HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 January 2008

TRACLEER 62.5 mg film-coated tablets
Pack of 56 (CIP: 563 621-1)

TRACLEER 125 mg film-coated tablets
Pack of 56 (CIP: 563 622-8)

Applicant : ACTELION PHARMACEUTICALS FRANCE

bosentan

List I
Medicinal product reserved for hospital prescription by specialists and/or departments specialising in cardiology, respiratory medicine, rheumatology, dermatology or internal medicine.
Medicinal product requiring special surveillance during treatment.

Orphan medicinal product

Date of the initial marketing authorisation (centralised procedure): 15 May 2002
Extension of indication: 13 June 2007

Reason for request: Inclusion on the list of medicines approved for hospital use and various public services in the extension of indication: **"Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease".**

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
bosentan

1.2. Indications
"Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with NYHA functional class III.
Efficacy has been shown in:
- Primary (idiopathic and familial) PAH
- PAH secondary to scleroderma without significant interstitial pulmonary disease

Indications already evaluated by the Committee (see opinion of 5 February 2003)
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

Indication already evaluated by the Committee (see opinion of 18 July 2007)

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease."

1.3. Dosage in the new indication
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 study experience in this indication is limited to 6 months.
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.

Special populations:
Dosage in hepatic impairment:
No dose adjustment is needed in patients with mild hepatic impairment (i.e., Child-Pugh class A). TRACLEER is contraindicated in patients with moderate to severe liver dysfunction.

Dosage in renal impairment
No dose adjustment is required in patients with renal impairment. No dose adjustment is required in patients undergoing dialysis.

Dosage in elderly patients
No dose adjustment is required in patients over the age of 65 years.

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

Patients with low body weight
There are few data concerning patients weighing less than 40 kg.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2007

C: Cardiovascular system
C02: Antihypertensives
C02K: Other antihypertensives
C02KX: Other antihypertensives
C02KX01: bosentan

2.2. Medicines in the same therapeutic category

Comparator medicines

Bosentan (TRACLEER) is the only mixed endothelin receptor antagonist currently indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

2.3. Medicines with a similar therapeutic aim

No other medicinal product is indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.
The following are used in practice:

- calcium channel blockers, particularly products based on nifedipine, which is indicated notably in the symptomatic treatment of Raynaud's phenomenon
- angiotensin-converting enzyme inhibitors (ACE-i)
- angiotensin receptor blockers
- iloprost in infusion (ILOMEDINE, prostaglandin), indicated in the treatment of severe Raynaud's phenomenon with ongoing trophic disorders
- prazosin (MINIPRESS), indicated in the symptomatic treatment of primary or secondary Raynaud's phenomenon.

3 ANALYSIS OF AVAILABLE DATA

The clinical development of bosentan (TRACLEER) for the indication "to reduce the number of digital ulcers" is based on 2 pivotal randomised, double-blind, placebo-controlled studies, RAPIDS-1[1] and RAPIDS-2[2], which included a total of 312 patients with digital ulcers secondary to systemic sclerosis for 16 to 24 weeks.

3.1. Efficacy data

3.1.1. RAPIDS-1 study

Objective: to evaluate the efficacy and safety of bosentan versus placebo in preventing the onset of new ischaemic digital ulcers in patients with systemic sclerosis.
This study was continued in a 12-week open-label follow-up period. The results of this extension phase will not be described.

[1] Korn JH et al. Arthritis and rheumatism 2004 – Korn JH et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan. NEJM 2002; 346: 896-903
[2] Seibold JR et al. Bosentan reduces the number of new digital ulcers in patients with systemic sclerosis. Ann Rheum Dis 2006; 65(suppl II): 90. Abstract presented at EULAR 2006.

Methodology:
Phase III, placebo-controlled, randomised 2:1, double-blind study including 122 patients (79 in the bosentan arm, 43 in the placebo arm).

Inclusion criteria: (ITT population)
- Men or (non-pregnant) women over 18 years of age, with body weight > 40 kg
- Patients with Raynaud's phenomenon and diffuse or limited systemic sclerosis as defined in LeRoy's classification (see Appendix 1)
- Patients with ongoing digital ulcers or a documented history of ischaemic digital ulcers within the previous year (scars due to digital ulcers, history of gangrene/amputation associated with digital ulcers).

Treatment regimen and duration:
The dosage regimen of bosentan was 62.5 mg twice a day for 4 weeks, then 125 mg twice a day for 12 weeks.
The total duration of treatment was 16 weeks.

Primary endpoint: number of new ischaemic digital ulcers occurring during the treatment period[3].

Secondary endpoints:
- percentage of patients with new digital ulcers
- time to onset of new digital ulcers
- time to complete or partial healing of digital ulcers initially present[4]
- quality-of-life assessment by means of a Scleroderma Health Assessment Questionnaire (SHAQ) supplemented with a VAS (see Appendix 2).

Results
Main patient characteristics:

	Placebo (n=43)	Bosentan (n=79)
Number of women* n (%)	37 (86)	59 (74.7)
Mean age (years)	48.0	53.9
Mean total number of digital ulcers per patient	2.2 ± 2.9	1.9 ± 2.1
Number of patients with at least one digital ulcer n (%)	24 (55.8)	53 (67.1)
Number of patients with Raynaud's syndrome n (%)	21 (48.8)	38 (48.1)
Mean time from digital ulcer diagnosis to randomisation (years)	5.4	8.2
limited systemic sclerosis n (%) diffuse systemic sclerosis n (%)	23 (53.5) 20 (46.5)	53 (67.1) 26 (32.9)
Prior and current treatment n (%) - Calcium channel blockers - Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers - analgesics, antipyretics or opioids	 48.8% 25% 41.9%	 36.7% 25% 29.2%

* The male/female ratio for systemic sclerosis is 1:5.

[3] A digital ulcer was defined as a painful area of skin at least 1 mm in width with a loss of surface epithelium integrity. Only digital ulcers located beyond the proximal interphalangeal joints were taken into account.
[4] Ulcers were considered completely healed if complete re-epithelialisation of all ulcers was observed.

Primary endpoint results (ITT analysis)

	Placebo n = 43	Bosentan n=78	Statistical tests	p
Mean number of new ulcers per patient in the ITT population 1*	2.7 ± 3.5	1.4 ± 1.9	Mann-Whitney test Poisson regression Permutation test	NS 0.0083 0.0042
Mean number of new ulcers per patient in the ITT population 2**	2.7 ± 3.4	1.4 ± 1.9	Mann-Whitney test Poisson regression Permutation test	NS 0.0094 0.0047
Mean number of new ulcers per patient in the ITT population 3***	2.3 ± 2.9	1.4 ± 1.9	Mann-Whitney test Poisson regression Permutation test	NS NS 0.0176

Several statistical tests were performed to check the robustness of the results, including the Poisson test, an adjustment method that takes the dispersion of values into account. The registration authorities considered the permutation test to be the most appropriate.
* missing data replaced with the worst value
** missing data replaced with the mean value observed during follow-up
*** missing data replaced with the last observation carried forward (LOCF)

The number of new digital ulcers per patient during the 16 weeks of treatment was 1.4 in the bosentan arm versus 2.7 in the placebo arm (p=0.004).

As planned in the protocol, a sub-group analysis was performed on patients who had active digital ulcers on inclusion (52 in the bosentan arm, and 24 in the placebo arm), who were considered to be at a higher risk of developing new ulcers.
The number of new digital ulcers per patient was 1.8 ± 2.2 in the bosentan arm versus 3.6 ± 3.3 in the placebo arm (p=0.034; p=0.0075 after applying Poisson's regression test). This difference was only significant when missing data were replaced with the values observed during follow-up.

Secondary endpoint results:

- Percentage of patients with new digital ulcers:

The proportion of patients with at least one new digital ulcer during the treatment period was similar in the two treatment arms (57.7% with bosentan versus 60.5% with placebo).

- Time to onset of new digital ulcers/Time to healing

No significant difference was observed between the two treatment arms.

- Quality of life

No significant difference was observed between the two treatment arms on the mean SHAQ disability index score.
Specific evaluation of improvement in hand function, based on a SHAQ composite criterion, showed a significant difference in favour of the bosentan arm (p=0.004).
Assessment of pain on the VAS showed no statistically significant or clinically relevant difference between the two treatment arms.

Comments and conclusion

In this study, a statistically significant difference was observed between the placebo arm and the bosentan arm in the onset of new digital ulcers in systemic sclerosis patients during the treatment period. The size of the effect, however, was minimal.
The proportion of patients who had at least one new digital ulcer during the treatment period did not differ between the bosentan arm and the placebo arm.

Several remarks can be made concerning the study methodology. In fact, the population included in the study seems to be less severely affected than the population seen in practice.

Only about 50% of patients had Raynaud's syndrome at baseline, while in practice 90% of systemic sclerosis patients have Raynaud's syndrome.
A low percentage of patients included in the study (about 50%) were being treated with ACE inhibitors or calcium channel blockers, which does not correspond to usual treatment. The relevance of the results is therefore limited, since the included population is hardly representative of the population seen in practice.
Furthermore, the patients were not all comparable at baseline in terms of the type of systemic sclerosis or their concomitant treatments, etc.
In the context of a preventive trial, it would have been more relevant to choose "absence of new ulcers" or "percentage of patients with no ulcers" as the primary endpoint, to assess the benefit to patients more effectively.

3.1.2. RAPIDS-2 study

Objective: to evaluate the efficacy and safety of bosentan (TRACLEER) versus placebo in the healing and prevention of ischaemic digital ulcers in patients with systemic sclerosis.
This study was continued in a 8-week open-label follow-up period. The results of this extension phase will not be described.

Methodology:
Phase III, randomised, double-blind, placebo-controlled study including 188 patients (98 in the bosentan arm, 90 in the placebo arm).

Inclusion criteria:
- Men or (non-pregnant) women over 18 years of age, with body weight > 40 kg
- Patients with diffuse or limited systemic sclerosis
- Patients with at least one active digital ulcer qualifying as a cardinal ulcer[5], less than 3 months and more than one week old at randomisation.
  NB: In contrast to RAPIDS-1 (in which included patients had to have a history of digital ulcers within the previous year without necessarily having active digital ulcers at baseline), patients had to have at least one active digital ulcer to be included in the study.

Treatment regimen and duration:
The dosage regimen of bosentan was 62.5 mg twice a day for 4 weeks, then 125 mg twice a day.
Treatment duration was 24 weeks for assessment of the primary outcomes.
Treatment was continued for a further 12 weeks to assess whether healing was maintained.
The total duration of treatment was therefore 24-36 weeks.

Primary endpoints:
- total number of new digital ulcers per patient appearing during the 24 weeks of treatment
- time to complete healing of the cardinal ulcer for patients whose healing was maintained for at least 12 weeks.

Secondary endpoints:
- Percentage of patients with no new digital ulcers
- Percentage of patients not developing any new digital ulcers after the first 4 weeks of treatment
- Percentage of patients achieving complete healing of all their digital ulcers (whether present at baseline or new)
- Time to complete healing of digital ulcers present at baseline
- quality-of-life assessment by means of a Scleroderma Health Assessment Questionnaire

[5] Cardinal ulcers were digital ulcers that were more than 2 mm in diameter, de-epithelialised with a distinct base, of vascular origin, possibly triggered by trauma, painful, without associated osteitis or calcinosis, and located beyond the proximal interphalangeal joint and away from the interphalangeal joint folds.

(SHAQ) supplemented with a VAS.

Results (ITT analysis)

Main patient characteristics:

	Placebo (n=90)	Bosentan (n=98)
Number of women n (%)	72 (80)	76 (77.6)
Mean age (years)	50.7 ± 12.0	48.4 ± 12.9
Mean total number of digital ulcers per patient	3.6 ± 3.3	3.7 ± 4.4
Number of patients with Raynaud's syndrome n (%)	90 (100)	98 (100)
Mean time from digital ulcer diagnosis to randomisation (years)	6.4	7.4
limited systemic sclerosis n (%) diffuse systemic sclerosis n (%)	52 (57.8) 38 (42.2)	59 (60.2) 39 (39.8)
Prior and current treatments n (%) - Calcium channel blockers - Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers - analgesics, antipyretics or opioids	 55.6% 23.3% 65.6%	 52.0% 25.5% 46.9%
Percentage of patients who smoke n (%)	19 (21.6)	12 (12.8)

Primary endpoint results:

The number of new digital ulcers per patient during the 24 weeks of treatment was 1.9 ± 2.2 in the bosentan arm (n=95) versus 2.7 ± 3.3 in the placebo arm (n=89; p=0.035)[6].

No effect on the healing of digital ulcers was observed in the bosentan arm compared with the placebo arm.

Secondary endpoint results:

- Percentage of patients with no new digital ulcers

No significant difference was observed between the two treatment arms.

- Percentage of patients not developing any new digital ulcers after the first 4 weeks of treatment

The proportion of patients not developing any new digital ulcers between the 4th and the 24th weeks did not differ between the two treatment arms.

- Time to complete healing of digital ulcers present at baseline

Complete healing of all digital ulcers (present at baseline or new) was observed in 39.3% of patients in the placebo arm and 36.8% of patients in the bosentan arm, with no significant difference between the arms.

At week 24, the mean time to complete healing of the digital ulcers already present at baseline was not significantly different between the two treatment arms.

- Quality of life

No difference in pain reduction was observed between the two arms after 24 weeks of treatment.

The evaluation of hand functionality as measured by the SHAQ composite score revealed no statistically significant difference between the two treatment arms.

Comments and conclusion

In this study, a statistically significant difference was observed between the placebo arm and the bosentan arm in the onset of new digital ulcers in systemic sclerosis patients. The size of the effect, however, was minimal.

[6] Result observed with the permutation test where missing data were replaced with the value observed during follow-up.

No difference in the healing of ischaemic digital ulcers was observed between the bosentan arm and the placebo arm.

Several remarks can be made concerning the study methodology.
The fact that patients who smoked were included in the study shows that the standard management for systemic sclerosis was not implemented, since smoking cessation is one of the primary prophylactic measures. The relevance of the results is therefore limited, since the included population is hardly representative of the population seen in practice.
The demographic characteristics of the patients included in this study were similar in the two treatment arms.
No data are available on the other treatments usually used in the management of digital ulcers, such as local treatments and anti-infectives.

3.2. Safety data

The most common adverse effects noted were:
- headache: 17.7% of patients in the bosentan arm in the RAPIDS-1 study and 16.5% of patients in the bosentan arm in the RAPIDS-2 study versus 16.3% of patients in the placebo arm in both studies.
- ALAT/ASAT > 3 times the upper limit of normal: 14.1% of patients in th bosentan arm only, in both studies.
- peripheral oedema: 18.8% of patients in the bosentan arm in the RAPIDS-2 study versus 4.4% of patients in the placebo arm.

Treatment discontinuations due to adverse effects were observed in 12.7% of patients in the bosentan arm versus 9.3% of patients in the placebo arm.
The adverse effects observed were identical to those already known and observed in the other trials conducted with bosentan.

3.3. Conclusion

The clinical development of bosentan (TRACLEER) for the indication “to reduce the number of digital ulcers” is based on 2 pivotal randomised, double-blind, placebo-controlled studies, RAPIDS-1 and RAPIDS-2, which followed a total of 312 patients (122 in RAPIDS-1 and 190 in RAPIDS-2) with digital ulcers (ongoing digital ulcers or a history of digital ulcers within the previous year) secondary to systemic sclerosis for 16 to 24 weeks.
The primary endpoint of the two studies was the number of new digital ulcers occurring between baseline and the end of the study. In the RAPIDS-1 study, patients in the bosentan arm developed an average of 1.4 new digital ulcers versus 2.7 new digital ulcers in the placebo arm ($p=0.004$); in the RAPIDS-2 study, patients in the bosentan arm developed an average of 1.9 new digital ulcers versus 2.7 new digital ulcers in the placebo arm ($p=0.035$).
Bosentan treatment led to a reduction in the number of new digital ulcers during the course of treatment compared with the placebo arm, but the differences observed between the bosentan and placebo arms were minimal.
The RAPIDS-2 study had an evaluation of the healing of digital ulcers as a further primary endpoint. Bosentan was not observed to have any effect on the time to healing of the digital ulcers compared with placebo.
The SHAQ quality-of-life assessment only showed a benefit in favour of bosentan compared with placebo in one study. The absence of any effect on pain limits the patient’s appreciation of any benefit.
It must be emphasised that there is no assurance that the results observed can be transposed.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Ischaemic digital ulcers are a common complication of systemic sclerosis (50% of systemic sclerosis patients are affected by digital ulcers). They are responsible for major functional disability and incapacitating pain. They are often complicated by infections and also ischaemia and gangrene, which may lead to amputation. Healing of these ulcers is slow and uncertain, and the risk of recurrence is high.
These medicinal products are intended for preventive treatment.
The efficacy/safety ratio is high.
This medicinal product is for use as first-line treatment.
There are few alternative medicinal treatments.

Public health benefit:
Systemic sclerosis complicated by ongoing ischaemic digital ulcers is a severe clinical condition resulting in major disability, but the public health burden it causes is low because of the small number of patients concerned.
The improved management of systemic sclerosis is a public health need falling within the scope of identified priorities (National rare diseases plan: GTNDO*). Nonetheless, the treatment of ischaemic digital ulcers is not identified as such.
Since morbidity was not assessed in the trials and since efficacy on quality of life was modest, no impact is expected on either of these two criteria.
In addition, it is not certain that the results of the studies can be transposed into clinical practice, since the profile of patients treated in real practice may differ from that of the patients included (who seemed to be less severely affected in one of the two studies).
At the present time, therefore, it cannot be said that TRACLEER will meet the identified public health need.
Consequently, TRACLEER is not expected to benefit public health in this indication.

* GTNDO: National Technical Group for Defining Objectives (DGS-2003)

The actual benefit is substantial.

4.2. Improvement in actual benefit

In light of the available data, the Transparency Committee considers that TRACLEER provides a minor improvement in actual benefit (IAB level IV) in reducing the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcers.

4.3. Therapeutic use

The goal of treatment for digital ulcers in systemic sclerosis patients is to prevent complications and the onset of new ulcers and to encourage healing.
Preventive measures consist of avoiding risk factors, rehabilitation, surgical treatment and vasodilator treatment.
Curative measures basically include local treatments, analgesics, the prevention and treatment of superinfections and vasodilator treatments.

Among the prophylactic avoidance measures, it is essential to reduce exposure to cold, limit the use of vasoconstrictors, quit smoking, and avoid injuries (by carrying dressings, in particular).
The aim of rehabilitation is to combat pain, cutaneous ischaemia and interstitial oedema, and to soften skin tissues. The main techniques implemented are postural adaptation, manual lymph drainage, non-compressive covering of fingers, tissue massage and physiotherapy. Orthotics are proposed for correcting deformations. (NB: no studies have objectively evaluated the use of these techniques with digital ulcers.)

Surgical indications remain rare. The main indications concern:

- ✓ joint surgery to counter excessive stiffening and to restore a functional position
- ✓ excision of calcinoses
- ✓ sympathectomy and digital amputation, which are only indicated when all medicinal treatment has failed or in hopeless cases that may result in self-amputation.

In practice, medicines are used off-label and with a low level of evidence. Calcium channel blockers (especially nifedipine) and iloprost by infusion are also prescribed for systemic sclerosis patients to reduce the risk of digital ulcers occurring.
The preventive use of these medicinal products on digital ulcers has never been assessed, and the level of evidence on the healing of digital ulcers is low.
It is therefore recommended that calcium channel blocker treatment should not be stopped on grounds of ineffectiveness if digital ulcers appear during treatment, but instead to intensify the treatment (expert consensus). Adverse effects, such as oedema of the lower limbs and orthostatic hypotension, may limit their use.
Iloprost is used for preventive treatment in combination with calcium channel blockers and other preventive measures in certain patients at high risk of developing digital ulcers (expert consensus).
Data on other substances such as sildenafil, epoprostenol and treprostinil are limited.

Bosentan (TRACLEER) is a new treatment option to reduce the number of digital ulcers in patients with systemic sclerosis. It is the only product with a marketing authorisation for this indication and given orally.

4.4. Target population

The population for TRACLEER consists of systemic sclerosis patients with ongoing digital ulcers who are liable to develop new digital ulcers.
The target population can be estimated from the available data only with a considerable degree of uncertainty. In fact, the prevalence of Raynaud's syndrome complicated by ischaemic digital ulcers is unknown. Most cases are known to occur during the development of certain types of systemic sclerosis.

The target population may be estimated from the following data:

- In France, 7,500 patients were affected by systemic sclerosis in 2007[7]
- 50-60% of systemic sclerosis patients had or will have ischaemic digital ulcers during the course of their disease[8], i.e. 3,750 to 4,500 patients
- 10-25% of these patients are likely to have new digital ulcers at any time during the course of their disease[8].

On this basis, the target population for TRACLEER is between 375 and 1,125 patients at most.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the extension of indication and at the dosage stated in the marketing authorisation.

[7] Le Guern V. et al. Prevalence of systemic sclerosis in a French multi-ethnic country. Rheumatology 2004; 43: 1129-1137. INSEE survey 1 January 2007.
[8] EPAR data for TRACLEER.

Appendix 1:

LeRoy EC et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988; 15: 202-5

The diffuse or limited forms of systemic sclerosis are defined as follows:

- diffuse systemic sclerosis: cutaneous scleroderma located above the elbows or knees, including the thorax or abdomen. In both studies, individuals who had shown thickening of the skin above the wrists within the 6 months following the first non-Raynaud symptoms as well as squeaking tendons in at least two locations were considered to have diffuse systemic sclerosis.

- limited systemic sclerosis is characterised by scleroderma of the skin limited to areas below the knees or elbows.

Appendix 2:

SHAQ (Scleroderma Health Assessment Questionnaire) assessment scale

Georges C et al. Validation of French version of the Scleroderma Health Assessment Questionnaire (SSc HAQ). Clin Rheumatol 2005; 24: 3-10

The functional disability and pain associated with digital ulcers in systemic sclerosis patients may be assessed by means of the SHAQ supplemented by a visual analogue scale (VAS).
The SHAQ is a self-assessment scale measuring the change over time in functional disability in the upper and lower extremities.
Through this questionnaire, patients assess their ability to carry out everyday activities, as measured by the "disability index". This consists of 8 items (dressing and grooming, arising, eating, walking, personal hygiene, grip strength, and other activities).
Each item includes 2-3 questions, and each question is rated from 0 (no disability) to 3 (severe disability).

Hand functionality is specifically assessed on a composite SHAQ criterion combining the questions on dressing, personal hygiene and grip.

The visual analogue scale supplementing the SHAQ evaluates both the pain associated with systemic sclerosis and the specific impact of Raynaud's syndrome, the digital ulcers, digestive disorders, lung disorders and systemic sclerosis in general on the patient's activities. The visual analogue scale is rated from 0 to 10 (maximum severity).