Bexarotene for cutaneous T-cell lymphoma refractory to previous systemic treatment

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Summary

The drug and the review

Bexarotene is the first available selective retinoid – it binds to and activates retinoid X receptor (RXR) subtypes. It was licensed in 2002 for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in patients who are refractory to at least one systemic treatment. The recommended dose is 300mg/m²/day orally, which may be subsequently adjusted based on the individual’s response to treatment and any toxicity. This review aims to summarise the best quality clinical evidence available for the use of bexarotene in the treatment of patients within its current license.

Background

The available clinical guidelines for the treatment of CTCL mainly cover the most common subtypes – mycosis fungoides (MF) and its leukaemic variant Sezary syndrome (SS). Generally it is recognised that there is a lack of evidence of sufficient quality to base treatment decisions upon in advanced disease, and the choice of therapies and their sequencing will often depend on the experience of the treating physician/institution.

Skin-directed therapies are usually used first-line in early-stage disease, and systemic treatments added in for refractory cases. Systemic treatments are used for patients with advanced disease (stage IIB or higher), and consist of chemotherapy (e.g. methotrexate, purine analogues), biological response modifiers (retinoids, rexinoids, interferon alfa, denileukin diftitox), immunotherapy (e.g. alemtuzumab), and extra-corporeal photo-immunotherapy. Consensus recommendations produced by the European Organisation for Research and Treatment of Cancer (EORTC) recommend bexarotene as one of several options for the second-line treatment of patients with MF (any stage) and SS.

Patients with early-stage, patch-plaque disease (IA, IB and IIA) have a good prognosis with a median survival of >12 years. Those with tumours or erythrodermic involvement skin involvement (stages IIB and III) have a median survival of around 4 years, whereas those with stage IV disease (including lymph node and visceral involvement) have a poor prognosis (median survival of <3 years, as with SS).

Literature searched

Embase (Bexarotene AND exp *Cutaneous T cell lymphoma) and Medline (exp Tetrahydronaphthalenes AND exp *Lymphoma, T-cell, cutaneous) were searched for relevant articles and the bibliographies of identified references used to identify any additional relevant material. A number of other references were searched for information on the drug, including SMC, NICE, Micromedex, AHFS (via Medicines Complete), EMC, EMA, and the British Association of Dermatologists (BAD) website. The manufacturers were asked to comment on the accuracy and comprehensiveness of the first draft.
The two main trials for bexarotene are Phase II-III; one looks at its use in early-stage disease (outside the current license) and the other looks at use in patients with advanced disease who have received at least one previous systemic treatment (the licensed indication). Single-centre studies reporting their experience of bexarotene have reported similar response rates as those seen in the main trials. There are no comparative data and studies of its use in combination with other treatments are limited (these are briefly discussed).

**Efficacy studies**

One published trial looks at the use of bexarotene in patients with refractory, advanced-stage disease (i.e. within its current license).

**Study design:** Open-label, Phase II-III study with historical controls.

**Population:** Adults with advanced-stage CTCL (stages IIIB-IVB) that were refractory to at least one systemic therapy (n=94)

**Treatments:** Initial dosing of bexarotene was 650mg/m²/day; this was amended due to observed dose-limiting toxicities and therefore 38 patients received an initial dose of >300mg/m²/day and the remaining 56 received the optimal dose of 300mg/m²/day initially (the study was not powered to detect differences between the two dose groups and they were separated for the purposes of analysis only). Dose modifications were permitted on the basis of efficacy and toxicity.

**Primary endpoint:** Overall response rate – this included patients who achieved either a complete or partial response according to either the Physician’s Global Assessment (PGA) or the Composite Assessment of Index Lesion Severity (CA). The former is a subjective measure and the latter a more objective measure.

**Key results:** The overall response rate for those starting at 300mg/m²/day was 45% (the response rates according to the two separate scales were 48.2% for PGA and 26.8% for CA). For those starting treatment >300mg/m²/day, the corresponding results were 55% overall, 52.5% for PGA and 47.4% for CA. For the optimal dose (300mg/m²/day), the median time to response was 180 days and the median time to relapse was 299 days. The 95% confidence intervals for the response rates excluded a maximal theoretical spontaneous response rate of 5%.

The EMEA EPAR separates out the data for those patients treated within the licensed indication and with the recommended dose. The overall response rates for these 61 patients were 31% according to the CA and 51% according to the PGA (complete clinical response in 6.6% and 3.3%, respectively). A comparison to historical controls was performed: taking into account that the response rates for other therapies were probably evaluated with an endpoint similar to PGA, it can be assumed that the efficacy of bexarotene is comparable to that of interferon (55% overall response) and other retinoids (58% response).

Data from single institutions have shown similar response rates in everyday clinical practice. There are some, albeit limited, data on the use of bexarotene in combination with other agents, and clinical trials are currently underway (please see the full text for further details).

**Safety**

In clinical trials almost all patients experienced drug-related adverse events; the most frequent ones in those treated with the recommended initial dose of 300mg/m²/day included hyperlipemia (74%), hypothyroidism (29%), hypercholesterolemia (28%), headache (27%), leucopenia (20%), pruritis (20%), asthenia (19%), rash (19%), exfoliative dermatitis (15%) and pain (12%).

Hyperlipidaemia (mainly elevated triglycerides) occurs in a large number of patients treated with bexarotene (74% in clinical trials at the recommended dose) and was dose-limiting in around half of patients in the clinical trials. It usually occurs within the first month of treatment and in practice a fibrate may be started one week before bexarotene is initiated in anticipation of this adverse effect. Blood lipids should be normalised before treatment is started and monitored carefully during, with lipid-lowering therapy used as required. The most common serious drug-related adverse event seen in the trials was pancreatitis secondary to hypertriglyceridaemia, although there were no further cases of this after guidelines for the monitoring and management of hyperlipidaemia were introduced.

Almost all patients taking bexarotene will experience central hypothyroidism; this generally occurs 4-8 weeks after treatment is initiated and responds to treatment with levothyroxine. Symptoms also reverse within a week of discontinuing bexarotene. In practice, a low dose of levothyroxine may be initiated at the same time as bexarotene. Hypothyroidism was not associated with any clinical sequelae in the clinical trials.
Critical evaluation

The main data to support bexarotene in its licensed indication consists of one Phase II-III study. Due to the absence of a placebo group, the PGA endpoint becomes extremely subjective; the CA is however more objective (although calculations were performed by the Marketing Authorisation Holder). There are currently no validated instruments for clinical assessment of CTCL and therefore the available data for other interventions would also presumably have this limitation.

There are no published comparative data for bexarotene available; the trial in advanced disease compared the response rates to historical controls. There are several treatment options in advanced stage disease and a lack of randomised, controlled trials to base treatment decisions upon. Recruitment into clinical trials is hampered by the rarity of the condition. The published experience of single centres suggests a similar response rate to bexarotene in clinical practice, with complete responses being rare.

Potential benefits over existing technologies

There are no direct comparative data on which to base comparisons of efficacy. The benefits of bexarotene include its oral route of administration (more convenient and avoids the invasive use of catheters), the lack of immunosuppression, and a low incidence of infection.

Potential disadvantages over existing technologies

There is a high incidence of hyperlipidaemia (mainly hypertriglyceridaemia) and hypothyroidism associated with bexarotene therapy. Although use of concomitant treatments (pre-emptively) may improve tolerability and reduce the need for early treatment cessation, these side-effects may be dose-limiting/require treatment cessation.

Health Economics

Health economic analyses are not available.

Estimated cost per 100 000 population

The incidence of CTCL is estimated at around 0.3 to 4.0 per 100,000 population. Many of these will not be eligible for treatment with bexarotene as it is currently only licensed for use in patients with an advanced stage of disease (around 15%) who are refractory to at least one previous systemic therapy.

Based on the recommended initial dose of bexarotene (300mg/m²/day) and a median time to relapse of nine months, the average cost of treatment per patient would be £17,965. Applying this to the incidence estimate above, the cost is estimated as £5,389 to £71,860 per 100,000 population. In practice this will vary as there are differences in individual responses and toxicities between patients, resulting in different doses being used. In addition the length of treatment will vary between patients and this is therefore an indication only.

Issues for consideration

- How many treatments should the patient be refractory to before bexarotene is used? It is licensed for use in patients refractory to at least one other systemic treatment.
- The use of invasive systemic therapy is associated with systemic infections in patients with CTCL – could bexarotene be used before invasive therapies to prevent such complications?
- Could bexarotene offer any additional benefit if it is used in combination with other established CTCL treatment?
- The current data for this are limited and the results of further trials are awaited.
- There are currently no studies directly comparing bexarotene to other available therapies for refractory patients.
- What treatment costs are associated with monitoring and treating the adverse effects associated with bexarotene (e.g. hyperlipidaemia)? These are likely to be modest.

This document reflects the views of the London New Drugs Group and may not reflect those of the reviewers.
Background

Cutaneous T-cell lymphoma (CTCL)

Cutaneous T-cell lymphomas (CTCLs) are a group of non-Hodgkin’s lymphomas that primarily develop in the skin, but may ultimately involve lymph nodes, blood and visceral organs (1). The incidence of CTCL in Europe is approximately 1,200 annually, with a prevalence of about 16,000 (2). It usually presents in individuals aged 45-65 years (2) and is more common in men and African Americans (3).

The revised European Organisation for Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas describes several subtypes of CTCL (4). The most common form is mycosis fungoides (MF), which accounts for approximately 60% of new cases (3). MF is generally considered an indolent malignancy in early stages, with slow progression over years or even decades (3, 4). Typically the initial lesions are flat and erythematous skin patches, which evolve over time into plaques and then to more aggressive forms of disease (4). Tumours are the presenting stage in about 10% of cases (3).

Sézary syndrome (SS) is a more aggressive leukemic variant of CTCL, with both blood and skin involvement (i.e. systemic disease) (4). This accounts for around 5% of cases of CTLC and is associated with a median survival of only 32 months from diagnosis (2, 3).

The most significant prognostic factors of survival in CTCL include age at presentation, the extent and type of skin involvement, disease stage, presence of extra-cutaneous disease and peripheral blood involvement (1). Staging of MF is based on a tumour-node-metastasis (TNM) system (please see Appendix 1 for details). Those with patch-plaque disease (stages IA, IB and IIA) have a good survival of >12 years; the majority do not progress to a more advanced stage (5). Those with tumours or erythrodermic skin involvement (stages IIB/III) have a less favourable prognosis (median survival of approximately 4 years), and those with stage IV disease (including those with lymph node or visceral involvement) have a poor prognosis (median survival of <3 years; similar to patients with SS) (4).

Current treatment options

CTCLs are rare diseases and there are few randomised controlled trials available to aid treatment decisions for MF/SS and the choice and sequencing of therapies will frequently depend on the experience of the treating physicians/institution, with consideration of patient factors and preferences (4).

The aims of treatment for CTLC include clearance of lesions in order to maintain or improve quality of life and prolong disease-free and overall survival (3). There are two broad forms of treatment – skin-directed therapies and systemic therapies. For patients with early stage disease where long-term remission is likely, the goal should be to avoid long-term treatment-related toxicities. For those with progressive disease, approaches often include skin-directed therapies as well as systemic treatment (2).

Skin-directed therapy comprises one or more of the following: topical corticosteroids, topical nitrogen mustard (e.g. chloroethamine), topical carmustine, bexarotene gel, phototherapy (with psoralen plus UVA, or UVB), and total skin electron beam therapy. Around 60% of patients with early stage disease that is limited to the skin (often at presentation in MF) will have an effective, long-term response to skin directed therapies (3).

Systemic treatments are usually used for patients who have stage IIB disease or higher, or in patients with early stage disease that are refractory or unable to tolerate skin-directed therapies. They consist of chemotherapy (methotrexate, gemcitabine, CHOP regimen, chlorambucil, doxorubicin, purine analogues), biological response modifiers (interferon alfa, retinoids, rexinoids [bexarotene], denileukin diftitox), immunotherapy (e.g. alemtuzumab) and extra-corporeal photoimmunotherapy (3).

In 2006 the EORTC produced consensus recommendations for the treatment of MF and SS and these are summarised in Table 1 below (3). The authors note that patients with more advanced stages of MF and those with SS have a poor prognosis; the lack of RCTs in this patient population means there is a lack of sufficient evidence (including studies adequately comparing the different systemic regimens) on which to base consensus treatment recommendations. None of the listed treatments have demonstrated an impact on disease outcome and they recommend that patients with late-stage disease be entered into clinical trials.

CTCL patients usually survive for many years after diagnosis, but there is a risk of secondary cutaneous malignancies, such as squamous cell carcinoma, because of the altered immunology caused by the disease or its treatment. The relative risk of skin cancers or melanoma is some 6-8 folds (2).
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Bexarotene

Oral bexarotene (Targretin®) was licensed in 2002 for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in patients who are refractory to at least one systemic treatment (6). Bexarotene therapy should only be initiated and maintained by physicians experienced in the treatment of patients with CTCL (6).

Retinoids have been used in the treatment of CTCL for over two decades; the first used in clinical practice bound to retinoic acid receptors (e.g. isotretinoin, acitretin) (7). Bexarotene is the first selective retinoid to be approved in the EU – it binds with and activates retinoid X receptor (RXR) subtypes (8). Once activated, these receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitisation (6). The exact mechanism of action of bexarotene in the treatment of CTCL is unknown (8).

Dose and administration

The recommended initial dose of bexarotene is 300mg/m² orally daily; this may be decreased to 200mg/m² then 100mg/m² if intolerable adverse effects occur, or the drug may be temporarily discontinued. When toxicity is controlled, the dosage may be carefully readjusted upward. With appropriate clinical monitoring, individual patients may benefit from doses above 300mg/m² daily (doses >650 mg/m²/day have not been evaluated in patients with CTCL) (6).

Bexarotene is administered orally once daily with a meal (safety and efficacy data are based upon administration with food). Treatment should be continued as long as the patient is deriving benefit from therapy. Although it was administered for up to 118 weeks in clinical trials (6) the optimum duration is not known (8).

Precautions and adverse effects

The most commonly reported adverse drug reactions in 109 patients with CTCL treated in clinical trials at the recommended initial dose of 300 mg/m²/day

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**Table 1: Consensus recommendations from EORTC on the treatment of MF and SS**

<table>
<thead>
<tr>
<th>Disease/stage</th>
<th>First-line</th>
<th>Second-line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycosis Fungoides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA, IB, IIA</td>
<td>Expectant policy with careful monitoring or skin-directed therapy (PUVA, UVB, topical CS, RT, TSEB, topical nitrogen mustard [mechlorethamine], carmustine)</td>
<td>Systemic therapies alone (oral <strong>bexarotene</strong>, IFN, IFN plus retinoids, DD, low-dose MTX) or in addition to SDT (IFN plus PUVA, retinoids plus PUVA, bexarotene plus PUVA)</td>
</tr>
<tr>
<td>IIB</td>
<td>PUVA plus IFN, TSEB and superficial X-irradiation, retinoids plus IFN, PUVA plus retinoids</td>
<td><strong>Bexarotene</strong>, chemotherapy (monotherapy or combination), DD</td>
</tr>
<tr>
<td>III</td>
<td>PUVA plus IFN, IFN, MTX, TSEB/X-irradiation, topical nitrogen or carmustine, ECP, PUVA plus retinoids</td>
<td><strong>Bexarotene</strong>, chemotherapy</td>
</tr>
<tr>
<td>IVA-IVB</td>
<td>Palliative - all the above may be considered but they should be chosen to be effective and have a favourable side-effect profile</td>
<td></td>
</tr>
<tr>
<td><strong>Sezary syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECP, IFN, DD, chlorambucil and prednisone</td>
<td><strong>Bexarotene</strong>, chemotherapy, alemtuzumab, MTX</td>
</tr>
</tbody>
</table>

PUVA - psoralen plus UVA; CS – corticosteroids; RT – radiotherapy; TSEB – total skin electron beam therapy; IFN – interferon; DD – denileukin diftitox; MTX – methotrexate; SDT – skin directed therapy; ECP – extra-corporeal photoimmunotherapy
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included hyperlipidaemia (74%; primarily elevated triglycerides), hypothyroidism (29%), hypercholesterolaemia (28%), headache (27%), leucopenia (20%), pruritus (20%), asthenia (19%), rash (16%), exfoliative dermatitis (15%), and pain (12%) (6). The most common drug-related serious adverse event was pancreatitis secondary to hypertriglyceridaemia; there were no further cases of this subsequent to the introduction of guidelines for the monitoring and management of hyperlipidaemia (2).

Hyperlipidaemia, which is common and was dose-limiting in around half of cases in clinical trials, usually occurs within 2-4 weeks of initiation. Fasting blood lipids should therefore be obtained and normalised where necessary, prior to starting treatment (9). Levels should then be monitored weekly until the lipid response to bexarotene has been established (usually 2-4 weeks) and then at least every month. Elevated triglyceride and cholesterol levels should be controlled using concomitant lipid-lowering therapy, with dose reductions or discontinuation of bexarotene if necessary (6). Most patients will require concomitant treatment with a lipid-lowering agent (3); in practice some advocate pre-treatment with a fibrate for one week before bexarotene is initiated (e.g. fenofibrate 145-200mg daily; gemfibrozil should not be used as it increases plasma concentrations of bexarotene) (10). Statin therapy may need to be added in during treatment if cholesterol levels become raised (the combination of a statin and fibrate should be used with caution due to the risk of myopathy/ rhabdomyolysis) (10). Lipid levels remained elevated despite anti-lipid therapy in some patients in the clinical trials. Cases of acute pancreatitis associated with elevated triglycerides have been reported; those with a history of pancreatitis or with risk factors should not receive treatment with bexarotene unless the benefit is considered to outweigh the risk (6).

Almost all patients taking bexarotene will experience a reversible decrease in thyroid-stimulating hormone, with reduced levels of free thyroxine and central hypothyroidism (this is a specific RXR-related effect of bexarotene) (2, 9). This generally occurs 4-8 weeks after treatment is initiated and responds to treatment with thyroxine; in practice some recommend starting treatment with low-dose levothyroxine (e.g. 50mcg daily; adjust according to response) at the same time as bexarotene, in anticipation of this complication (9). Symptoms of hypothyroidism reverse within a week of discontinuing bexarotene (11). Thyroid function should be checked at baseline and then at least monthly during treatment and as indicated by the emergence of any symptoms suggestive of hypothyroidism. Those with uncontrolled thyroid disease should not initiate treatment with bexarotene (6).

As leucopenia and anaemia have been reported in clinical trials, white blood cell count and haemoglobin should be checked at baseline, weekly during the first month of treatment and then monthly thereafter (6).

Special populations

There are no special population dosage recommendations at this time. Although no specific studies have been conducted, pharmacokinetics may be altered in patients with hepatic or renal impairment (8). The SPC recommends that patients with renal insufficiency be monitored carefully while on bexarotene therapy (6).

It is contra-indicated in hepatic insufficiency as liver function test (LFT) abnormalities have been reported (6). Baseline LFTs should be obtained at baseline and subsequently monitored weekly during the first month of treatment and monthly thereafter (6).

As the clinical safety and effectiveness of bexarotene in patients below 18 years of age have not been studied, the SPC recommends against its use in the paediatric population until further data are available (6). The use of bexarotene in pregnancy is contra-indicated, and women of childbearing potential should have a negative pregnancy test within one week of starting treatment, and use adequate birth-control measures (two reliable forms of contraception are recommended, including a non-hormonal method due to possible interaction hormonal contraceptives) throughout treatment and for at least one month following discontinuation (6).

Drug interactions (SPC)

No formal interaction studies of bexarotene have been conducted. As it is metabolised by cytochrome P450 3A4 (CYP3A4), it may theoretically be affected by concomitant use of inhibitors or inducers of this enzyme, or of other CYP3A4 substrates. Bexarotene may induce CYP3A4 and therefore repeated use may reduce the concentrations of other substrates of this enzyme – examples are tamoxifen and oral contraceptives. Efficacy of oestrogen/progesterone contraceptives may theoretically be reduced and women of childbearing potential must use two reliable forms of non-hormonal contraception, including a non-hormonal method (see below).

Because of bexarotene’s mechanism of action, caution should be exercised when administering it to patients using insulin, agents that enhance insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones), as it may enhance their action (6). Because of its relationship to vitamin A and the potential for additive adverse effects, patients receiving bexarotene should be warned to limit concomitant use of preparations containing vitamin A to ≤15,000 IU/day (6, 8).

Concomitant administration of gemfibrozil is not recommended as it may result in substantial increases in plasma concentrations of bexarotene via
an unknown mechanism. Bexarotene concentrations have not been shown to be affected by concomitant administration of atorvastatin or levothyroxine (6).

Guidelines
The Scottish Medicines Consortium (SMC) issued advice on the use of bexarotene within NHS Scotland in November 2002. This recommended its use as a second-line treatment for patients with advanced (stages IIb or III) CTCL. Its use is restricted to patients who have proved refractory both to local skin directed therapy and to at least one systemic treatment, and it should be initiated and supervised by haematologists, dermatologists or oncologists (12).

The British Association of Dermatologists (BAD) and the UK Cutaneous Lymphoma Group issued joint guidelines on the management of primary CTCL in 2003 (17). These discuss the clinical trial results for bexarotene and comment that future studies need to clarify its role in later stages of disease and specifically in erythrodermic patients. At the present time, they note that bexarotene can only be prescribed for early stages of MF in the context of clinical trials.

The EORTC has produced consensus recommendations for the treatment of MF and SS; these state that bexarotene is an option for the second-line treatment of patients with MF (any stage) or SS (please see Table 1 above for further information) (3).

The National Comprehensive Cancer Network (NCCN) have produced recommendations on the treatment of CTCL (MF and SS), as part of their larger guidance on the management of non-Hodgkin’s lymphoma (1).

Clinical efficacy
To date, two open-label, multicentre phase II–III studies of bexarotene as monotherapy for CTCL have been published. Both were historically-controlled, by a comparison to the natural evolution of patients with untreated refractory CTCL. The EMEA EPAR notes that it may be possible nowadays to identify and exclude patients with aggressive forms of CTCL from enrolment, as they need different, frequently more aggressive treatment. However, this distinction was probably impossible when the studies were conducted (2). No data directly comparing bexarotene to other treatment options are available.

Phase II-III trial in early-stage patients
The first study evaluated bexarotene in the treatment of adults with stage I to IIA CTCL (early-stage disease) (11). A total of 58 patients who were refractory/intolertant to therapy, or who had reached a 6-month or greater response plateau with at least two qualifying prior therapies (see Appendix 2), were included in the trial and randomised to open-label treat-ment with oral bexarotene at either 6.5mg/m² per day (low-dose) or 650mg/m² per day (high-dose).

Based on response and dose-limiting effects, the starting dose for the high-dose group was reduced to 500mg/m²/day and then to a final recommended initial dose of 300mg/m²/day. This resulted in an initial assigned dose of 6.5mg/m²/day for 15 patients, 300mg/m²/day for 28 patients and >300mg/m²/day for 15 patients. Dose increases for efficacy (in the absence of toxic effects) and dose reductions for toxicity were permitted. The dose of 6.5mg/m²/day was however not reduced; those who progressed after 8 weeks or failed to respond after 16 weeks could cross over to high-dose therapy. An interim analysis found a significant difference in rate of progressive disease between the two dose groups and randomisation was discontinued at this stage.

As there are no validated instruments for clinical assessment of CTCL, the Physicians Global Assessment of Clinical Condition (PGA) and Composite Assessment Index Lesion Severity (CA) grading scales were used to assess response to treatment. The primary endpoint was the overall response rate according to either PGA or CA - responses to treatment were classified as a complete clinical response (CCR) or partial response (PR), as assessed by trained clinical evaluators who assessed the same patients throughout the study (please see Appendix 3 for details of the scales). Secondary efficacy endpoints included body surface area (BSA) involvement, time to response, time to disease progression and two quality of life (QOL) questionnaires (one of which was a non-validated CTCL-specific QOL questionnaire). The duration of treatment was planned for 16 weeks, but was extended if treatment was beneficial and no unacceptable toxic effects were occurring.

The study was not powered to compare response rates based on dose, but rather for point estimates and 95% CIs for each treatment group. The paper states that a ‘successful clinical trial’ was defined as a response rate of ≥20%, with the lower boundary of the 95% CI excluding 5% (considered as a conservative estimate of the theoretical maximal spontaneous response rate). Efficacy was based on the intention to treat (ITT) population.

Baseline characteristics were balanced among the three initial dose groups. The majority (59%) had stage IB disease, with a median time of 6.6 years since diagnosis. The majority (78%) were refractory to two or more therapies; the optimal dosing group had received a median of 3 prior therapies (range 2-8). Previous irradiation or phototherapy (97%) and topical nitrogen mustard (93%) were common and over half (59%) had received prior systemic treatment, including interferon (38%).

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The main findings reported included the following:

- The overall response rates (primary endpoint) were 20% (95% CI 0-40%), 54% (35-72%) and 67% (43-91%) in the 6.5mg/m²/day, 300mg/m²/day and >300mg/m²/day groups, respectively.

- When split into the different scales used, the overall response rates for the different dose groups were 6.7%, 50% and 60% according to the PGA (subjective endpoint) and 20%, 36% and 46.7% according to the CA (a more objective measure) (EMEA EPAR).

- A CCR occurred in 7% of patients starting at 300mg/m²/day and 27% of patients starting on >300mg/m²/day.

- At the optimal dose, responses were similar by disease stage, with no evidence of preferential response by age, sex or race (these subgroup analyses are however limited due to the small patient numbers).

- 73% patients receiving 6.5mg/m²/day progressed or did not improve and were crossed over to high dose therapy. The response rate in this group was 18% prior to crossover and 73% after.

- The median time to onset of response (Kaplan-Meier estimates based on patients remaining in the study at any given time) was 8.1 weeks (range 3.9 – 16.3 weeks) for the 300mg/m²/day dose group. The time to response at higher doses was longer (13.1 weeks) but interruptions in therapy due to development of toxicities may have contributed to this.

- The median time to progression was 13.6 (range 4.0-17.7) weeks in the low-dose group, 30 (1.1-30.0) weeks in the optimum dose group and 73.7 (2.1-73.7) weeks for initial doses >300mg/m²/day.

- The projected median duration of response was 73.7 weeks (although the median had not been reached in the low-dose group and the 300mg/m²/day group).

- 95% of responders rated their change in CTCL on QOL questionnaires as moderate or much improved and 84% were moderately or very satisfied with bexarotene treatment at week 16. [No data is presented from the QOL questionnaires of those patients who were not primary endpoint classification responders].

Eleven patients (19%) were treated for 40 weeks or more and 16 (28%) remained on drug therapy at the time of data cut-off. The most common reason for withdrawal from treatment was adverse events (18/42; 43%). 15 of which were attributed to bexarotene, and either progressive disease or withdrawal of consent (6 patients [14%] each). Of 28 starting treatment with the optimal dose, 7 withdrew due to adverse events and 3 due to disease progression.

The authors state that although higher rates of response and lower rates of progression related to the dose level occurred, the study was not powered to determine statistically significant differences between the groups. They note that although other retinoids may appear to have similar response rates to bexarotene in available published reports, these previous studies were not conducted as rigidly controlled clinical trials and they did not use the same response criteria.

Phase II-III trial in advanced stage CTCL

The second study evaluated the safety and efficacy of bexarotene in the treatment of adults with refractory, advanced stage (IIB-IVB) CTCL (13). Patients were eligible for entry into this study if they were refractory to at least one systemic anticancer therapy (with refractory defined as lack of response of at least 50% improvement [resistance] or progression of disease whilst still on therapy after an initial response). The median number of systemic therapies that the patients were refractory to was two (range 1 – 6). Prior therapy required washout (with duration dependent on the type); they could remain on topical therapy provided the dose had been stable for at least two weeks.

This study was not randomised as only one dose was evaluated – initially all patients were to receive 650mg/m²/day, but this was reduced to 500mg/m²/day and then to a final optimal starting dose of 300mg/m²/day, due to observed dose-limiting toxicities. This resulted in an initial assigned dose of >300mg/m²/day for 38 patients and 300mg/m²/day for 56 patients (total n=94). Dose modifications (increases for efficacy, up to maximum of 400 m²/day, or decreases due to toxicity) were permitted for individual patients.

The primary endpoint was the overall response rate according to PGA or CR; secondary endpoints measured were similar to the study of early-stage disease. Although the trial was not powered to find differences between the groups of patients treated with 300mg/m²/day and those treated with >300mg/m²/day, the patients were grouped into these two initial dose levels for the purposes of analysis. All analyses were based on ITT, and were performed after all patients had either completed 16 weeks on the study or had withdrawn before week 16. At the database cut-off, 63 (67%) patients had withdrawn from the study.
Patients were classified as stage IIB (43%), III (31%), IVA (16%) or IVB (10%). The patient group had a median age of 64 years (range 27-89), with a median of 4 years (range 0.5-28) since diagnosis. All but two patients (protocol violations) had been refractory to at least one prior systemic treatment; the patients had received a median of the median number of 5 (range 1-11) previous systemic treatments and were refractory to a median of 2 (range 1-6). The majority of patients (85%) had received at least one irradiation therapy, 79% had received at least one topical therapy, and 68% had received one or more therapies from each of the systemic, topical and irradiation categories. The most common previous systemic treatment was interferon (65%); 28 (30%) had previously been treated with retinoids.

The main findings reported were as follows:

- The overall response rate was 45% in patients starting at 300mg/m²/day and 55% in those starting at >300mg/m²/day. Although the specific values are not given, the authors state that the lower bounds of the 95% CI for both dose groups excluded a conservative estimate of the maximal theoretical spontaneous response rate of 5%, and that the response rates of the two dose groups were 'statistically indistinguishable' based on the 95% CIs.

- When split into the different scales used, the overall response rates for the different dose groups were 48.2% and 52.5% for the PGA and 26.8% and 47.4% for the CA.

- A CCR occurred in 2% and 13% of patients receiving 300mg/m²/day and >300mg/m²/day respectively.

- The median time to response was 180 days (range 14-197) for patients entered at 300mg/m²/day and 59 days (22-169) for those entering at >300mg/m²/day respectively.

- For the responders, 36% in the 300mg/m²/day group and 38% in the higher-dose group had relapsed, for a projected median time to relapse of 299 days (range 57-299) and 385 days (94-456), respectively.

- Of the subgroup that had previously been treated with a retinoid (n=28), 15 (54%) had a response to oral bexarotene (including 14% CCR and 39% PR). The authors conclude from this that prior retinoid therapy did not seem to influence the response to subsequent therapy.

- Analysis of secondary endpoints showed decreases in overall BSA involvement, improvement in cutaneous tumours and clinically abnormal lymph nodes, improvements in pruritus and patient assessed CTCL-specific QOL measures.

The most common reason for withdrawal from the study was progressive CTCL (51% of those who withdrew and 34% of all enrolled patients); nine patients (10%) withdrew due to an adverse event possibly related to bexarotene. The most common dose-limiting toxicities included hypertriglyceridaemia/ hypercholesterolaemia (43%), and neutropenia/leukopenia (9%).

The authors comment that although the study was not powered to confirm difference based on initial dose, there are 'strong indications' of a dose-response relationship; they note that this was also observed in the parallel study of bexarotene in early-stage disease. They note that not all patients in this study had classic MF and that the response rate in those with this disease type may possibly be higher than that observed here. They conclude that oral bexarotene is a convenient therapy due to its oral route of administration, the lack of immunosuppression, and low incidence of infection.

Due to the gradual onset of action (up to 197 days in this trial), it has been recommended that bexarotene therapy be continued for 3-6 months before evaluating response to treatment (10).

**Data from EPAR on licensed population**

The EMEA EPAR notes that the Marketing Authorisation Holder analysed 193 patients included in both studies; of these there were 61 who had advanced disease refractory to at least one systemic treatment and were treated with the recommended dose of 300mg/m²/day. The overall response rates in these patients were 31% (according to CA) and 51% (PGA), including CCR in 6.6% and 3.3%, respectively. The projected median time to progression was 16.1 weeks for CA. For the 30 patients with at least one pre-existing abnormal lymph node, 30% had ≥50% sustained improvement in the number of nodes and/or aggregate nodal area. For the 14 with at least one pre-existing cutaneous tumour, 21% had ≥50% sustained improvement in the number of tumours and/or aggregate volume of tumours (2).

The efficacy of bexarotene was compared to historical controls, although this was difficult as patients treated with bexarotene were refractory to at least one systemic treatment. Taking into account that the response rates in the literature for other therapies were probably evaluated with endpoints like the PGA, it can be assumed that the efficacy of bexarotene is comparable to that of interferon (CR+PR=55%) and other retinoids (CR+PR=58%) in patients refractory to at least one systemic treatment; however the rate of complete response to bexarotene is lower than that seen with other treatments (2).
Clinical experience from single centres

Abbott et al note that there are no long-term studies available that allow determination of the optimum duration of therapy with bexarotene for CTCL, and how best to adjust the dose according to response. They describe their experience of treating 66 patients with MF (n=40) or SS (n=26), the majority with advanced-stage disease (stage IIB to IVB; n=47), at their centre (7).

Patients who had received at least one dose of bexarotene between August 2002 and 2007 (starting dose 150-300mg/m²) were retrospectively identified from patient records (n=66). Of these, 28 were taking it as monotherapy (75% had received at least one previous systemic therapy – chemotherapy, ECP and/or interferon alfa), 26 with concurrent, stable therapy and 12 with new concurrent therapy. Each patient was co-prescribed fenofibrate (starting one week prior to bexarotene) and levothyroxine (starting the same time). Doses of these were adjusted as necessary according to the results of monitoring during treatment; atorvastatin was added if hypercholesterolaemia developed. Treatment was continued until disease progression, intolerable toxicity, or until bone marrow transplantation was performed.

A total of 52 patients (79%) completed over one month of treatment; the mean duration of treatment was 11 months (median 6 months). The ITT response rate was 44%. A complete response, defined as no evidence of disease for a minimum of four weeks, was seen in 6 patients overall (9%) and in 2 patients (3%) at 8 weeks. A partial response (improvement in skin disease for a minimum of four weeks and at least a 50% reduction of lymphocyte count [if peripheral blood involvement] and reduction in number and size of palpable nodes [if lymph node involvement]) was seen in a further 23 patients (35%), and had occurred in the majority (30%) by 8 weeks. The median time to maximal response was 3 months (1-9 months), the median time to progression was 9 months (range 3-44 months) and the median event-free survival was 7 months (1.5-54). Overall response rates were similar in those treated with monotherapy and those treated with concurrent therapies (new or stable); a higher response was achieved as bexarotene as part of combination treatment.

18 out of the 24 patients (75%) with SS who completed over one month of treatment with bexarotene had a skin response. Of the 17 with blood involvement, 13 (76%) had a blood response, including 7 (41%) with a complete response (normal lymphocyte count) and 6 (35%) with a partial response.

Of the 14 patients who completed less than one month of treatment, 11 were unable to tolerate it (mainly due to hyperlipidaemia), one was lost to follow-up, one was found to have alcoholic liver disease, and one died from their disease.

The authors comment that the response rates seen in their study are similar to those reported previously in clinical trials, and they emphasize that it is important to continue bexarotene for over 8 weeks to reach the maximal response. They note that quantitative assessment of the skin was difficult as this was a retrospective analysis; blood responses were easier to measure objectively.

Talpur et al prospectively evaluated 70 patients with MF treated with bexarotene at their centre in the US (14). This evaluation included 41 patients who were enrolled in one of the two Phase II-III studies; the remainder were treated after FDA approval was obtained. It was administered either as monotherapy (n=54; including the 41 included in one of the clinical trials) or in combination with other treatments (n=16). Bexarotene was used in combination with PUVA/interferon alfa, ECP, ECP/interferon alfa, ECP/interferon alfa/PUVA and with interferon alfa/PUVA/topical nitrogen mustard. Lipid-lowering agents were generally started 1-2 weeks in advance of the bexarotene therapy (atorvastatin or fenofibrate), and levothyroxine (25-50mcg daily) was started at the same time as bexarotene.

A total of 26 patients (48%) receiving bexarotene as monotherapy achieved a partial response, as did 11 (69%) of those receiving it as part of combination treatment. Of the 41 with advanced disease (IIB to IVB), the response rate was 46% (including two complete responses). The authors note that overall there were 42 patients who required one or more lipid lowering agents – those treated with both atorvastatin and fenofibrate were seen to have a higher response rate (90%) than those treated with monotherapy (48%) or no lipid-lowering agent (p<0.0001). The authors speculate that controlling lipid levels from the beginning of treatment may allow patients to receive uninterrupted bexarotene therapy at maximal doses; however care should be taken when combining a statin and a fibrate due to the risk of myopathy and rhabdomyolysis.

**Bexarotene in combination with other therapies for CTCL**

Various combination therapies are used in the treatment of patients with CTCL; the majority of the available studies are however non-randomised and/or retrospective, with a number of limitations including poorly defined response criteria and variable doses, amongst others. In general it is difficult to conduct studies comparing different combination strategies with sufficient power to detect statistically significant differences, due to the rarity of CTCL (9).
Available randomised studies have mainly looked at interferon alfa – e.g. interferon-alfa plus PUVA versus interferon alfa plus acitretin (showing superiority of the former), and PUVA versus PUVA plus interferon alfa (showing benefit of the combination). The available data for the use of bexarotene in combination with other therapies are more limited (9).

A number of case reports/small case series in the published literature report beneficial effects in individual patients from the combination of oral bexarotene with other agents for CTCL, including photopheresis, methotrexate, narrowband UVB, ECP, PUVA, interferon (alfa or gamma), and denileukin diftitox.

One Phase II trial of bexarotene use in combination therapy was located from a search of the literature (15). This open-label trial evaluated the safety and efficacy of oral bexarotene combined with interferon alfa-2b in 22 patients with stage IB-IV CTCL; of whom four had previously received systemic chemotherapy, 18 topical chemotherapy, and 12 total skin electron beam therapy (one patient had received no prior therapies). The planned duration of treatment was 16 weeks – this included eight weeks of bexarotene (300mg/m²/day) alone, with interferon alfa-2b (Intron A, 3MU three times a week; increased if no toxicity) added if there was no CR. 19 patients completed the first 8 weeks and 18 completed the full 16 weeks, with interferon added in all cases (as there were no CRs seen within the first 8 weeks). The overall response rate was 39% (95% CI 17-64%), including one CCR and 6 PRs. The median duration of response was 2.7 months (range 1.1-7.6 months). Three patients had a PR during the first 8 weeks (bexarotene alone); four additional responses were seen during weeks 8-16 (including one CCR in a patient who achieved PR in the first 8 weeks). The authors note that this rate is slightly lower than that previously reported for bexarotene alone; the duration does however limit conclusions as the maximum effect of combination therapy may take months to become apparent (case reports of the combination have shown PRs as late as 6 months after the combination was started). In addition the wide confidence intervals suggest that a small advantage cannot be ruled out. However, the clinical usefulness of the combination is limited by the inconvenience of interferon administration and its somatic side-effects.

Retrospective studies have suggested that the use of PUVA in addition to bexarotene is an effective and safe combination treatment for CTCL. For example, Papadavid et al reviewed the charts of 14 patients who had received the combination for relapsed or refractory MF at their centre in Athens between 2003 and 2006 (16).

Disease stage ranged from IA to III and all had received monotherapy with at least one of the following: topical corticosteroids (n=1), PUVA (n=13), narrowband UVB (n=1), oral retinoids (n=4), oral bexarotene (n=3), or interferon alfa (n=5). The nine patients who were evaluable for response (five withdrew due to hyperlipidaemia) received treatment for a median of 4 months (range 2.5-8) - four (44%) achieved a CR, and two (22%) a PR.

The EORTC is conducting a Phase III study comparing PUVA alone to PUVA plus oral bexarotene in stage IB and IIA disease which will provide further, more robust evidence on the efficacy of this combination (use in this stage of disease is currently outside of the license). Use of bexarotene in combination with other agents is also under investigation in early-stage trials (e.g. denileukin diftitox, vorinostat, gemcitabine, pralatrexate) (17).

Health economics

The incidence of CTCL is around 0.3 to 4.0 per 100,000 population. Many of these will not be eligible for treatment with bexarotene as it is currently only licensed for use in patients with an advanced stage of disease (around 15%) who are refractory to at least one previous systemic therapy. The recommended initial dose of bexarotene is 300mg/m²/day; however some advocate starting it at a lower dose (150mg/m²/day) for the first 2-4 weeks, with subsequent titration up to the recommended dose if there are no problematic side-effects (10).

In the advanced stage study, the median time to relapse was 299 days (approximately nine months). Based on treatment for this length of time, the average cost of treatment per patient would be £17,965 for 300mg/m²/day. In practice this will vary as there are differences in individual responses and toxicities between patients, resulting in different doses being used. In addition the length of treatment will vary between patients and this is therefore an indication only.
References


Acknowledgements:
Contributions from many clinicians and commissioners within London
## Appendix 1: TNM classification of CTCL, the resulting stages and their prognostic implications (3)

### TNM DEFINITIONS

<table>
<thead>
<tr>
<th>Skin</th>
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<tbody>
<tr>
<td>T1</td>
<td>Patches, plaques, or both, involving &lt;10% of the body surface</td>
</tr>
<tr>
<td>T2</td>
<td>Patches, plaques, or both, involving ≥10% of the body surface</td>
</tr>
<tr>
<td>T3</td>
<td>One or more cutaneous tumours</td>
</tr>
<tr>
<td>T4</td>
<td>Generalised erythroderma</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph nodes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Lymph nodes clinically uninvolved</td>
</tr>
<tr>
<td>N1</td>
<td>Lymph nodes clinically enlarged but not histologically involved</td>
</tr>
<tr>
<td>N2</td>
<td>Lymph nodes clinically non-palpable but histologically involved</td>
</tr>
<tr>
<td>N3</td>
<td>Lymph nodes clinically enlarged and histologically involved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visceral organs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No visceral metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Visceral metastases</td>
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<table>
<thead>
<tr>
<th>Blood involvement</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B0</td>
<td>No circulating atypical cells (Sezary cells), &lt;5%</td>
</tr>
<tr>
<td>B1</td>
<td>Circulating atypical cells (Sezary cells), ≥5%</td>
</tr>
</tbody>
</table>

### STAGE GROUPING

<table>
<thead>
<tr>
<th>Clinical stages</th>
<th>Expected 5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1-2 N1 M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3 N0-1 M0</td>
</tr>
<tr>
<td>III</td>
<td>T4 N0-1 M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T1-4 N2-3 M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T1-4 N0-3 M1</td>
</tr>
</tbody>
</table>
Appendix 2: Inclusion and exclusion criteria for the two studies (2):

Patients were to have met the following:

- a clinical diagnosis of CTCL (stage I to IIA in the early stage study, stage IIB to IVB in the advanced study) confirmed by a biopsy within 30 days prior to entry
- refractory to, or intolerant to, or have reached a response plateau for at least 6 months on at least two prior therapies in the early stage study (PUVA, UVB, electron-beam therapy, photopheresis, topical nitrogen mustard, BCNU, interferon, systemic cytotoxic chemotherapy). At least one of qualifying prior treatments must have been topical nitrogen mustard, BCNU or PUVA, UVB, or electron-beam therapy. Previous topical steroids and systemic retinoids did not qualify.
- Refractory CTCL: resistance to therapy due to lack of response of at least 50% improvement or progression on therapy after initial response.
- Intolerant CTCL: discontinuation of therapy due to side effects/toxicity, whether or not a response occurred.
- no antipruritic therapy or no change before and during the trial
- systemic therapy of CTCL indicated
- no topical CTCL treatment within 2 weeks, no PUVA or UVB within 3 weeks, no EBT, photopheresis, systemic anticancer therapy or oral retinoid therapy for any indication within 4 weeks prior to study entry.
- a Karnofsky performance score >60 and acceptable organ function (notably normal lipid levels)
- negative HCG test and effective means of contraception in female patients of child-bearing potential

Appendix 3: Primary measures of efficacy used in the trials

The Physician’s Global Assessment (PGA) is the investigator’s subjective assessment of the overall improvement or worsening of the patient’s overall disease compared to baseline. It grades the patient’s clinical condition as 0-6 (see table below), with confirmation of response by two consecutive observations over at least four study weeks:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – completely clear</td>
<td>No evidence of disease; 100% improvement</td>
<td>Clinical complete response</td>
</tr>
<tr>
<td>1 – almost clear</td>
<td>Very significant clearance (≥90% to &lt;100%); only traces of disease remains</td>
<td>Partial response</td>
</tr>
<tr>
<td>2 – Marked improvement</td>
<td>Significant improvement (≥75% to &lt;90%); some evidence of disease remains</td>
<td></td>
</tr>
<tr>
<td>3 – Moderate improvement</td>
<td>Intermediate between slight and marked improvement (≥50% to &lt;75%)</td>
<td></td>
</tr>
<tr>
<td>4 – Slight improvement</td>
<td>Some improvement (≥25% to &lt;50%); however, significant evidence of disease remains</td>
<td>Stable disease</td>
</tr>
<tr>
<td>5 – No change</td>
<td>Disease has not changed from baseline condition (±&lt;25%)</td>
<td></td>
</tr>
<tr>
<td>6 - Worse</td>
<td>Disease is worse than at baseline evaluation by ≥25%</td>
<td>Progressive disease</td>
</tr>
</tbody>
</table>

In addition, a complete response was seen if the PGA was Grade 0 and there was absence of CTCL on cutaneous biopsy of a clinically cured lesion.

The EMEA EPAR notes that the PGA could possibly be influenced by knowledge of the daily dose received; in addition the absence of a placebo group makes this primary endpoint very subjective (2).

The Composite Assessment (CA) of Index lesion Severity evaluates up to 5 representative index lesions using a scale of 0 (no evidence of symptoms) to 8 (very severe). Signs and symptoms used include erythema, scaling, plaque elevation, hypo/hyperpigmentation, and lesion surface area (scale of 0 to 18). The CA response was then calculated as the ratio of summation of all clinical signs at each visit compared to baseline (CA ratio). Summing all the grades for each index lesion generated a CA grade; the CA grade at baseline was then divided by CA grades at each subsequent visit to determine the CA ratio. A CA ratio <1.0 indicated improvement in disease and a ratio >1.0 indicated a worsening of disease. The response was calculated as follows (only the positive responses are included here for information):
- **Complete response**: CA ratio=0, no skin lesions, no clinically abnormal lymph nodes or visceral tumours, and a cutaneous biopsy documenting absence of histology signs of CTCL from a cleared lesion
- **Clinical complete response**: CA ratio=0 and no evidence of disease
- **Partial response**: CA ratio ≤0.5 and less than 25% increase in the number or aggregate area of clinically abnormal lymph nodes, cutaneous tumours or visceral disease and no new pathologically abnormal lymph nodes or new visceral disease in an area documented to be free of disease within 14 days of entry in the study

The EMEA EPAR notes that the CA is a more objective measure of index lesion response to treatment; however calculations of the grade and ratio were conducted by the marketing Authorisation Holder (i.e. the final response to treatment according to this endpoint was assessed by them and not the investigators) (2).