

In order to assess specific effects of digital ulcers on hand functionality, a hand disability index was introduced that comprised the dressing, hygiene, and grip scores of the Scleroderma Health Assessment Questionnaire (SHAQ).

Summary of the change from baseline to Week 24 in selected SHAQ components assessing hand functionality, all treated set

SHAQ component (mean ± SD)	**Placebo (n =90)**	**Bosentan (n =98)**	**p-value (Mann-Whitney U-test)**
Dressing and grooming	-0.05 ± 0.09-	-0.33 ± 0.09	0.0327
Hygiene	0.22 ± 0.07†	-0.07 ± 0.08	0.1745
Grip	-0.13 ± 0.08	-0.12 ± 0.07	1.0000
Hand functionality*	-0.13 ± 0.05	-0.17 ± 0.06	0.6234

* Hand functionality (hand disability index) is a composite of the dressing, hygiene, and grip components.
† n = 86.
SEM = standard error of the mean,

The hand functionality one component of SHAQ showed improvement from baseline with bosentan therapy at Weeks 12 and 24 (Table above). However, improvement in hand functionality was also seen in the placebo group, and unlike in RAPIDS-1, the treatment effect for bosentan was not statistically significant. However, a treatment effect was observed for dressing activities, the SHAQ remains most reflective of fingertip function.
Secondary endpoints assessing the quality of life were also evaluated in subgroups defined by the number of digital ulcers at baseline. In general some composite showed a trend of improvement. Compared with placebo, patients on bosentan showed improvements in most SHAQ assessments, but the differences were small in most cases in the pooled analysis.

c) Safety results

The most frequently reported adverse event was headache, which occurred with similar incidence in the two treatment groups (16.5% and 16.3%, respectively). Clinically relevant marked elevations in liver aminotransferases (more than three times the upper limit of normal [ULN]) were more frequent among bosentan- than placebo-treated patients (14.1% vs 0%), and an abnormal liver function test was the main reason for discontinuation of bosentan therapy (five patients vs none on placebo among the 12.7% and 9.3% of patients, respectively, who were discontinued due to an adverse event). These laboratory abnormalities were asymptomatic, had an incidence, severity, and timing similar to those in bosentan-treated PAH patients, and decreased with treatment discontinuation, interruption, and/or dose reduction.
The small mean decreases in systolic and diastolic blood pressures with bosentan (-3.0 and -2.6 mmHg, respectively) were similar to those observed with placebo (-3.9 and -3.1 mmHg, respectively), and there was no relevant change in pulse rate. The small mean decreases in blood pressures and small mean increase in body weight observed at Week 4 with bosentan either remained stable or returned towards baseline with continued treatment and were not associated with symptomatic or postural hypotension.

In bosentan-treated PAH patients, elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to > 3 × ULN have been observed in approximately 11% of patients (vs 2% on placebo) and associated increases in bilirubin to >3 × ULN in 0.3%. The clinical database shows that the incidence of elevations in aminotransferases associated with bosentan treatment are dose dependent, and that the elevations are typically asymptomatic, usually occur early in treatment and progress slowly, and to date have reversed spontaneously on continued treatment or decreased after dose reduction, interruption, or permanent discontinuation of bosentan treatment. Bosentan treatment is also associated with dose-related decreases in hemoglobin concentration and hematocrit, considered to be related to hemodilution. There is no evidence for hemorrhage, hemolysis, or bone marrow toxicity of bosentan. In patients with severe chronic heart failure, fluid retention (weight gain, leg edema) was observed during the first weeks of treatment.

No deaths on bosentan and placebo occurred during the treatment but some occured up to 56 days after the end of study treatment.
One patient died due to acute respiratory distress syndrome 36 days after completing placebo treatment.
One patient died due to a general deterioration in physical health 58 days after bosentan treatment was prematurely discontinued due to pneumonia. The general worsening of the patient's condition was considered by the investigator to be unrelated to study treatment but began on an unknown date that could have been within the 56-day follow-up period.
Two additional deaths were known to occur after the 56-day cut-off for the safety follow up.

Suspected pulmonary hypertension and/or pneumonia were unconfirmed, but the investigator felt pulmonary hypertension could have been the result of stopping study treatment (i.e., potentially related to study medication).

Serious adverse events (SAEs) were less frequent in patients on bosentan than placebo (9.4% vs 16.7%) during the treatment period and similar in the two groups during the 56-day safety follow-up (4.2% and 4.4%). However, two Pneumonia were experienced by bosentan-treated patients vs none on placebo group, one episode of diplopia, one case of severe anemia and one case of dyspnea. Imputability of pneumonia cases is not clearly established as well as respiratory adverse events observed with bosentan treatment.

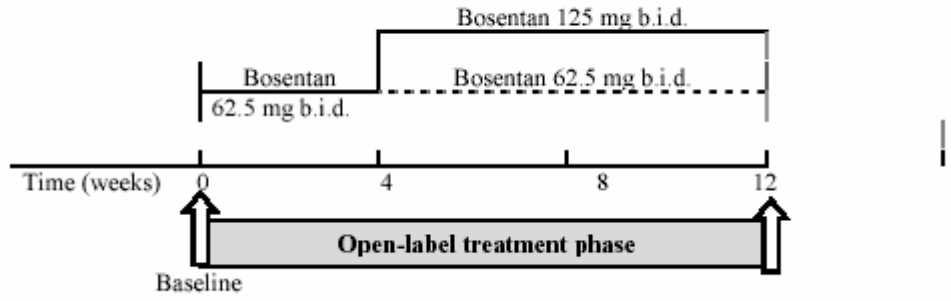
2.5 Uncontrolled trials

Patients in the two double-blind, placebo-controlled studies had the opportunity to continue in following extension studies of RAPIDS-1 and RAPIDS-2.

2.5.1 Open-label follow up RAPIDS-1 study

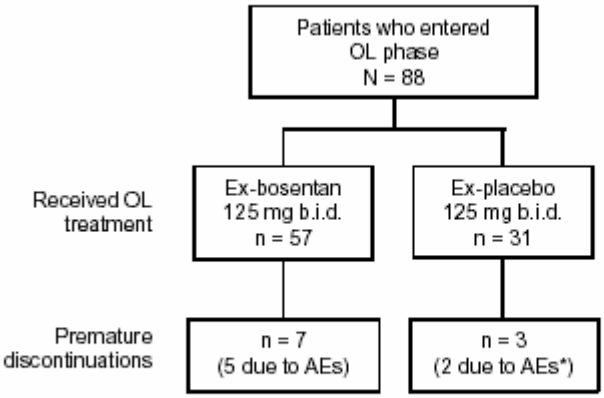
Patients who completed the Week-16 assessments RAPIDS-1 study entered the open-label part.
Irrespective of the previous double-blind study medication, all patients were to be started on bosentan 62.5 mg b.i.d., up-titrated after 4 weeks to bosentan 125 mg b.i.d., and treated for the remainder of the open-label phase (Figure below).

Figure 14 Study design for the open-label treatment phase



The 88 patients who continued in the open-label phase represented 72.1% and 72.2% of the original randomized bosentan and placebo groups, respectively. The open-label treatment was started, without knowledge of treatment in the previous controlled trial. Patients who did not continue with open-label treatment did not have digital ulcers at the end of the double blind phase, did not feel they needed treatment, and/or did not continue for reasons of convenience.

Figure 15 Disposition of patients during the open-label phase



* For one ex-placebo patient, the reported reason was treatment failure, which was in association with an adverse event (see Sections 14.4.3 and 14.6.4).

AE = adverse event, b.i.d. = twice daily, OL = open label.

Efficacy results :

Summary of new digital ulcers during the 12-week open-label treatment period, OL all-treated set

	Ex Placebo N=31	Ex Bosentan N=57	All patients N=88
Number of new digital ulcers			
n	31	57	88
Mean	0.5	0.8	0.7
Standard deviation	0.9	1.5	1.3
95% CL of mean	0.2 , 0.9	0.4 , 1.2	0.4 , 1.0
Median	0.0	0.0	0.0
95% CL of median	0.0 ,1.0	0.0 ,1.0	0.0 ,0.0
Min, Max	0.0 , 4.	0.0 , 7.0	0.0 , 7.0

95% CL of median

Summary of new digital ulcers during the 12-week open-label treatment period in patients with and without baseline digital ulcers, OL all-treated set

	Ex Placebo N=31	Ex Bosentan N=57	All patients N=88
Patients with digital ulcers at baseline(*)			
Number of new digital ulcers			
n	18	35	53
Mean	0.8	1.1	1.0
Standard deviation	1.1	1.8	1.6
95% CL of mean	0.2 , 1.3	0.5 , 1.7	0.5 , 1.4
Median	0.0	0.0	0.0
95% CL of median	0.0 , 1.0	0.0 , 1.0	0.0 , 1.0
Min , Max	0.0 , 4.0	0.0 , 7.0	0.0 , 7.0
Patients without digital ulcers at baseline			
Number of new digital ulcers			
n	13	22	35
Mean	0.2	0.4	0.3
Standard deviation	0.5	0.8	0.7
95% CL of mean	-0.1 , 0.5	0.1 , 0.8	0.1 , 0.6
Median	0.0	0.0	0.0
95% CL of median	0.0 , 1.0	0.0 , 1.0	0.0 , 0.0
Min , Max	0.0 , 1.5	0.0 , 3.0	0.0 , 3.0

(*) This population corresponds to the analysis set

CL=confidence limits.

The incidence of new digital ulcers was evaluated during the 12-week open-label treatment phase and also in the subgroups consisting of patients with or without digital ulcers at baseline. During the 12-week open label treatment phase, patients had a 0.5 mean number of new digital ulcers in the placebo group versus 0.8 mean number of digital ulcers in the bosentan group.

The proportions of patients who had no new digital ulcer during the 12 weeks of open label treatment were similar in bosentan and placebo groups respectively 57.1% and 56.6%. Therefore the minor difference observed on number of new ulcers is not clinically relevant.

- Safety results :

The most frequent event, headache, was more frequent among ex-placebo patients newly treated with bosentan during the open-label phase (12.9% vs 8.8% in ex-bosentan patients). Also more frequent among ex-placebo patients were diarrhoea (9.7% vs 5.3% on bosentan) and nausea (9.7% vs none). Events of arthralgia, exacerbated dyspnoea, infected skin ulcer, and peripheral oedema were reported only in the ex-bosentan group (8.8%, 7.0%, 7.0%, and 5.3%, respectively).

SAEs were reported by 12.5% of patients during the open-label phase. All SAEs during the open-label phase were considered by the investigator to be unrelated to bosentan treatment.
No deaths occurred during or within 28 days of the end of open-label treatment.

2.5.2 Open-label follow up RAPIDS-2 Study (AC-052-333) :

This study enrolled patients who completed the 24- to 36-week treatment period and the 8-week follow-up period of RAPIDS-2 (AC-052-331) and who still had digital ulcers or who developed a new digital ulcer after the last follow-up visit.
Eligible patients must have met all of the following inclusion criteria before study treatment initiation :
• Completed the full study period (24- to 36-week treatment period and 8-week follow up) of the RAPIDS-2 study

• Presented with digital ulcers at the end of the RAPIDS-2 study or developed new digital ulcers thereafter until the RAPIDS-2 study results were released to the investigators
The MAH submitted data from an interim report intended to summarize the limited safety data available as of the clinical cut-off date (19 May 2005). Only the information on demographics, premature withdrawals, and serious adverse events (SAEs), including those with fatal outcome, has been included.

- Study Treatments

Bosentan: bosentan 62.5 mg b.i.d. for the first 4 weeks, followed by up-titration to bosentan 125 mg b.i.d. for the remainder of the study. Tablets were to be administered orally, irrespective of food intake, in the morning and approximately 12 hours later.

This open-label extension study for patients who had been exposed to a 24- to 36-week treatment period in RAPIDS-2 was requested by Health Authorities (US Food and Drug Administration) to document the long-term efficacy and tolerability of bosentan in the treatment of SSc patients with ischemic digital ulcers. The results of final report will provide information to verify if the small effect observed is sustained over.

2.6 Discussion on the clinical efficacy data provided to support the new indication

- ***Baseline characteristics***

The CHMP requested during the procedure additional information regarding the baseline characteristics for both bosentan and placebo groups.
Several concerns were addressed:
1) The included population appears to be less severely affected as compared to what would have been expected. In RAPIDS-1, only 48.1% and 48.8% respectively in bosentan and placebo groups were

recorded to have Raynaud's phenomenon while all patients were supposed to have Raynaud's phenomenon as an inclusion criteria.

In RAPIDS-1 study, in both treatment groups, more patients were classified as having limited than diffuse skin disease, but limited systemic sclerosis occurred in a larger proportion of patients on bosentan than on placebo. Also in RAPIDS-2, more patients had limited than diffuse form, which reflects the general pattern of the disease. However, in RAPIDS-2, the bosentan and placebo groups were balanced at baseline regarding the sub-type of Systemic Sclerosis.

2) Concomitant treatments at baseline and ulcer management
In view of the high risk population included, defined as documented digital ischaemic ulcers within the past year, patients entering in the study were allowed to continue treatment with oral vasodilatating drugs and other oral medications for Raynaud syndrome, including ACE inhibitors and calcium channel blockers (CCB). However, only 14.0% of patients and 17.7% of bosentan group had ACE-inhibitors as previous/concomitant treatments at baseline. In addition, only 36.7% and 48.8% patients respectively to bosentan and placebo had selective calcium channel blocker treatment at baseline. Respectively in RAPIDS-2 only 14.4% of placebo groups and 16.3% of bosentan group had ACE-inhibitors as previous/concomitant treatments at baseline. In addition, only 52.0% and 55.6% patients respectively to bosentan and placebo had selective calcium channel blocker treatment at baseline.
The low representation (around 50%) of patients treated with ACE and CCB in the trial appears much lower than what would have been expected in a population suffering from Raynaud disease. This also limits the robustness of the results as they might not be obtained in a representative population.

There is no clear data on digital ulcer management (topical treatments, surgery, grafting, local infection) in bosentan vs placebo group. A possible difference in DU management might represent a major bias on efficacy assessment (healing).
The low representation (around 50%) of patients treated with ACE and CCB in the trial appears much lower than what would have been expected in a population suffering from Raynaud disease. This also limits the robustness of the results as they might not be obtained in a representative population.

Differences in baseline characteristics in control and treatment arms in both trials could have led to a more pronounced benefit in treatment groups.

- For RAPIDS-1 this applies to the times from diagnosis of systemic sclerosis and of digital ulcers, total number of digital ulcers per patient, ulcers interference with daily activity, Raynaud interference with daily activity and pain.
- For RAPIDS-2 this applies to patients who were current smokers, concomitant disease (history of digital amputation, history of hypothyroidism, concomitant/previous treatments (psychotropes with vascular effects, systemic antibiotherapy, antiseptics, cicatrisant, emollients

The MAH was asked to discuss the impact of the imbalance between the active group and the placebo group in disease classification, and, for RAPIDS-1, the potential importance of the differences in concomitant treatment.

Despite numerous studies on the management of Raynaud's phenomenon, definitive guidelines have not been established, and good scientific evidence for treatment is often lacking (Hummers LK, Wigley FM. Management of Raynaud's phenomenon and digital ischaemic lesions in scleroderma. Rheum Dis Clin North Am 2003; 29(2): 293 -313).

A meta-analysis reviewed all the studies of calcium channel blockers that are used for the treatment of Raynaud's phenomenon in patients who have SSc, and showed only a moderate reduction in mean number of Raynaud's attacks and a 35% improvement in severity. This modest improvement in SSc was less robust than the one reported in studies of primary Raynaud's phenomenon (Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. Arthritis Rheum 2001;44(8):1841–7.).

The treatments used for Raynaud's phenomenon and digital ulcers in SSc include mainly calcium channel blockers, ACE inhibitors, Angiotensin II antagonists, ketanserin, sympatholytics such as prazosin, and peripheral vasodilators such as pentoxifylline or buflomedil.

The use of these different classes was different across countries in RAPIDS-1 and RAPIDS-2. Calcium channel blockers were less often used in France and the UK than in the USA, Canada, Italy or Germany. ACE inhibitors were used more frequently in the UK, France and Canada than in other countries. Angiotensin II antagonists were used more frequently in the UK than in other countries. Peripheral vasodilators such as pentoxifylline were predominantly used in France.

Most of the patients were exposed to vasodilators, making it unlikely that nasal preparations with a vasoconstrictive effect used in both groups in a very small subset of patients (2%) could have had any influence on the overall treatment outcome.

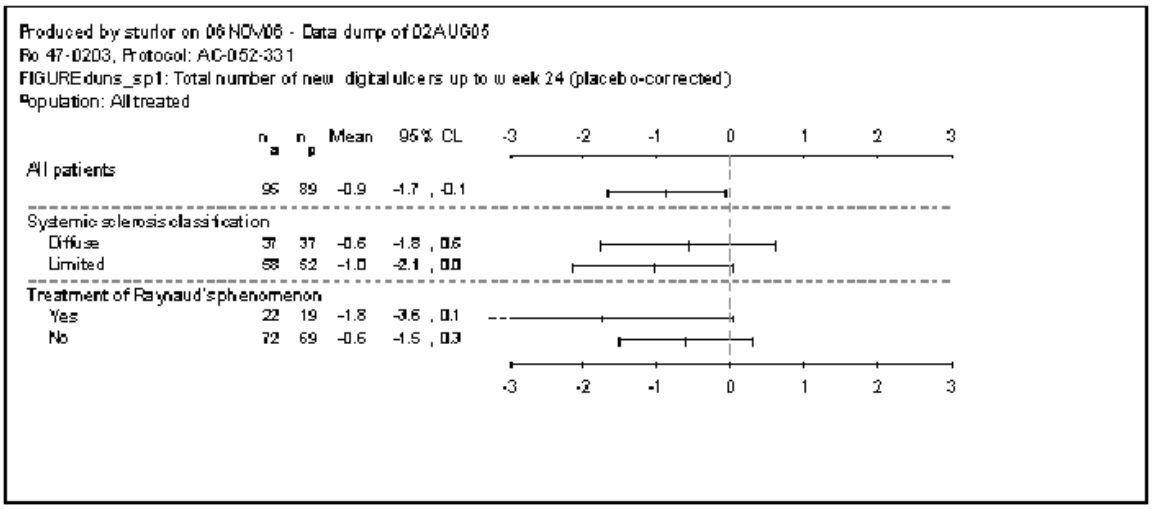
Smoking cessation should be a first step in the treatment of DU and the included population does not appear to be representative as regards this recommendation. This reinforces the concerns related to the robustness of the results, as these results are really relevant only for patients who do not smoke.
Although the number is very small it could also impact (even if marginally) on the results. Robustness is discussed in more details later in this document.

Taken all together, patients' baseline characteristics suggest that the population included in the trials might not exactly fit the population to be treated (high proportion of smokers, relatively low frequent use of ACE and CCB). This limits the extrapolability of the observed results.

The MAH argued that the investigators were informed that they should not list the components of the Systemic Sclerosis condition in the medical history. There was however an over-reporting of formal inclusion criteria such as Raynaud's phenomenon or Systemic Sclerosis in the medical history page and by cleaning convention over-reporting was kept in the database.

The analysis of the primary endpoint "number of new DU" in RAPIDS-2 according to the SSc sub-type as a pre-defined co-variable showed that the treatment effect was similar in both sub-types (Figure below).

Figure 6 **Number of new digital ulcers up to Week 24 (placebo corrected) by predefined baseline factors, trial RAPIDS-2, all-treated set**



Note: The heading "Treatment of Raynaud's phenomenon" is a truncation, and should read "Dose adjustment of treatment of Raynaud's phenomenon"

The fact that, in RAPIDS-2, proportion of limited and diffuse SSc was balanced in the two arms and that this trial resulted in effect size similar to what had been obtained from RAPIDS-1 (where an imbalance was observed) is an indirect demonstration that RAPIDS-1 results are not affected by this imbalance. In addition, the variable limited/diffuse SSc does not appear to affect the treatment effect in RAPIDS-1 when a subgroup analysis is performed.

- ***End points/ effect size and its robustness***

As the study design of RAPIDS-1 was a "prevention trial", the CHMP highlighted that the primary endpoint that may have been used is "no new ulcers" as it is more stringent for a better assessment of the benefit for the patient. The secondary endpoint should have been "percentage of patients with 50% less new ulcers". If the aim of the company is to study also the healing properties of bosentan, then in a "treatment trial", the primary endpoint should have been "complete healing"; and as secondary endpoint "twice more of healed ulcers" and "pain".
It is acknowledged that the reduction in the number of new ulcers has been recognized as a possible endpoint for clinical trials in SSc during a scientific advice meeting with the Rapporteur. However, during this advice, a 40% (or even 50%) reduction was recognized as the lower limit to consider such an effect as relevant. In addition, importance of other possible indicators of a clinical benefit have been highlighted. Pain reduction (especially overall pain of the hand) was particularly mentioned.

In the design phase of these studies, possible alternative endpoint definitions were explored, including the definition "occurrence of at least one new (or no new) ulcer. However, the MAH pointed out that the following should be taken into account :

• DU in SSc reflect one consequence of an ongoing, chronic obstructive vasculopathy, characterised by immune-mediated endothelial damage, platelet activation, disruption of the balance between endothelial-derived vasodilators and factors favouring vasoconstriction, including endothelin-1 (ET-1), as well as by vascular and perivascular fibrosis and inflammation. Apart from being a potent vasoconstrictor, ET-1 is a mitogen for fibroblasts, smooth muscle cells, and endothelial cells, and a mediator for the release of pro-inflammatory cytokines.

• The potential benefit of the ET-1 receptor antagonist bosentan in this condition 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.

Therefore, the MAH considered not possible, or even pathophysiologically relevant, to power the trials for the outcome measure of incidence of no new ulcers, given the target population of patients with active DU disease. The incidence of patients with/without new DU was evaluated in both trials (secondary endpoint in RAPIDS-1, exploratory endpoint in RAPIDS-2). A nominal benefit of bosentan versus placebo was seen in both trials. In the pooled dataset, the incidences of patients with no new ulcers up to study endpoint in the placebo and bosentan groups were 32.6% and 37.6% respectively (RR 1.15, 95% CI 0.84;1.58).

On the other hand, the finally selected endpoint of number of new DU, if assessed over a reasonable time-span, was considered a realistically achievable measure of an effect of bosentan that could also translate into relevant benefit for the patient, reducing the accretion of new DU and their consequences, through modification of the activity of the underlying of SSc vasculopathy.

The co-primary healing endpoint used in trial RAPIDS-2 was specifically requested by the FDA. The CHMP acknowledged that an effect of bosentan on healing of established ulcers would be unlikely, considering the known pharmacological properties of bosentan. Retrospectively, the Applicant considered the inclusion of a healing endpoint as a mistake, which, from a formal, methodological viewpoint weakened trial RAPIDS-2. However, and as acknowledged by the CHMP, this should not detract from the possibility of assessing the effect of bosentan on the primary endpoint of number of new DU in both studies. The analysis of ulcer healing in trials RAPIDS-1 and RAPIDS-2 also provided consistent evidence regarding the neutral effect of bosentan on the healing of established DU.

Robustness of the efficacy findings

The overall conclusion of an effect on new digital ulcers was questioned by the CHMP due a withdrawal pattern and imputation rules that may have favoured the active treatment. The applicant presented upon request of the CHMP, alternative analyses of RAPIDS-1 as well as of the pooled data, using the post hoc imputations rules applied to RAPIDS-2, i.e. one analysis with the inter-group cross method (replacing a missing value in one with a random value from completers in the other group), one analysis assigning the worst observed outcome to non-completers in both groups and one analysis assigning the best observed outcome to non-completers in both groups (it should be noted that even this method was more conservative than the primarily specified method in RAPID-2). Finally, alternative analyses were also requested, applying a modified inter-group cross method (replacing a missing value in one group with the average value among completers in the other group).

The MAH was asked to discuss the claimed effect in relation to the different imputation rules for missing data and address the baseline imbalances between the treatment groups.

Rapids-1 Study: Analysis of primary endpoint according to different imputation rules of missing data

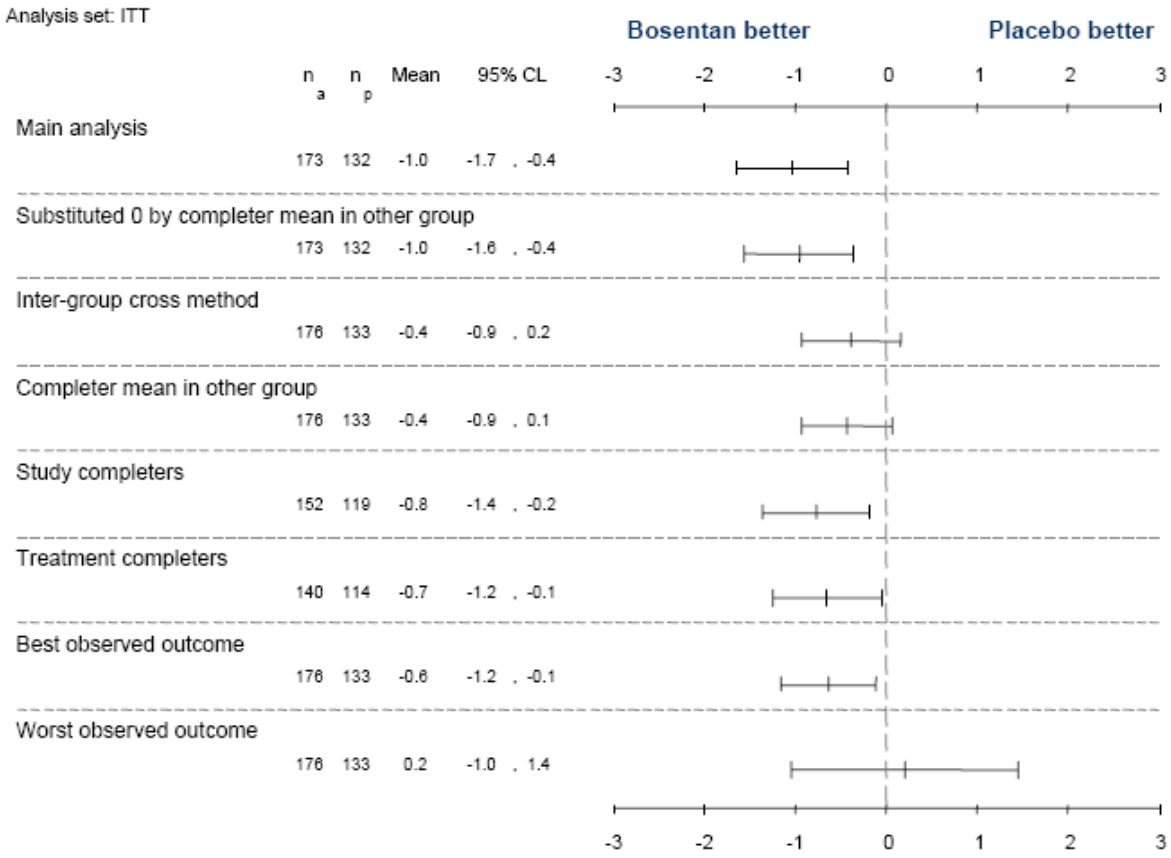
Rapids-1 study :	placebo	bosentan	différence	Test	p
At baseline :	N = 43	N = 79			
Number of ulcers per patient : mean (sd)	2.2 (2.9)	1.9 (2.1)			
During 16 weeks :	N = 43	N = 78			
Methods used in Rapids-1					
ITT population (1)	2.7 (3.5)	1.4 (1.9)	1.3	Permutation Test	p = 0.0042
ITT population (2)	2.7 (3.4)	1.4 (1.9)	1.3	Permutation Test	p = 0.0047
ITT population (3)	2.3 (2.9)	1.4 (1.9)	0.9	Permutation Test	p = 0.0176
Methods used in Rapids-2					
ITT Population (A)	2.2	1.8	0.4	Permutation Test	p = 0.2297
ITT Population (B)	3.9	3.2	0.7	Permutation Test	p = 0.3552
ITT Population (C)	2.1	1.3	0.8	Permutation Test	p = 0.0287
Method required by the CHMP					
ITT Population (D)	2.3	1.7	0.6	Permutation Test	p = 0.0678
Supplementary Method					
ITT Population (E)	2.8	1.6	1.2	Permutation Test	p = 0.0077

Most analyses show a benefit associated with bosentan albeit of small size (see table above and figure below). This is a strong clue indicating that bosentan has an activity in the included population. The robustness of the primary efficacy findings were extensively discussed at the CHMP during the oral explanation thus the benefit of the treatment.

The different analyses presented by the MAH were reviewed during the oral explanation, especially the robustness of the efficacy findings. A detailed explanation of the different analyses with substitution principles and rationale is presented below:

Method	Substitution Principle For patients who discontinued treatment early the replacement value was assigned as follows	Comment
Main analysis (protocol specified)	The worst between a) time-adjusted LOCF b) value observed at study end if available	The time-adjusted LOCF substitution resulted in an imputed value of "0" in • 7% of bosentan patients • 5% of placebo patients
Substituted to "0" by completer mean in other group	Same as main analysis except: • for 7% of bosentan and 5% of placebo patients who had an imputed value of "0" the missing values were replaced by the mean value of the completers from the other group	More conservative than main analysis as it eliminates the higher number of "0" imputations in the bosentan group.
Inter-group cross method (requested by FDA)	Missing values in both treatment groups were replaced by a randomly selected completer value from the other treatment group based on a predefined set of random numbers.	Reduces the differences between groups and penalizes active treatment group as there were more withdrawals in the active group Assesses the lower boundary of treatment effect
Completer mean in other group (requested by CHMP)	Mean value of completers from other group (a single value)	Result is very similar to the inter-group cross method. Assesses the lower boundary of treatment effect.
Study completers	All available values at study end were used including those with early discontinuation of study drug - other patients are excluded	This analysis is consistent with the main analysis
Treatment completers	All available values at study end were used for those patients who completed the treatment period – other patients are excluded	This analysis is consistent with the main analysis
Best observed outcome	Best value of any patient in study population regardless of treatment group ("0" DU)	
Worst observed outcome	Worst value observed in the respective study (13 new DU in RAPIDS-1, and 16 new DU in RAPIDS-2)	This high number is extremely unlikely to be seen in real-life. The worst observed outcome unrealistically biases against the bosentan group where the worst outcome was much lower

In terms of statistical significance, the effect on the primary endpoint, number of new digital ulcers, is not robust to all possible methods of imputation for missing data. For the MAH, this is related to the limitations of the database that could be made available in this orphan indication. From the additional analyses done, it is clear that a true treatment effect is present, however, and that the imputation method used in the protocol-specified analysis did not bias the overall conclusions of the two trials in favour of bosentan (see figure below). Compared with placebo, bosentan treatment was also associated with a larger proportion of patients with no new DU, smaller proportions of patients with multiple new DU, and a longer time to each successive new DU. In some cases the treatment differences were small, but the findings consistently indicated a preventive effect with bosentan treatment.



Among the several analyses performed, the worst observed outcome analysis (non significant results), was considered not relevant and not adapted to the real clinical experience. Indeed, the worst outcome considered was from the placebo group 16 new ulcers, is not expected to happen in clinical practice in this period of time (16-24 weeks).

Different results are observed depending on the analysis performed. The CHMP considered mainly the main analysis and the analysis where missing data are replaced by the mean completers of the other group. In both analyses no real difference in the point estimate was observed. This is due to the fact the missing data represented a low number of patients. (7% in the bosentan group and 5% in the placebo group.)

Finally, the CHMP, based on the discussion at the oral explanation, was convinced by the efficacy analyses and considered that an effect, although limited in size, was present.

A *post hoc*, exploratory analysis in trial RAPIDS-1, focusing on the relationship between number of ulcers at baseline and the number of new ulcers during the study period has been performed. Obviously, and as illustrated by the small numbers of patients per group, the trial was not powered for this analysis.
It is acknowledged that no statistically significant treatment effect was observed for subgroups of patients with 0 or 1–3 ulcers at baseline, independently of the imputation method used.
However, regardless of the imputation method, patients on placebo developed consistently higher numbers of new DU, compared with the bosentan group. The figures also illustrate that disease severity/activity expressed as number of DU at baseline predicts the tendency to form new DU during the observation period. .

A potential subpopulation benefiting from the treatment was difficult to determine, based on the results from the two studies. The MAH presented convincing data about the use of the treatment in the population initially proposed, without further restriction. However, it was highlighted by the CHMP that the prospective registry will enable to define the best use of the product in patients with digital ulcers with systemic sclerosis.

Clinical relevance

The MAH acknowledged that the effect on the primary endpoint, number of new digital ulcers, is limited but argued that there was a high, unmet medical need in this orphan indication.

DU 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.

DU impact on day-to-day functioning, and may 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.
Thus, DU represents a severe manifestation of SSc, contributing significantly to morbidity and resource-consuming medical and hospital care in this disease.

The CHMP specifically raises the suggestion that a decrease in hand pain would have indicated a simple clinical benefit to the patient. Pain is a multifactorial event and it is acknowledged that DU treatment is not expected to completely control pain. This is well confirmed that, at a given time of observation, pain intensity is not strongly correlated with the number of DU.
A prolonged trial might have evidenced a benefit on pain. However, pain is an early event in the disease and should be reduced early by an efficient DU prevention. One likely explanation for the lack of effect on pain observed in the submitted trials is that the preventive effect of Bosentan on DU is too small to make a pain improvement possible, at least on the time span explored by these trials.

However an effect of 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, i.e., dressing, for which a consistent response to treatment with bosentan was seen in both trials and in pooled data (Figure below).

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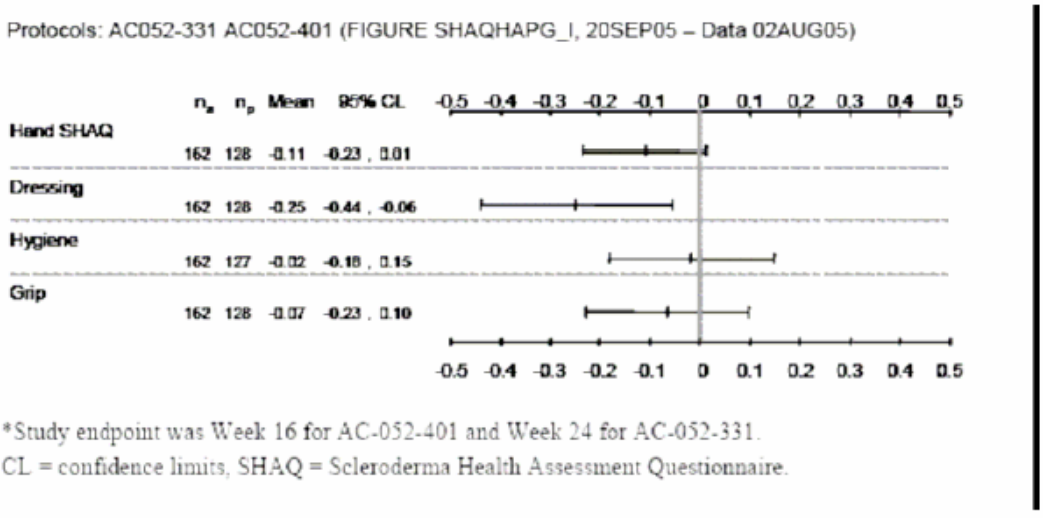
Figure 1 **SHAQ: Placebo-corrected changes from baseline to study endpoint in hand disability and component scores in trials RAPIDS-1 and RAPIDS-2, pooled ITT set**



*Study endpoint was Week 16 for AC-052-401 and Week 24 for AC-052-331.
CL = confidence limits, SHAQ = Scleroderma Health Assessment Questionnaire.

The CHMP finally considered that although no effect on pain was demonstrated, which limits the benefit for the patient, the effect on prevention of new ulcers could be sufficient and clinically relevant in this population where there is a high unmet need in terms of medication.

2.7 Discussion on Clinical Safety

Toxicology studies revealed no concern for the clinical use of bosentan, except for a teratogenic potential in humans.

In reproductive studies, teratogenicity appears to be a class effect for endothelin antogonists and appropriate precautions have been taken for women of childbearing potential.
There was no finding in the non-clinical studies that would be of specific concern to the new target population.
The CHMP agree that no new pre-clinical concerns have been identified in the new target population.

2.7.1 *Overview of the human safety experience with bosentan*

The safety and tolerability of bosentan have been extensively studied in a variety of indications in clinical trials and in the post-marketing experience in PAH patients. Twenty-eight clinical trials, mainly in PAH and chronic heart failure (CHF) exposed 2,214 patients to bosentan at dose levels ranging from 100–2,000 mg/day. Including post-marketing experience, at least 26,500 patients have been exposed to bosentan, with continuous treatment exceeding 4 years in some patients.
The post-marketing safety experience in the EU was enhanced through the Tracleer PMS (previously TRAX) surveillance programme during the first 2.5 years following EU marketing approval. Key safety data, entered into the system by the prescribing physicians, were gathered from a total of 4,994 patients between May 2002 and November 2004, representing 79% of patients prescribed Tracleer in the EU during that period. Of these, 4,623 patients, previously naïve to Tracleer treatment, had a mean exposure time of 38.6 weeks (by the most conservative calculation), representing more than 3,400 patients years of exposure.
This overview is based on the aggregate information from the above sources, in which bosentan has shown a consistent safety profile in all studied populations.
The primary safety concern with bosentan therapy is hepatotoxicity, manifesting primarily as an increased incidence of elevated liver aminotransferases. In placebo-controlled trials, elevations reaching at least three times the upper limit of the normal range (3 × ULN) occurred in about 10% to 14% of patients, generally within the first 26 weeks of therapy. However, they can also occur late in treatment, as demonstrated in post-marketing experience. The elevations usually develop gradually, are asymptomatic (90%), and return to pre-treatment levels, without sequelae, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation. In rare cases, resolution has occurred only several months after treatment interruption or cessation.
Uncommonly, elevated aminotransferases have been associated with hepatitis (including autoimmune hepatitis, cytolytic hepatitis) and/or jaundice. In the post-marketing period and in the setting of close monitoring, an exacerbation of superimposed acute on chronic hepatitis has been reported in occasional cases with pre-existing liver disease. Rare cases of unexplained hepatic cirrhosis have been reported after prolonged (> 12 months) therapy in patients with multiple comorbidities and drug therapies. There have also been rare reports of liver failure. In some of these infrequent cases, the contribution of bosentan treatment could not be excluded.

As a result of the potential for hepatotoxicity of bosentan, stringent treatment guidelines, incorporated into the approved SPC, include monthly liver test monitoring for the duration of bosentan therapy, monitoring 2 weeks after any up-titration or resumption of therapy, and an algorithm for the dose reduction, temporary interruption, or permanent discontinuation of bosentan treatment based on the degree of the liver enzyme elevation. From preclinical studies, the elevations in liver aminotransferases are thought to be due to the inhibition by bosentan of bile salt transport.
Bosentan therapy is also associated with a decrease in haemoglobin concentration, thought to be due to fluid shift. Haemoglobin concentration stabilises after the first 4 to 12 weeks of bosentan treatment, and clinically relevant decreases (> 15% decrease from baseline resulting in values < 11 g/dL) have been reported in 5.6% of patients on bosentan, compared with 2.6% of patients on placebo in previous clinical studies. Anaemia required blood transfusions in a few cases, and although each of the patients was receiving medications such as platelet inhibitors, anticoagulants, aspirin, and steroids that could contribute to bleeding and therefore anaemia, a relationship to bosentan could not be completely ruled

out. There is no evidence for increased haemolysis, bleeding, or bone marrow depression among bosentan-treated patients.

In patients with CHF, bosentan treatment has been associated with fluid retention, as evidenced by an increase in mean body weight, a decrease in mean haemoglobin concentration, and an increase in the incidence of leg oedema. This increase in fluid retention with bosentan in patients with systolic dysfunction is likely to be the reason for the increased incidence of worsening CHF seen during the first 4 to 8 weeks of treatment in clinical studies in this population. In addition to abnormal hepatic function of note include nausea (common), abdominal pain, diarrhoea, vomiting, hypersensitivity reactions such as dermatitis and rash (uncommon), and changes in international normalised ratio (INR). Despite bosentan's effect on the cytochrome P450 isoenzymes CYP3A4 and 2C9 that would suggest a possible need to up-titrate anticoagulants to maintain the patient's INR, most reported post-marketing changes in INR have been elevations, sometimes associated with gastrointestinal or other haemorrhage. Thrombocytopaenia and decreased platelets have also been reported uncommonly. Confounding factors such as lupus or scleroderma were frequently present, but, as before, in rare cases a contribution by bosentan could not be excluded. Rarely, anaphylaxis and/or angioedema have been reported, as has pulmonary oedema in patients who had a suspected diagnosis of pulmonary veno-occlusive disease.

Blood pressures generally remained stable or normalised with continued bosentan treatment. No clinically meaningful changes in other safety or tolerability parameters have been observed.
Most adverse experiences reported during the post-marketing period have been similar to those observed during clinical trials. Apart from the rare late liver reactions discussed above, additional related adverse events of note include nausea (common), abdominal pain, diarrhoea, vomiting, hypersensitivity reactions such as dermatitis and rash (uncommon), and changes in international normalised ratio (INR). Despite bosentan's effect on the cytochrome P450 isoenzymes CYP3A4 and 2C9 that would suggest a possible need to up-titrate anticoagulants to maintain the patient's INR, most reported post-marketing changes in INR have been elevations, sometimes associated with gastrointestinal or other haemorrhage. Thrombocytopaenia and decreased platelets have also been reported uncommonly. Confounding factors such as lupus or scleroderma were frequently present, but, as before, in rare cases a contribution by bosentan could not be excluded. Rarely, anaphylaxis and/or angioedema have been reported, as has pulmonary oedema in patients who had a suspected diagnosis of pulmonary veno-occlusive disease.

Teratogenicity appears to be a class effect for endothelin antagonists, and studies in animals have shown bosentan to have reproductive toxicity. The relevance of these findings to humans is unknown, but Tracleer is contraindicated for pregnancy. There have been uncommon post-marketing reports of pregnancy in patients taking Tracleer, including some patients taking hormonal contraceptives. Oestrogens and progestogens are partially metabolised by CYP isoenzymes, and bosentan has been shown to decrease exposure to norethisterone and ethinyl oestradiol. Thus, women of childbearing potential must practise an additional or alternative reliable method of contraception during treatment with, and for at least 3 months after stopping, Tracleer. These precautions are clearly set out in the approved SPC, Package Leaflet (PL) and Patient Reminder Card. Many endothelin receptor antagonists have induced atrophy in the seminiferous tubules of the testes and reduced sperm counts and male fertility in rats. Where studied, these effects appear irreversible. Small decreases in systolic and diastolic blood pressures were observed during the first 2 weeks of bosentan treatment, which were usually asymptomatic.

Actelion acknowledges the need for continued efforts to prevent pregnancy during treatment with Tracleer, as specified in the approved SPC, and also acknowledges that the target population proposed in the current application may include a higher proportion of women of child-bearing potential, and with fewer disease-related contraindications to pregnancy, compared with the currently approved population.
As previously requested following the last PSUR, the MAH committed to provide an action plan on pregnancy covering all indications.

2.7.2 *Safety experience with bosentan in patients with digital ulcer disease*

The integrated safety set from the clinical trials in this indication (RAPIDS-1, RAPIDS-2 and open-label extensions) comprises 308 patients. Of these, 175 and 133 patients respectively were exposed to bosentan and placebo in double-blind treatment. The mean duration of exposure to bosentan was 19.5 weeks in double-blind treatment phases. Including open-label extension phases, overall 206 patients received a mean 21.8 weeks of bosentan treatment, and 116 patients received bosentan for at least 24 weeks.

The population enrolled in these trials had, on average, long-standing SSc, which was classified as diffuse in 39% of patients. Consistent with this, the integrated population consisted primarily of females (79%), with a mean age of about 50 years (range 22 to 84 years). Eighty-nine percent (89%) were Caucasian. Baseline characteristics were similar to those previously reported for patients with SSc and digital ulcers in the published literature. A wide range of concomitant medications were used.

A summary of adverse events during the placebo-controlled treatment phase is given in the table below.

Table 1 Summary of adverse events occurring during or up to 1 day after the end of study treatment in placebo-controlled trials in patients with digital ulcers, safety set

Produced by madesu on 28SEP05 - Data dump of 02AUG05
Ro 47-0203, Protocols: AC-052-331 AC-052-401
Table AEF5S_DB_S: Summary of adverse events (including unrelated) occurring from the start up to 1
calendar day after the end of study treatment by frequency
Analysis set: Safety

Protocols: AC-052-331 AC-052-401 (Table AEF5S_DB_S, 28SEP05 - Data 02AUG05)

System Organ Class / Preferred Term	Placebo N=133 No.	%	Bosentan N=175 No.	%
ALL SYSTEM ORGAN CLASSES				
Total patients with at least one AE	116	87.2%	154	88.0%
Total number of AEs	415		585	
OEDEMA PERIPHERAL	6	4.5%	24	13.7%
HEADACHE	18	13.5%	23	13.1%
DIARRHOEA	10	7.5%	16	9.1%
UPPER RESPIRATORY TRACT INFECTION	12	9.0%	15	8.6%
INFECTED SKIN ULCER	8	6.0%	15	8.6%
ARTHRALGIA	13	9.8%	14	8.0%
ASPARTATE AMINOTRANSFERASE INCREASED	2	1.5%	11	6.3%
ALANINE AMINOTRANSFERASE INCREASED	1	0.8%	11	6.3%
PAIN IN EXTREMITY	7	5.3%	10	5.7%
VOMITING	8	6.0%	9	5.1%
OTHER	107	80.5%	147	84.0%

The preferred term 'DISEASE PROGRESSION' was associated to each of the symptoms/diagnosis terms reported together with it.
All AEs with an overall bosentan incidence < 5% are pooled under 'Other'.
AE = adverse event.

The safety profile of bosentan in these trials was consistent with that in other indications. No new events were identified.

Elevated liver aminotransferases to ≥3 × ULN occurred in 11.3% of patients on bosentan versus 0.8% on placebo. The elevations were asymptomatic in all but one patient (associated with fatigue), associated with an increase in bilirubin to ≥ 2 × ULN in one patient, and reached > 8 × ULN in four patients. The abnormality was transient during continued treatment in one patient, and in all other cases resolved or returned to < 2 × ULN following a decrease in the bosentan dose, or a temporary interruption or permanent discontinuation of bosentan treatment.

Although events denoting anaemia were more frequent among bosentan- than placebo-treated patients (5.1% versus 2.3%), marked decreases in haemoglobin concentration and marked decreases to < 10 g/dL were similar in the two treatment groups (placebo-subtracted differences of 0.6% and 1.1% respectively).

The early onset of peripheral oedema coincided with a small mean increase in body weight by Week 4 among bosentan-treated patients. These events did not worsen with longer treatment duration, and are

likely to be related to fluid retention at the start of bosentan treatment. A small mean decrease in blood pressure was observed by Week 4 and did not worsen with continued treatment, and there were no reports of hypotension among bosentan-treated patients.

2.7.3 *Limitations of the human safety database*

The data in the currently targeted indication, active digital ulcer disease in patients with SSc, are from two adequate, well-controlled studies and their extensions, and represent the largest, controlled database ever presented in this rare disease. As detailed in the study reports and integrated summaries, these trials enrolled a typical population of patients with SSc, characterised by long-standing disease, female/Caucasian predominance, and multiple concomitant medications. The safety data generated with Tracleer in this population are further supported by previous study data generated in patients with SSc and PAH, who comprised 21% of patients in the pivotal registration studies for Tracleer in the PAH indication, as well as by post-marketing surveillance data from the Tracleer PMS programme. The Tracleer PMS programme reported safety outcomes for 1,017 patients with PAH secondary to SSc, treated with Tracleer for a median of 28.9 weeks (ranging up to 131 weeks). Eighty-four percent (84%) of these patients were female, and the median age was 63 years. The reporting rates for potential safety signals within the Tracleer PMS programme for this population did not differ from those of the overall Tracleer PMS population. Specifically, the reporting rate for elevated aminotransferases (> 3 × ULN) was 9.4%. These findings have previously been assessed by the CHMP.

2.7.4 *The Tracleer PMS programme (formerly TRAX) and related activities*

In addition to routine pharmacovigilance activities, a post marketing surveillance project, the Tracleer PMS (formerly TRAX) was established in order to provide pharmacovigilance data related to the main safety concern with bosentan, i.e., hepatotoxicity.

Further to the assessment of 2 years of TRAX PMS reports, the CHMP agreed with the MAH's request to terminate the post-marketing surveillance programme in September 2004.

A component of the Tracleer PMS programme that remains in operation is the system of controlled distribution of Tracleer. This system allows the ready identification of prescribers of Tracleer, including new prescribers. The Tracleer Prescriber Kit is distributed to all new prescribers of Tracleer, identified through the controlled distribution system within the EU. The Prescriber Kit includes:

- Information for the prescriber/pharmacist, explaining the controlled distribution system for Tracleer and the specific monitoring requirements for liver enzymes and pregnancy testing, as well as the need for use of reliable contraception by women of childbearing age
- The SPC and PIL
- A patient information booklet

New prescribers are approached on an ongoing basis to be given information 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 for the duration of treatment with Tracleer, as detailed in the approved SPC.

The Tracleer Patient Reminder Card, which facilitates the patient's awareness of the need for regular blood tests, contains important information about the need for regular blood tests for liver unction test monitoring, and warnings relating to pregnancy and the special requirements for reliable contraception and monthly pregnancy testing in women of childbearing potential.

As part of its risk management plan, the MAH committed to set up a surveillance programme/registry to collect information on the demographics, safety and outcome data from patients prescribed Tracleer to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. The data to be collected shall be agreed with the CHMP. Details of the operation of the

surveillance programme/registry shall be agreed with the National Competent Authorities in each Member State.

In addition, the extension of use of the indication into a new target population, requires the need for more frequent safety updates. Therefore, the CHMP asked the MAH to provide 6 monthly PSURs including liver safety reports.

3. Summary of product information changes

The modifications of the product information agreed in this variation are detailed below:

SPC changes

- Section 4.1

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see section 5.1).

- Section 4.2

Systemic sclerosis with ongoing digital ulcer disease

Treatment should only be initiated and monitored by a physician experienced in the treatment of systemic sclerosis.

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Tablets are to be taken orally morning and evening, with or without food.

Controlled clinical trial experience in this indication is limited to 6 months (see section 5.1).

The patient's response to treatment and need for continued therapy should be re-evaluated on a regular basis. A careful risk/benefit assessment should be made, taking into consideration the liver toxicity of bosentan (see sections 4.4 and 4.8).
….

Systemic sclerosis with ongoing digital ulcer disease

There are no data on the safety and efficacy in patients under the age of 18 years.

- Section 4.4

Tracleer has not been shown to have a beneficial effect on the healing of existing digital ulcers.

- Section 4.8

Placebo-controlled trials in digital ulcers

The table below shows the adverse drug reactions that occurred in ≥ 3% of patients treated with Tracleer (125 mg twice daily) in the two pivotal placebo-controlled trials in digital ulcers, and which were more frequent in Tracleer-treated patients:

Adverse drug reactions occurring in ≥ 3% of patients, and more frequently in patients on Tracleer (125 mg twice daily), in the placebo-controlled trials in digital ulcers

Body system / Adverse event	Placebo N = 133 No.	%	Tracleer (all) N = 175 No.	%
Infections and infestations				
Infected skin ulcer	8	6%	15	9%
Urinary tract infection	3	2%	7	4%
Gastrointestinal disorders				
Diarrhoea	10	8%	16	9%
Gastrointestinal reflux disease	2	2%	8	5%
Abdominal pain	1	1%	6	3%
Constipation	1	1%	6	3%
Musculoskeletal system disorders				
Pain in extremity	7	5%	10	6%
Back pain	4	3%	7	4%
General disorders and administration site conditions				
Peripheral oedema	6	5%	24	14%
Peripheral oedema-worsening	0	0%	5	3%
Fatigue	3	2%	5	3%
Skin and subcutaneous tissue disorders				
Erythema	2	2%	6	3%
Dermatitis	2	2%	5	3%
Investigations				
Aspartate aminotransferase increased	2	2%	11	6%
Alalanine aminotransferase increased	1	1%	11	6%
Liver function test abnormal	0	0%	8	5%
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	3	2%	5	3%
Vascular disorders				
Flushing	2	2%	6	3%

Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. One patient could have had more than one AE.

Liver abnormalities

In the two studies in patients with digital ulcers the incidence of elevated liver aminotransferases (> 3 × ULN) was 11.3% in bosentan-treated patients (N = 168) compared with 0.8% in placebo-treated patients (N = 129). Elevations to > 8 × ULN were seen in 2.4% of bosentan-treated patients with digital ulcers.

- Section 5.1

Systemic sclerosis with ongoing digital ulcer disease

Two randomised, double-blind, multi-centre, placebo-controlled trials have been conducted in 122 (Study AC-052-401, RAPIDS-1) and 190 (Study AC-052-331, RAPIDS-2) adult patients with systemic sclerosis and ongoing digital ulcer disease (either ongoing digital ulcers or a history of digital ulcers within the last year). In study AC-052-331, patients had to have at least one digital ulcer of recent onset, and across the two studies 85% of patients had ongoing digital ulcer disease at baseline. After 4 weeks of Tracleer 62.5 mg twice daily, the maintenance doses studied in both these trials were 125 mg twice daily. The duration of double-blind therapy was 16 weeks in study AC-052-401, and 24 weeks in study AC-052-331.

Background treatments for systemic sclerosis and digital ulcers were permitted if they remained constant for at least 1 month prior to the start of treatment and during the double-blind study period.

The number of new digital ulcers from baseline to study endpoint was a primary endpoint in both studies. Treatment with Tracleer resulted in fewer new digital ulcers for the duration of therapy, compared with placebo. In study AC-052-401, during 16 weeks of double-blind therapy, patients in the bosentan group developed a mean of 1.4 new digital ulcers *vs*. 2.7 new digital ulcers in the placebo group ($p = 0.0042$). In study AC-052-331, during 24 weeks of double-blind therapy, the corresponding figures were 1.9 *vs.* 2.7 new digital ulcers, respectively ($p = 0.0351$). In both studies, patients on bosentan were less likely to develop multiple new digital ulcers during the study and took longer to develop each successive new digital ulcer than did those on placebo. The effect of bosentan on reduction of the number of new digital ulcers was more pronounced in patients with multiple digital ulcers.
No effect of bosentan on time to healing of digital ulcers was observed in either study.

Changes to Annex II:

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that prior to prescribing all health care professionals who intend to prescribe and/or dispense Tracleer are provided with a Prescriber Kit containing the following:

- Information about Tracleer
- Patient Information Booklet/Patient Reminder Card

The MAH shall set up a surveillance programme/registry to collect information on the demographics, safety and outcome data from patients prescribed Tracleer to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. The data to be collected shall be agreed with the CHMP. Details of the operation of the surveillance programme/registry shall be agreed with the National Competent Authorities in each Member State.

The information provided about Tracleer shall contain the following key elements:

- That Tracleer is teratogenic in animals
    - Use in pregnant women is contraindicated
    - The need for effective contraception
    - That there is an interaction with hormonal contraceptives
    - Monthly pregnancy tests in women of child bearing potential are recommended.
- That Tracleer is hepatotoxic
    - Tracleer should not be used in Child Pugh Class B or C, ie moderate to severe hepatic impairment.
    - Need for liver function tests to be measured:
        - Prior to initiation of treatment
        - At monthly intervals during complete course of the treatment
        - Two weeks after any dose increase.
    - Need for close monitoring and dosage adjustment if levels rise above 3 x upper limit normal (ULN):
        - >3 and ≤ 5 x ULN: Confirm levels and if confirmed, reduce the daily dose or stop treatment and monitor liver function at least every 2 weeks.
        - >5 and ≤ 8 x ULN: Confirm levels and if confirmed stop treatment and monitor liver function at least every 2 weeks.

      In the above circumstances, if the levels return to pre-treatment values, continuing or re-introducing Tracleer may be considered.
        - > 8 x ULN or any of the above with associated clinical symptoms of liver injury: Treatment must be stopped and re-introduction of Tracleer is not to be considered.

- That treatment with Tracleer is associated with a decrease in haemoglobin.
    - Need for blood monitoring
        - Prior to initiation of treatment
        - Monthly during the first 4 months
        - Quarterly thereafter.
- That co-administration of Tracleer with cyclosporine is contraindicated.
- That the safety database of Tracleer in the indication to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease is limited and physicians are encouraged to enrol patients in the surveillance programme/registry to further increase knowledge about the product. The surveillance programme/registry should prompt doctors to report adverse reactions.

The patient information shall contain the following information:

- That Tracleer is teratogenic in animals
- That pregnant women must not take Tracleer
- That women of child bearing potential must use effective contraception
- That hormonal contraceptives on their own may not be effective
- The need for regular pregnancy tests
- That Tracleer causes a decrease in haemoglobin and the need for regular blood tests
- That Tracleer is hepatotoxic and the need for regular monitoring of liver function

- **OTHER CONDITIONS**

The MAH commits to performing the additional Pharmacovigilance activities detailed in the Pharmacovigilance plan.

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products of human use.

The MAH will submit 6-monthly PSURs including liver reports, unless otherwise specified by the CHMP.

Patient leaflet changes

Tracleer tablets are also indicated in digital ulcers (ulcers of the fingers) in people with a condition called scleroderma. Tracleer reduces the number of new finger ulcers that appear.

4. Benefit / risk assessment

Based on the data provided by the MAH, the CHMP considered that the efficacy provided was sufficiently robust. The effect size, although limited, was considered relevant for this orphan population with a high unmet need.
In addition, upon request from the CHMP, the proposal from the company to establish a prospective surveillance program/registry was ackknowledged.
The CHMP reinforces the need to implement a controlled distribution system as proposed by the MAH in patients with systemic sclerosis and ongoing digital ulcers.

In conclusion, the CHMP is of the opinion, that the benefit/risk is positive and agreed to extend the indication to reduce the number of new ischemic digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

5. Conclusion

On 22 March 2007, the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, and Package Leaflet.