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EMA/453346/2012
Committee for Medicinal Products for Human Use (CHMP)

# Final CHMP assessment report

**Folotyn**

International non-proprietary name: **pralatrexate**

Procedure No. **EMEA/H/C/002096**

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| µg | microgram |
| AE | adverse event |
| ADR | adverse drug reaction |
| ALCL | anaplastic large cell lymphoma |
| ALK | anaplastic lymphoma kinase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{0-\infty}$ | area under the curve extrapolated to infinity |
| C10, C19 | carbon 10, carbon 19 |
| CHMP | Committee for Medicinal Products for Human Use |
| CHOP | cyclophosphamide, doxorubicin, vincristine, prednisone |
| CI | confidence interval |
| CLL | chronic lymphocytic leukaemia |
| $CL_{tot}$ | total clearance |
| $C_{max}$ | maximum concentration |
| COV | coefficient of variation |
| CT | computed tomography |
| CR | complete response |
| CRu | complete response unconfirmed |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP450 | cytochrome P450 |
| DHF | dihydrofolate |
| DHFR | dihydrofolate reductase |
| DLBCL | diffuse large B-cell lymphoma |
| DNA | deoxyribonucleic acid |
| dTMP | deoxythymidine monophosphate |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| FPGS | folylpolyglutamyl synthetase |
| G-CSF | granulocyte colony stimulating factor |
| GCP | Good Clinical Practice |
| GM-CSF | granulocyte/macrophage colony stimulating factor |
| HR | hazard ratio |
| HTLV | human T-cell leukaemia virus |
| ICH | International Conference on Harmonisation |
| IPI | International Prognostic Index |
| IWC | International Workshop Criteria |
| IV | intravenous |
| LFT | liver function test |
| $m^2$ | square meter |
| MALT | mucosa-associated lymphoid tissue |
| mg | milligram |
| min | minute |
| mL | milliliter |
| mos | months |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| ND | not determined |
| NHL | non-Hodgkin's lymphoma |
| NK | natural killer |
| NSAID | nonsteroidal anti-inflammatory drug |
| NSCLC | non-small cell lung cancer |
| OS | overall survival |
| PD | progressive disease |
| PDCO | Paediatric Committee |
| PET | positron emission tomography |
| PFS | progression-free survival |

| | |
|---|---|
| Pgp | P-glycoprotein |
| PK | pharmacokinetic(s) |
| PR | partial response |
| PTCL | peripheral T-cell lymphoma |
| QTc | QT interval corrected for heart rate |
| RFC-1 | reduced folate carrier 1 |
| RMP | Risk Management Plan |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SCT | stem cell transplant |
| SD | stable disease |
| SmPC | Summary of Product Characteristics |
| SOC | system organ class |
| $t_{1/2}$ | terminal elimination half-life |
| TEN | toxic epidermal necrolysis |
| THF | tetrahydrofolate |
| T-PLL | T-cell prolymphocytic leukaemia |
| UE | unevaluable |
| US | United States |
| WBC | white blood cell |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Allos Therapeutics Ltd submitted on 23 November 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Folotyn, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2009.

Folotyn was designated as an orphan medicinal product EU/3/07/444 on 13 April 2007. Folotyn was designated as an orphan medicinal product in the following condition: Treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated).

The applicant applied for the following indication: treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy.

**The legal basis for this application refers to:**

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/270/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/270/2010 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

**Similarity**

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Applicant's requests for consideration*

## Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claim(s):

The Applicant outlined that the conditional marketing authorisation would be based on a pivotal single-arm Phase II study (PDX-008), since the lack of approved or well-researched therapies for relapsed or

refractory PTCL within the EU is suggested to represent a clear unmet medical need. The application included a specific commitment to conduct and complete a Phase 3 confirmatory study (see below) within an agreed timetable.

The Applicant considered that this application for Folotyn 20 mg/ml solution for infusion (pralatrexate) for the "Treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy." meets both the scope and requirements of Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

The Applicant has provided a document justifying that the medicinal product falls within the scope of the conditional marketing authorisation Regulation (Article 2) and that the requirements for conditional marketing authorisation are fulfilled (Article 4), in particular:

• The risk-benefit balance of the product is positive

• It is likely that the Applicant will be able to provide comprehensive clinical data

• Unmet medical needs will be met

• The benefit to public health of the immediate availability of the product outweighs the risk inherent in the fact that additional data are still required

Initially, the Applicant proposed a study to be provided as a part of fulfilling the conditional approval, i.e. the ongoing Phase 3 multi-centre, randomised clinical trial (PDX-017) of sequential pralatrexate versus observation in patients with previously undiagnosed PTCL who have not progressed following initial treatment with CHOP-based chemotherapy.

During assessment, the Applicant proposed to perform as a specific obligation a randomised study with pralatrexate versus single-agent systemic treatment of physician's choice. The Applicant considered it unlikely that patients in the post-approval study will be those considered to be eligible for transplant in the second-line relapsed setting and suggested a choice of commercially available, single-agent chemotherapeutics and biologicals as comparator.

## New active Substance status

The Applicant requested the active substance pralatrexate contained in the above medicinal product to be considered as a new active substance in itself.

### *Protocol Assistance*

The Applicant received Protocol Assistance from the CHMP on 5 March 2008. The Protocol Assistance pertained to clinical aspects of the dossier, in particular the potential registration under Exceptional Circumstances of pralatrexate for the treatment of relapsed or refractory PTCL on the basis of a single open-label Phase 2 study. However, the CHMP did not endorse the proposal to base a registration file on a single uncontrolled trial and suggested that a randomised study of pralatrexate in PTCL would provide the most convincing evidence of efficacy and safety. A randomised, controlled, superiority trial design with physicians' choice as the comparator was suggested. The CHMP also considered that a control group reflecting clinical practice would enhance interpretability of results seen following pralatrexate administration. Furthermore, response rate was not considered an acceptable primary endpoint for a pivotal trial to support marketing authorisation in this condition. Given the high mortality rate expected in this population and the obvious relevance to the patient, OS was considered the preferred primary endpoint.

### *Licensing status*

Folotyn has been given a Marketing Authorisation in the United States on 24 September 2009.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Jens Ersbøll**

- The application was received by the EMA on 23 November 2010.
- The procedure started on 15 December 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 March 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 March 2011.
- During the meeting on 14 April 2011, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant. The final consolidated List of Questions was sent to the Applicant on 15 April 2011.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 21 July 2011.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 2 September 2011.
- During the CHMP meeting on 22 September 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the Applicant.
- The Applicant submitted the responses to the CHMP List of Outstanding Issues on 17 October 2011.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Outstanding Issues to all CHMP members on 1 November 2011.
- During the CHMP meeting on 16 November 2011, outstanding issues were addressed by the Applicant during an oral explanation before the CHMP and the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the Applicant.
- During a meeting of a SAG on 1 December 2011, experts were convened to address questions raised by the CHMP.
- The Applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 19 December 2011.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 4 January 2012.
- During the meeting on 19 January 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a conditional Marketing Authorisation to Folotyn.

### *1.3. Steps taken for the re-examination procedure*

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **Pierre Demolis**

- The Applicant submitted written notice to the EMA on 27 January 2012 to request a re-examination of Folotyn CHMP opinion of 19 January 2012.
- During its meeting on 16 February 2011, the CHMP appointed Ian Hudson as Rapporteur and Pierre Demolis as Co-Rapporteur.
- The Applicant submitted the detailed grounds for the re-examination on 14 March 2012 (Appendix 2 of Final Opinion). The re-examination procedure started on 15 March 2012.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 2 April 2012. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 2 April 2012.
- During a meeting of the SAG-Oncology on 10 April 2012, experts were convened to consider the grounds for re-examination
- During the CHMP meeting on 17 April 2012, the detailed grounds for re-examination were addressed by the Applicant during an oral explanation before the CHMP.
- During the meeting on 19 April 2012, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the conditional marketing authorisation.

# 2. Scientific discussion

### *2.1. Introduction*

## Problem statement

Peripheral T cell lymphoma (PTCL) is a very rare condition with an estimated prevalence rate of 0.8 per 10,000 in the European Union.

PTCL represents a heterogeneous group of non-Hodgkin's lymphomas that, with the exception of anaplastic large cell lymphoma (particularly the subtype positive for anaplastic lymphoma kinase), has a dismal prognosis. In patients characterized as high risk by the International Prognostic Index, 5-year survival has been reported to be as low as 6%. Several clinical studies have reported a median survival of less than 2 years for patients with T-cell neoplasms and 5-year survival rates of less than 30%.

Because of having an aggressive clinical course with poor outcomes, PTCL is typically treated with combination chemotherapy regimens like CHOP and its variants. The first-line response rates to CHOP chemotherapy have been reported to range between 50% and 70%. However, patients frequently relapse soon after responding to first-line treatments (Vose et al., 2008).

In the case of relapsed or refractory PTCL, there have been relatively few studies of potential therapeutic agents. Agents tested have included gemcitabine, deoxycoformycin, denileukin diftitox, alemtuzumab, and lenalidomide. Published reports are, however, difficult to interpret and generalise

as few patients were typically enrolled, with various compositions of different PTCL entities, and no randomised studies are presented.

## About the product

Folotyn solution for infusion 20 mg/ml contains pralatrexate, an antineoplastic folate analogue. Antifolates are anticancer agents used in the treatment of malignancies such as acute lymphoblastic leukaemia, lymphomas, and breast and lung cancer. Pralatrexate is a structural analogue of the widely used antifolate, methotrexate.

Pralatrexate inhibits folic acid metabolism by inhibiting dihydrofolate reductase (DHFR). It is an efficient permeant for reduced folate transporters, including reduced folate carrier 1 (RFC-1) and is an efficient substrate for polyglutamylation by the enzyme folylpolyglutamyl synthetase (FPGS), resulting in extensive internalisation and accumulation within tumour cells. Pralatrexate exerts antifolate activity via the inhibition of dihydrofolate reductase (DHFR), which leads to depletion of intracellular THF resulting in a disruption of DNA synthesis and subsequent tumour cell death.

*In vitro* studies in CCRF-CEM leukaemia cells have shown that pralatrexate is 14 times more efficiently transported into CCRF-CEM cells and 10 times more efficiently polyglutamated than methotrexate. These improvements in cellular pharmacokinetics are suggested to lead to improved cytotoxic activity of pralatrexate compared with methotrexate.

The proposed indication for pralatrexate is for the treatment of adult patients with peripheral T-cell lymphoma (PTCL) (nodal, other extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy. The recommended dose of Folotyn is 30 mg/m$^2$ administered as an intravenous (IV) infusion over 3-5 minutes, once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity.

Patients receiving Folotyn should take low-dose oral folic acid on a daily basis. Patients should also receive a vitamin $B_{12}$ intramuscular injection.

Doses may be omitted or reduced based on patient's tolerance. Full blood cell counts and severity of mucositis should be monitored weekly. In addition, serum chemistry tests including renal and hepatic function should be performed regularly.

## *2.2. Quality aspects*

### 2.2.1. Introduction

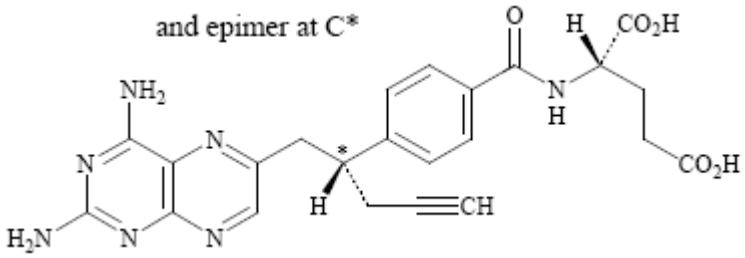
Folotyn is a solution for infusion containing pralatrexate as the active substance. The finished product is formulated as an aqueous solution containing sodium chloride and pH adjusters in addition to the active substance. Pralatrexate is an antineoplastic folate analogue with a chemical structure similar to methotrexate.

The excipients used in Folotyn are water (WFI), tonicity agent (sodium chloride) and pH adjusters (NaOH and HCl).

Folotyn 20 mg/ml solution for infusion is filled into glass vials with chlorobutyl rubber stoppers and crimp seals.

### 2.2.2. Active Substance

Pralatrexate is chemically designated as (2*S*)-2-[[4-[(1*RS*)-1-[(2,4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid and has the following structure




The molecule contains two asymmetric carbon centres (C10) and (C19). The C10 position exists in the *RS*-configuration (approx. 50:50 ratio) on the link between the two aryl groups. The C19 position is contained in the glutamic acid moiety and predominantly exists in the *S*-configuration.

Pralatrexate is an off-white to yellow crystalline material, soluble in aqueous solutions at pH 6.5 or higher and practically insoluble in chloroform, and ethanol. It predominantly exists as a single polymorph (form A).

## *Manufacture*

Full information on the active substance pralatrexate is provided in the dossier.

The active substance is manufactured by a four step synthesis by the two active substance manufacturers. The manufacturing process is described in detail and critical steps and controls discussed. Rationales are provided for the specifications for the three isolated intermediates and the origin and fate of impurities during the process.

## *Specification*

The pralatrexate active substance specification including parameters, analytical procedures and acceptance criteria is considered suitable for release of batches of active substance.

The specification includes tests for description, identification by Infrared and by High Performance Liquid Chromatography assay, water content, sulphated ash, heavy metals, clarity and colour of solution, related substances, C10-diastereomers, chiral purity, residual solvents by Gas Chromatography, microbiological content and bacterial endotoxins.

Impurities have been evaluated and found to be acceptable from the point of view of safety.

Satisfactorily justification for the chosen parameters and related limits in the active substance specification are presented in the dossier according to relevant guidelines (ICH Q6a and Q3A) and European Pharmacopoeia (Ph. Eur.) standards

The descriptions of the analytical methods are considered acceptable and their validations are performed in accordance with ICH standards and Ph. Eur. requirements.

Batch data from 31 batches are enclosed covering the different manufacturing sites which have been used during the development of the manufacturing process and testing in non-clinical and clinical studies. Results confirm batch to batch consistency and support uniformity of the quality of the active substance.

### *Stability*

Satisfactory stability data on three commercial batches of pralatrexate manufactured by one of the active substance manufacturers has been provided. Batches were stored in containers simulating the market packaging for 24 months according to ICH conditions at long-term (5°C) and 6 months at accelerated conditions (25°C/60%RH).

The parameters tested were appearance, water content, assay, related substances, chiral purity and $C_{10}$-diastereomers. As non routine tests bacterial endotoxins and microbial content tests are included in the stability testing plan.

Additionally, supportive stability data has been provided on three validation batches for each of the two active substance manufacturers. Three of the batches have been stored for 12 months at long-term condition (5°C) and 6 months at accelerated (25°C/60%RH) and the other three batches from the other active substance manufacturer for 3 months at both conditions and all of them in containers simulating those for commercial purposes.

The parameters tested were appearance, water content, assay and related substances. As non routine tests bacterial endotoxins and microbial content are included in the stability testing plan.

Forced degradation studies have also been performed demonstrating that the most pronounced degradation was seen at acidic condition.

The photo stability study was performed according to ICH Q1B and demonstrated that pralatrexate is sensitive to light.

The stability data provided support the recommended retest period at the proposed packaging and storage conditions.

## 2.2.3. Finished Medicinal Product

### *Pharmaceutical Development*

Pralatrexate is an antineoplastic folate analogue which consists of active substance contained in a non-pyrogenic, sterile, aqueous, isotonic, pH-adjusted solution.

The excipients have remained the same throughout development also in relation to quantities. All meet the corresponding requirement in the Ph. Eur. They have been selected to achieve an aqueous isotonic solution (280-300 mOsm) with a near neutral pH.

No specific studies have been performed concerning the compatibility between excipients and the active substance. Compatibility is considered self evident and was inferred from the product stability studies.

Compatibility of the active substance with other excipients not included in the formulation has not been assessed, since a simple saline solution was desired and achieved.

Aseptic filtration was selected as the sterilisation method as terminal sterilisation was not considered an alternative due to the heat sensitivity of pralatrexate. The manufacturing process has remained consistent throughout development with only minor changes in relation to the optimisation and in relation to process transfer. The manufacturing process consists of the compounding of bulk solution, filtration and filling of solution and finally capping and labelling. The changes that have been performed are detailed in the dossier.

The selection of the container closure system was based on being able to contain a sterile parenteral solution intended for intravenous injection, single use and protected from light. Standard packaging materials were chosen.

The compatibility of the product has been assessed with syringes and intravenous physiological sodium chloride solution. The results demonstrated compatibility of the finished medicinal product with the syringes as well as with 0.9% intravenous normal saline solution, the only intended diluent.

## *Adventitious agents*

All excipients are of non-animal origin except for calcium stearate which is used as a processing aid in the manufacture of the elastomeric closure of the packaging. It is certified by the manufacturer that the manufacturing process is in compliance with EMEA/410/01 Revision 2 Note for Guidance on Minimizing Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

## *Manufacture of the product*

Folotyn 20 mg/ml solution for infusion is manufactured using a conventional aseptic process for sterile aqueous solutions packaged in glass vials that cannot withstand terminal steam sterilisation.

The manufacturing process consists in compounding, filtration, filling into vials and inspection of vials.

The manufacturing formula, flow chart and description of the manufacturing process are presented.

The process has been validated for three batches manufactured to the commercial scale and with the commercial process. The validation of the manufacturing process has been well documented and satisfactory data provided.

## *Product specification*

Satisfactory specification has been presented for the finished product and includes tests for appearance, identification, pH, assay, related substances, volume in container, particulate matter, osmolality, sterility and bacterial endotoxins.

The proposed test procedures and acceptance criteria comply with the requirements of the Ph. Eur. and current guidelines. Analytical procedures are described and validated.

Batch analysis data are provided for a substantial amount of batches (clinical, site qualification batches, stability batches and process validation batches). Data batches confirm consistency and uniformity of the product indicating that the process is under control.

## *Stability of the product*

The conditions used in the stability studies are in accordance with the ICH stability guideline (25°C, 25 °C / 60% RH and 40 °C / 75% RH).

The results of the following tests were submitted: appearance, pH, assay, related substances, particulate matter, osmolality, C10-diastereomers, chiral purity, container closure integrity, particulate matter, sterility and bacterial endotoxins.

Analysis of the stability samples has been performed by applying the validated and stability indicating test methods.

Photostability testing confirms that the product is sensitive towards light.

Based on the stability results provided, the proposed shelf-life and storage conditions are acceptable.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The new active substance is an antineoplastic folate analogue with a chemical structure similar to methotrexate. Information on development, manufacture and control of the active substance and finished medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues.

## 2.2.6. Recommendation(s) for future quality development

Not applicable.

# *2.3. Non-clinical aspects*

## 2.3.1. Pharmacology

### *Primary pharmacodynamic studies*

*In vitro studies*

Studies performed showed that compared to methotrexate, pralatrexate is more effectively taken up by cancer cells through increased affinity for reduced folate transporters such as RFC-1 and more efficiently polyglutamylated by FPGS (Sirotnak et al., 1998). The increased cellular influx of pralatrexate and more effective polyglutamylation of pralatrexate by FPGS translate into more potent in vitro anti-cancer activity as compared to the cytotoxic activity of methotrexate and edatrexate (Sirotnak et al., 1998; Wang et al., 2003).

In a separate series of studies, Izbicka et al (Izbicka et al., 2009) confirmed the relative biochemical and cellular activities of pralatrexate that differentiate it from methotrexate and expanded the studies to further differentiate pralatrexate's profile from that of pemetrexed. Using a cell-free recombinant human DHFR system, the approximate 2-fold difference in DHFR inhibitory constant (Ki) between pralatrexate and methotrexate was confirmed (45 vs 26 nM, respectively). In addition, pralatrexate in a non-polyglutamylated form, was significantly more potent than pemetrexed at inhibiting recombinant human DHFR (Ki > 200 nM). Using the NCI-H460 human NSCLC cell line, it was further demonstrated that pralatrexate was more effectively internalized and polyglutamylated than either methotrexate or pemetrexed.

The increased cellular influx of pralatrexate via the RFC-1 transporter and more effective polyglutamylation of pralatrexate by FPGS suggest that pralatrexate may be a more effective antineoplastic agent than other folate analogs. Pralatrexate is significantly more potent than edatrexate or methotrexate in inhibiting in vitro cell growth of a number of human cancer cell lines. The half maximum growth inhibitory concentration (GI50) of these cells by pralatrexate are about 3-fold lower than those for edatrexate and at least more than 10-fold lower than those for methotrexate, despite that edatrexate and methotrexate are marginally more potent DHFR inhibitors.

Thus, the enhanced *in vitro* activity of pralatrexate appears to correlate well with its greater cellular uptake and intracellular retention as compared with edatrexate and methotrexate.

*In vitro* cytotoxicity studies in a panel of 15 human solid tumour cell lines showed that pralatrexate is more potent than methotrexate, with pralatrexate IC50's on average 9-fold lower compared with methotrexate (Serova et al., 2009). In addition these studies showed that sensitivity to pralatrexate correlated with higher FPGS messenger ribonucleic acid (mRNA) expression, suggesting that polyglutamylation of pralatrexate is important for its cytotoxic activity.

Pralatrexate was evaluated in the NCI cancer cell panel and showed growth inhibitory activity across a broad spectrum of tumour types. Fifty-three cancer lines from the NCI-60 cell panel were grown in cell culture and treated for 48 hours with different concentrations of pralatrexate (serial ½-log dilutions). At the end of the treatment period the growth of the cancer cells was determined and GI50's were calculated using NCI Developmental Therapeutics Program standard procedures. Of the 53 cancer cell lines tested, 36 cell lines (68%) were highly sensitive to the growth inhibitory effect of pralatrexate with GI50's < 0.1 µM. Pralatrexate activity of GI50 < 0.1 µM was observed across a variety of tumour types tested, with leukaemia (4 of 4 tested), colon (7 of 7 tested), and central nervous system (4 of 5 tested) showing the highest frequency of pralatrexate-sensitive cancer cell lines.

Pralatrexate was evaluated for growth inhibitory activity against human tumour cell lines representing head and neck cancer (HLaC), breast cancer (MDA-MB-231, MDA-MB-435), and NSCLC (A549, MV522). Growth inhibition was measured in the MTS cell proliferation assay after 3 hours of treatment followed by a 72-hour recovery. Under the experimental conditions, pralatrexate was most active in the MV522 NSCLC and MDA-MB-231 breast cell lines with half maximum inhibitory concentration (IC50) values of 12.8 nM (MV522) and 18.0 nM (MDA-MB-231). Cytotoxicity of pralatrexate was comparable in HLaC and MDA-MB-435 with IC50 values of 25.8 nM and 24.1 nM, respectively. The A549 lung adenocarcinoma line was slightly less sensitive to pralatrexate (IC50 = 65.1 nM). In a head-to-head comparison with conventional therapeutics, pralatrexate was more active than cisplatin in every line tested and superior to paclitaxel in the MDA-MB-231 breast line and both lung lines. Pralatrexate also demonstrated superior activity versus docetaxel in the MV522 lung cancer line.

Pralatrexate and methotrexate were evaluated in 5 human lymphoma cell lines: RL (transformed follicular lymphoma), HT, SKI-DLBCL-1 (diffuse large B-cell), Raji (Burkitt's), and Hs445 (Hodgkin's disease) (Wang et al., 2003). After 5 days of continuous *in vitro* exposure, pralatrexate demonstrated approximately 10-fold greater potency than methotrexate in all cell lines.

To investigate the anti-proliferative activity of pralatrexate alone and in combination with cytidine analogs, pralatrexate combinations with the cytidine analog gemcitabine were studied in a cytotoxicity assay against SKI-DLBCL-1 cells using the standard Trypan Blue Exclusion Assay (Toner et al., 2006). The data support the contention that combinations of a folate analog and a cytidine analog are better than either single agent alone, and that the schedule of the folate analog preceding the cytidine analog is important.

To better understand the potential link between the expression of certain genes involved in folic acid metabolism and sensitivity to pralatrexate, the gene expression level of a subset of genes was analyzed in 181 archived lung cancer patient samples that were grouped into 9 categories based on pathology reports, including a control group consisting of 29 normal tissue samples. Of 7 folate metabolism genes analyzed, 5 showed significant differential expression between 1 or more lung cancer groups and the reference normal lung samples.

Pralatrexate was found to be inactive against normal human hepatocytes. Marchi et al, further showed that pralatrexate was not cytotoxic against normal human peripheral blood mononuclear cells (PBMC's).

*In vivo studies*

The *in vivo* anti-tumour activity of pralatrexate was studied in mouse xenograft models (MX-1 mammary carcinoma, LX-1 lung carcinoma, and A549 squamous cell lung cancer). Studies with mammary carcinoma and lung carcinoma showed more complete regressions with pralatrexate than with methotrexate (Sirotnak et al., 1998).

Pralatrexate was compared with docetaxel, paclitaxel, and combinations of pralatrexate with these 2 agents in immune-compromised mice with LX-1 lung tumour cell xenografts. Pralatrexate as a single agent produced a significant reduction in tumour size that was superior to that observed with the other single agent treatments and comparable to that observed with combination therapies.

The schedule-dependent efficacy of pralatrexate was studied in 2 different human tumour xenograft models using 3 different schedules of administration. Pralatrexate was administered by intraperitoneal (IP) injection at its MTD, for each dose schedule, to mice engrafted with MX-1 (human breast) and LX-1 (human lung) tumours (6 mice per group). The greatest regression in the 2 different tumour types was obtained with the daily and biweekly schedules, compared with the weekly schedule, which was reproducible in 2 separate experiments. The results indicate some schedule dependence on the ability of pralatrexate to effect tumour growth. The schedule dependence had a greater effect than dose per se.

Comparison of pralatrexate to methotrexate, pemetrexed and docetaxel dosed at their respective MTD in 2 NSCLC cell tumour xenograft models showed an effective tumour growth inhibitory activity of pralatrexate compared with these reference agents.

Pralatrexate was compared with cisplatin and carboplatin and combinations with these 2 agents in the JMN human mesothelioma xenograft model (Khokhar et al., 2001). Pralatrexate as a single-agent was more potent than either cisplatin or carboplatin alone.

To further investigate the potential of combining pralatrexate with an EGFR inhibitor, pralatrexate was studied in combination with cetuximab in a human squamous cell carcinoma xenograft in athymic nu/nu mice. In this particular model pralatrexate alone showed no significant activity whereas cetuximab as a single agent showed good. The combination of pralatrexate plus cetuximab did not show improved activity over cetuximab as a single agent.

The in vivo effects of pralatrexate were compared with those of methotrexate in 3 established human NHL xenografts in non-obese, diabetic/severe combined immunodeficient (NOD/SCID) mice (Wang et al., 2003). Tumour-bearing animals were treated with saline (control) or the MTDs of methotrexate (40 mg/kg) or pralatrexate (60 mg/kg) via the IP route twice weekly for 2 weeks. Almost 90% of HT lymphomas treated with pralatrexate completely regressed, whereas those treated with methotrexate had only modest growth delays.

In 2 other xenograft models, treatment with pralatrexate resulted in complete regression rates of 56% (RL) and 30% (SKI-DLBCL-1). No regressions and only minor growth inhibition were noted with methotrexate therapy.

To investigate the anti-proliferative activity of pralatrexate alone and in combination with cytidine analogs, pralatrexate combinations with the cytidine analog gemcitabine were studied in the SKI-DLBCL-1 NHL xenograft model. In addition, the activity of the standard combination of methotrexate/ara-C was compared with that of pralatrexate/gemcitabine to determine if schedule dependency of this combination is important in the treatment of lymphoma (Toner et al., 2006). Cytotoxicity assays using the standard Trypan Blue Exclusion Assay showed that most combinations of pralatrexate and gemcitabine were superior to methotrexate and ara-C, with the best activity seen when pralatrexate was followed by gemcitabine. Based on these in vitro results, xenograft experiments

were conducted using one-quarter of the MTD of pralatrexate and gemcitabine (both 15 mg/kg). A similar dose reduction for methotrexate and ara-C was not performed given the lower activity in the in vitro growth inhibition assay. Treatment with pralatrexate alone showed better tumour growth inhibition than either methotrexate or ara-C alone or in combination. The combination of pralatrexate and gemcitabine dosed each at 25% of their MTD was markedly more efficacious than any methotrexate- and/or ara-C-treated group. Although fewer complete remissions were noted, a complete remission was only observed in those animals receiving pralatrexate followed by gemcitabine.

## *Secondary pharmacodynamic studies*

A study in the rat type-II collagen-induced arthritis model showed a similar efficacy of methotrexate and pralatrexate in inhibiting joint inflammation.

The potential for pralatrexate to bind to secondary targets (receptor screening assay) has not been evaluated.

## *Safety pharmacology programme*

Safety pharmacology studies performed with pralatrexate are listed below.

**Table 1** List of safety pharmacology studies

| Type of Study and Test System | Study Period | GLP Compliant | Study Number |
|---|---|---|---|
| Cardiac safety, isolated dog Purkinje fibers | 2003-2004 | Yes | PDX-T-04005-D |
| Cardiac safety, hERG | 2003-2005 | No | PDX-T-05018-H |
| Cardiovascular and respiratory safety, | 2006-2007 | Yes | PDX-T-07036-D |
| Neurobehavioral, Sprague-Dawley rats | 2006-2007 | Yes | PDX-T-07037-R |

GLP = Good Laboratory Practice, hERG = human ether-a-go-go related gene

The effect of pralatrexate on the hERG K+ current was studied in a hERG-transfected cell line (CHO-K1/hERG). At the concentrations of 0.8, 2, and 4 mg/ml, pralatrexate inhibited hERG K+ currents by 37, 54, and 54%, respectively. At 0.4 mg/ml, pralatrexate had no effect on hERG K+ currents. The reference compound, E-4031 inhibited hERG K+ currents by 98%.

A study was performed to assess the effect of pralatrexate on dog isolated Purkinje fiber action potential recorded using intracellular microelectrodes. Four Purkinje fibers were isolated from four dogs and perfused with vehicle followed by pralatrexate. Pralatrexate, at target concentrations of 0.4, 0.8, and 2.0 mg/ml (0.34, 0.67 and 1.66 mg/ml, according to the concentration analysis results) did not induce any statistically significant of biologically relevant (<15%) changes in RMP, OS, APA, $V_{max}$, $APD_{30}$, $APD_{60}$, or $APD_{90}$ at stimulation frequencies of 1.0 Hz or 0.5 Hz. The positive control agent (dl-sotalol) prolonged $APD_{60}$ and $APD_{90}$.

A cardiovascular and respiratory function safety assessment study in conscious, telemetry-instrumented, male and female beagle dogs (4/sex/group) showed no effects of pralatrexate dosed IV up to and including 0.7 mg/kg (the MTD) on respiratory function (respiratory rate, blood oxygen saturation, and end tidal CO2), blood pressure (systolic, diastolic, and mean arterial pressure), heart rate, body temperature, electrocardiographic parameters (heart rate, PR, QRS, RR and QT/QTc intervals), or mortality.

Electrocardiographic assessments were also performed in a 9-month IV toxicity study in Beagle dogs. Pralatrexate was given to male and female Beagle dogs by slow bolus IV injection at doses of 0.1, 0.3, and 0.7 mg/kg for 2 or 6 cycles (1 cycle consists of 6 weekly doses followed by 1 drug-free week). At interim study days 81-83 one female doses at 0.3 mg/kg had a slightly prolonged PR interval of 0.17 seconds (normal range is 0.06-0.14 seconds). This slight PR prolongation has no biological

significance. All other measurements (at predose, study days 81-83, end of study day 282 and after a 4-week recovery period day 309) were within normal limits.

CNS effects were studied in Sprague-Dawley rats. Rats were administered a single dose of 5, 10, or 25 mg/kg pralatrexate via IV bolus infusion. Parameters evaluated during the study included body weight, body temperature, clinical and cageside observations. In addition, rats were assigned for functional observational battery (8/sex/group) or locomotor activity (8/sex/group) evaluations at predose, 5 minutes post-dose, and 24 hours post-dose. Treatment with pralatrexate did not result in any mortality. There were no pralatrexate-related abnormal observations and the body weights were comparable to the control group. The quantitative and qualitative functional observational battery observations and the locomotor activity data were comparable to control group at all time points. The body temperature was also comparable at all measured time points.

### *Pharmacodynamic drug interactions*

Pralatrexate was used in combination with a number of marketed cancer therapeutics in various mouse xenograft models (see section on Primary pharmacodynamics).

## 2.3.2. Pharmacokinetics

Pralatrexate PK was investigated in rat and dog using the clinical product, schedule, and route of administration in single-dose PK and GLP-compliant repeat-dose TK studies. Tissue distribution and excretion of pralatrexate were studied in GLP-compliant mass balance studies in rats. Plasma protein binding and metabolism were studied using human biomaterials.

### *Methods of analysis*

Analytical methods have been developed and validated for the quantification of the 2 diastereomers, designated PDX-10a (S configuration) and PDX-10b (R configuration) in plasma and urine of rats, dogs, and humans, and in plasma for mice and. Validation assessed parameters of specificity, matrix effect, intrabatch and interbatch precision (relative standard deviation [%RSD]) and accuracy (relative error [%RE]), linearity, and recovery in each matrix. The lower limit of quantisation (LLOQ) for each diastereomer in all matrices is 0.5 ng/mL and the linear range is 0.5-1,000 ng/mL.

### *Absorption*

The PK of pralatrexate diastereomers PDX-10a and PDX-10b were characterized following a single IV dose of pralatrexate to male and female rats (12/sex/group). PK analysis of concentration data from plasma and urine samples obtained from these animals showed a biphasic disposition pattern with an initial, rapid decline followed by a more gradual, terminal decline. The volume of distribution at steady state indicated extensive tissue distribution. No significant differences in PK parameters were observed for the two diastereomers. Females exhibited approximately 2-fold higher clearance values.

A single-dose intravenous PK study in Beagle dogs (3/sex/group) showed in general the same pattern as the study in rats. There was no gender difference in dogs. PDX-10b had 2-fold higher clearance values compared with PDX-10a; however, this stereoselectivity diminished with increasing doses.

**Table 2** Summary of PK data

| Study ID | Species | Dose (mg/kg \ mg/m$^2$) | Cmax (ng/ml) | $AUC_{0-\infty}$ (ng/ml •min) | $T_{1/2\ term}$ (hr) |
|---|---|---|---|---|---|
| PDX-K-05010-R | Rat | 5 \ 30<br>10 \ 60<br>25 \ 150 | 4,225<br>9,298<br>27,275 | 100,807<br>203,341<br>597,323 | 4<br>3<br>18 |
| PDX-K-05009-D | Dog | 0.3 \ 6<br>1 \ 20<br>3 \ 60 | 458<br>1,858<br>4,833 | 31,690<br>102,177<br>247,271 | 6<br>6<br>15 |
| PDX-008 | Human | 0.81 \ 30 | 5,815 | 267,854 | 12 - 18 |

Individual pralatrexate diastereomers (ie, PDX-10a and PDX-10b) were analyzed.
$C_{max}$ and AUC∞ values are sums of values for PDX-10a and PDX-10b
$t_{1/2term}$ values are the average for the pralatrexate diastereomers in male and female.

The pralatrexate plasma exposure after single and repeat dose in rat and dog pivotal toxicity studies showed a biphasic disposition with an initial rapid decline followed by a more gradual terminal decline. The exposure was dose proportional without evidence of drug accumulation. No apparent gender difference was noted. $C_{max}$ values showed some degree of variability between species; however, due to the initial rapid decline in plasma concentrations, the variability in bolus infusion time (1-2 minutes in animals 3-5 minutes in man) and sampling time immediately following infusion may have contributed to these differences.

## *Distribution*

Tissue distribution of pralatrexate over time has not been studied; however, tissue distribution at 168 hours after a single IV $^{14}$C-pralatrexate dose (10 mg/kg) in a mass balance study in rats showed that the highest measurable content of radioactivity 168 hours post-dose was observed in the liver (0.33 vs. 0.24 µg pralatrexate equivalents/g) and kidneys (0.39 vs. 0.27 µg pralatrexate equivalents/g) for male vs. female rats, respectively.

The potential of pralatrexate to penetrate the blood-brain barrier was assessed in an *in situ* rat brain perfusion model. The dose-normalized brain uptake rate of pralatrexate was comparable to that of the low penetration controls, methotrexate and atenolol.

No studies using animal biomaterials were performed with respect to protein binding. The result of plasma protein binding studies with pralatrexate indicate moderately high (67-86%) human plasma protein binding. Pralatrexate did not partition into human red blood cells in an in vitro assay.

No placental transfer studies have been performed.

## *Metabolism*

Metabolism studies of pralatrexate have been performed by incubation with human hepatocytes and human liver microsomes. No significant metabolism was observed in these studies. In addition to the apparent lack of hepatic metabolism, no striking interspecies differences in PK parameters were observed, and therefore, no studies investigating interspecies metabolism differences were performed. No studies on *in vivo* metabolism have been performed in animals. A human mass balance study with $^{14}$C-pralatrexate is ongoing.

## *Excretion*

GLP-compliant mass balance studies in rats using $^{14}$C-pralatrexate showed that the primary route of excretion is faecal (44%-66%), followed by urine (21%-31%) and expired $CO_2$ (6.4%-10%). 70 to 92% of the radioactivity was excreted in the first 24 hours following administration.

Biliary excretion or enterohepatic circulation was not investigated.

### *Pharmacokinetic drug interactions*

In competitive binding studies, pralatrexate did not significantly interfere with human plasma protein binding of 6 reference drugs (phenytoin and warfarin [albumin site I], ceftriaxone [albumin site II], digoxin [albumin site III], disopyramide [α1-acid glycoprotein and albumin], and propranolol [albumin, α1-acid glycoprotein, and lipoproteins]), nor was pralatrexate displaced to a significant extent from human plasma proteins by 6 reference drugs (phenytoin and warfarin [albumin site I], ibuprofen [albumin site II], digoxin [albumin site III], propranolol [α1-acid glycoprotein, albumin, and lipoproteins], and disopyramide [α1-acid glycoprotein and albumin]).

No drug transporter studies were performed in animal model systems. Further, pralatrexate did not significantly inhibit or induce CYP450 enzymes or P-glycoproteins in two human model systems as assessed by bidirectional permeability determination.

### *Other pharmacokinetic studies*

No other pharmacokinetic studies were performed.

## 2.3.3. Toxicology

### *Single dose toxicity*

An exploratory IV dose-range finding study in Beagle dogs was performed to determine appropriate doses of pralatrexate for subsequent repeat-dose studies. The lack of a dedicated single-dose toxicity studies was justified in accordance with the current recommendations from EMA (CHMP/SWP/302413/08 and EMA/CHMP/SWP/81714/2010). Data from the dose-range finding study showed that all dogs developed bloody diarrhoea at day 3, and lethality of a single IV dose 3 mg/kg (60 mg/m$^2$).

### *Repeat dose toxicity*

Pralatrexate repeat-dose toxicity was evaluated in the rat and dog. Eight- and 14 weeks dose-range finding studies preceded the pivotal 28-week repeat-dose toxicology study in the rat and the pivotal 9-month study in the dog. Treatment included the clinical formulation, route, and schedule of administration. The pivotal rat and dog repeat-dose toxicology studies were GLP-compliant and included toxicokinetic evaluations. The repeat-dose toxicity studies with pralatrexate are summarised in the following table:

**Table 3**

| Study ID | Species/Sex/ Number/Group / Duration | Dose (mg/kg) Route | NOAEL (mg/kg) | Major findings |
|---|---|---|---|---|
| PDX-T-05013-R | Sprague Dawley rats<br><br>5/sex/group<br><br>8-week (two 4-week cycles consisting of 3 weekly doses followed by 1 dose-free week) | 0, 25, 50, 75<br>(0, 150, 300 or 450 mg/m$^2$)<br><br>IV slow bolus<br><br>Dosing days: 1, 8, | NA | Mortality: Males; 1/5 (control), 2/5 (50 mg/kg), and Females; 1/5 (25 mg/kg), 3/5 (50 mg/kg), and 4/5 (75 mg/kg).<br><br>Pralatrexate-related effects in males included diarrhoea, hunched posture, rough hair coat, and thin appearance at 50 mg/kg. In females, clinical signs of toxicity included thin appearance at 50 and 75 mg/kg, hunched posture and languidness at 25, 50, and 75 mg/kg, and rough hair coat and few |

| | | | | |
|---|---|---|---|---|
| | | 15, 29, 36 and 43. | | faeces at 75 mg/kg.<br><br>Changes in erythrocyte parameters were observed at doses ≥ 25 mg/kg.<br><br>There was no histopathology evaluation. |
| PDX-T-07039-R | Sprague Dawley rats<br><br>5/sex/group<br><br>`4 weeks (two 7-week cycles consisting of 6 weekly doses followed by 1 dose-free week) | 0, 5, 10, 25 (0, 30, 60 or 150 mg/m$^2$)<br><br>IV slow bolus<br><br>Dosing days: 1, 8, 15, 22, 29, 36, 50, 57, 64, 71, 78 and 85 | 25 (150 mg/m$^2$) | No adverse effects were noted in mortality, cageside observations, food consumption, clinical chemistry parameters, or gross pathology. A trend toward lower absolute body weight was noted in the 25 mg/kg females but there was no corresponding effect on food consumption. A significant decrease in testes weight was noted in the 25 mg/kg males. A significant increase in spleen-to-body weight ratio was noted in two of the five 25 mg/kg males. Changes in erythroid parameters consistent with minimal anaemia were observed at doses ≥ 5 mg/kg, but most erythroid parameters returned to normal after the 1-week dose free period, suggesting that the effect was transient and reversible with cessation of treatment.<br><br>There was no histopathology evaluation. |
| PDX-T-07034-R | Sprague Dawley rats<br><br>Interim group (SD 92)<br>10/sex/group<br><br>Main group (SD 190)<br>10/sex/group<br><br>Recovery group (vehicle and high dose group, SD 211)<br>5/sex/group<br><br>28 weeks (four 7-week cycles consisting of 6 weekly doses followed by 1 dose-free week) | 0, 5, 10, 25 (0, 30, 60 or 150 mg/m$^2$)<br><br>IV slow bolus<br><br>Dosing days: 1, 8, 15, 22, 29, 36, 50, 57, 64, 71, 78, 85, 99, 106, 113, 120, 127, 134, 148, 155, 162, 169, 176 and 183 | 5 (30 mg/m$^2$) | See text below the table |
| PDX-T-05015-D | Beagle dogs<br><br>2/sex/group<br><br>8 weeks (two 4-week cycles consisting of 3 weekly doses followed by 1 dose-free week) | 0, 0.3, 1, 3 (0, 6, 20 or 60 mg/m$^2$)<br><br>IV slow bolus<br><br>Dosing days: 1, 8, 15, 29, 36 and 43. | NA | Mortality: 1 male and 1 female in the 3 mg/kg group.<br><br>Pralatrexate caused multiple GI effects, including emesis and abnormal faeces at all doses and in both genders. In both genders these GI effects were associated with dehydration at doses ≥ 1 mg/kg and thin appearance at 3 mg/kg. Weight loss and/or lack of weight gain were apparent in all pralatrexate-treated animals. There were no effects on clinical pathology and pathology parameters.<br><br>There was no histopathology evaluation. |
| PDX-T-07035-D | Beagle dogs<br><br>Group 1-3: 2/sex/group<br>Group 4: 3/sex/group from SD 57 | 0, 0.1, 0.3, 1.0 (0, 2, 6 or 20 mg/m$^2$)<br><br>**Group 4: 1.0 → 0.7 mg/kg SD** | 0.3 (6 mg/m$^2$) | Mortality: 1 male and 2 females in the 1 mg/kg group.<br><br>Weekly administration of pralatrexate at 1 mg/kg caused severe toxicity resulting in early terminations. Although tolerated by the animals, a nominal dose of 0.7 mg/kg/week also resulted in |

| | | | | |
|---|---|---|---|---|
| | 14 weeks (two 7-week cycles consisting of 6 weekly doses followed by 1 dose-free week) | **22**<br><br>IV slow bolus<br>Dosing days: 1, 8, 15, 22, 29, 36, 50, 57, 64, 71, 78 and 85 | | signs of toxicity. Pralatrexate-related and dose proportional signs of toxicity at this dose included emesis, soft faeces, diarrhoea, and thin appearance. Pralatrexate-related decreases in body weight and food consumption were noted in doses of 1 mg/kg/week. Pralatrexate-related changes in clinical pathology parameters included an increase in absolute reticulocyte count and lowered electrolytes, which was secondary to various signs of gastrointestinal disturbance noted. Pralatrexate-related necropsy findings included reduction in thymic size and weight<br><br>There was no histopathology evaluation. |
| PDX-T-07054-D | Beagle dogs<br><br>Interim group (SD 87)<br>5/sex/group<br><br>main group (SD 283)<br>5/sex/group<br><br>recovery group (vehicle and high dose group, SD 309)<br>2/sex/group<br><br>9 months (six 7-week cycles consisting of 6 weekly doses followed by 1 dose-free week) | 0, 0.1, 0.3, 0.7<br>(0, 2, 6 or 14 mg/m$^2$)<br><br>**Group 4: Vitamin $B_{12}$+folic acid from week 4**<br><br>IV slow bolus | 0.1<br>(2 mg/m$^2$) | See text below the table |

A GLP-compliant 6-month study was performed in rats with the clinically relevant 7-week cycle (IV dose once weekly for 6 weeks followed by 1 dose-free week). Doses were 0, 5, 10, 25 mg/kg. No adverse clinical observations were noted. Three animals were euthanized moribund and three were found dead, but these events were not considered pralatrexate-related because they were also noted in controls and were associated with procedure injury and isolated incidence.

Mean body weight was lower in males and females dosed at 25 mg/kg. Erythroid parameters were affected in males and females at all pralatrexate doses after 2 and 4 cycles, most notably at 25 mg/kg and more pronounced in males. Parameters included dose-related decreases in RBC count, haemoglobin, and haematocrit, with dose-related increases in mean corpuscular volume, absolute reticulocyte count, RBC distribution widths, and mean corpuscular haemoglobin, and with erythroid morphology changes in males. All hematologic parameters were reversible during the 2-week recovery period. Higher spleen weights in male and females and lower testes weights at 25 mg/kg were pralatrexate related.

A GLP-compliant 9-month study was performed in dogs with the same 7-week cycle. Doses were 0.1, 0.3 and 0.7 mg/kg. Due to adverse clinical signs (including death and early termination, body weight losses, and poor appetite), all 0.7 mg/kg dogs were supplemented with vitamin B12 (0.5 mg/animal/week) and folic acid (5 mg/animal/day) beginning during study week 4. Treatment with pralatrexate at 0.7 mg/kg without vitamin B12 or folic acid supplementation resulted in mortality. 1 female was found dead on SD 19 and 1 male and 1 female were euthanized due to moribund condition on SD 11 and 19, respectively. An additional Group 4 male was euthanized moribund on SD 88. Animals administered pralatrexate at doses ≥0.3 mg/kg had lower food consumption, lower body weight changes and signs associated with GI distress. No abnormal ocular findings were noted

and there were no pralatrexate-related electrocardiographic changes. Lower RBC counts, haemoglobin concentration, haematocrit, absolute lymphocyte count, and absolute basophil counts were noted in all pralatrexate-treated groups, while slightly higher platelet counts were observed in male and female dogs administered 0.7 mg/kg. Changes in chemistry parameters were considered a result of individual animal variation or reduced food consumption. Pralatrexate-related findings seen at interim necropsy (SD 87) were generally limited to discoloration of the intestinal tract (small and large intestine, rectum) and reddened mesenteric lymph nodes in both genders and reddened injection sites in the females; findings were seen in all pralatrexate-dosed groups. At the terminal necropsy (SD 283), darkened and/or reddened duodenum, jejunum, ileum, cecum, colon, and/or rectum were observed in control animals as well as dogs administered pralatrexate. There were no pralatrexate-related macroscopic lesions at the recovery necropsy (SD 309). Microscopic lesions in dogs found dead or euthanized moribound prior to the vitamin B12/folic acid supplementation consisted of hypocellularity of the femoral and sternal bone marrow, thymic atrophy, acinar atrophy of the mandibular salivary gland, and necrosis in the intestinal tract. Findings at interim necropsy consisted of epithelial and crypt necrosis within the small intestine in dogs administered pralatrexate at ≥ 0.3 mg/kg. Findings at terminal necropsy consisted of villous fusion in the small intestine with infrequent dilation and necrosis of crypt epithelium in dogs administered pralatrexate at ≥0.3 mg/kg and thymic atrophy in 3/5 female dogs administered 0.7 mg/kg. There were no pralatrexate-related microscopic lesions after a 4 week recovery period.

## *Genotoxicity*

Pralatrexate was not mutagenic in standard *in vitro* and *in vivo* mutagenicity assays (Ames Test, CHO cell chromosome aberration assay, and mouse micronucleus assay). The results from these genotoxicity studies are further summarized in the table below.

**Table 4**

| **Type of test/study ID/GLP** | **Test system** | **Concentration range/ Metabolising system** | **Results** |
|---|---|---|---|
| Gene mutations in bacteria | *Salmonella* strains TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA | 5-5,000 µg/plate +/- S9 | **Negative.** No toxicity was observed. |
| Gene mutations in mammalian cells | CHO-cells | 0.125, 0.25, 0.5, 1.0 µg/mL -S9 0.25, 0.5, 1.0, 2.5 µg/mL+ S9 | **Negative.** Dose-dependent reduction of mitotic index but no inhibition of DNA synthesis at the evaluated doses. |
| Chromosomal aberrations *in vivo* | CD-1 Mouse, 5/sex/group micronuclei in bone marrow | 0.5, 1.0, 2.0, 3.0 mg/kg IP for three consecutive days | **Negative.** Reduction of PCE. Mean PDX-10a and PDX-10b plasma exposure was 374 ng/mL following 3 mg/kg IP. |

PCE: polychromatic erythrocytes

## *Carcinogenicity*

In accordance with ICH S9, no carcinogenicity studies have been performed with pralatrexate because it is intended to treat patients with serious, life threatening cancer.

## *Reproduction Toxicity*

*Fertility and early embryonic development*

No fertility and early embryonic development studies were performed with pralatrexate because it is intended to treat patients with serious, life threatening cancer.

*Embryo-foetal development*

Embryo-foetal development studies were conducted in rats and rabbits.

The effects of pralatrexate on maternal and/or foetal development were investigated after IV administration of pralatrexate to pregnant Sprague-Dawley rats from gestation day (GD) 7 through GD 20. Twenty five rats/group received pralatrexate at 0, 0.01, 0.03, or 0.06 mg/kg/day (0, 0.06, 0.18, and 0.36 mg/m$^2$/day, respectively). Pralatrexate had no effect on maternal, clinical or cage side observations, or gross pathology. At 0.06 mg/kg, pralatrexate caused significant decreases in maternal body weight, body weight changes, and food consumption. At 0.06 mg/kg pralatrexate, there was a significant increase in intra-uterine deaths and post-implantation loss and lower gravid uterine weight. At 0.06 mg/kg, pralatrexate treatment resulted in significantly lower mean litter weight, mean foetal weight, and mean male and female weights per litter, but there was no effect on foetal morphology (external, visceral, skeletal). Pralatrexate had no effect on these parameters at 0.01 or 0.03 mg/kg. The maternal NOEL and maternal reproductive NOEL were considered to be 0.03 mg/kg/day (0.18 mg/m$^2$/day).

The effects of pralatrexate on maternal and/or foetal development were investigated after IV administration of pralatrexate to pregnant New Zealand White rabbits from GD 8 through GD 21. Twenty rabbits/group received pralatrexate at 0, 0.03, 0.1, or 1 mg/kg/day (0, 0.36, 1.2, and 12 mg/m$^2$/day, respectively). Red vaginal discharge was noted during the latter gestational period (GD 18-26) and 3 animals in the 1 mg/kg/day group were euthanized after signs of aborted litters; no gross pathology findings were noted at necropsy. There were no significant differences in body weights. At 1 mg/kg, there was a significant increase in number of intra-uterine deaths and percent post-implantation loss compared to control, and mean gravid uterine weights and adjusted body weight change were lower compared to controls. Pralatrexate dosed at 0.03 or 0.1 mg/kg/day had no effect on these parameters. Treatment with pralatrexate had an adverse effect on foetal viability and mean litter weight at 1 mg/kg/day. There was no effect on foetal morphology (external, visceral, skeletal). The maternal NOEL and maternal reproductive NOEL were considered to be 0.1 mg/kg/day (1.2 mg/m$^2$/day).

*Prenatal and postnatal development, including maternal function*

No prenatal and postnatal development and maternal function studies were performed with pralatrexate because intended to treat patients with serious, life threatening cancer.

*Studies in which the offspring (juvenile animals) are dosed and/or further evaluated*

No studies in juvenile animals were performed with pralatrexate. The applied indication is for adult PTCL patients only.

## *Toxicokinetic data*

The repeat-dose toxicity studies in rats and dogs included blood sampling for toxicokinetic analysis. The analysis included determination of the individual diastereomers PDX-10a (S configuration) and

PDX-10b (R configuration). The plasma AUC values in the table below are given as the mean value observed for PDX-10a and PDX-10b. For comparison, human data from the phase 2 trial PDX-008 are shown as well. The values are the sums of the two diastereomers.

**Table 5**

| **Study** | **Daily Dose (mg/kg)** | **AUC (ng•min/ml)** | **Cmax (ng/ml)** |
|---|---|---|---|
| Rat<br>(Cycle 4/Dose 6) | 5<br>10<br>25 | 355,864<br>841,482<br>2,269,911 | 14,884<br>40,840<br>64,868 |
| Dog<br>(Cycle 6/Dose 6) | 0.1<br>0.3<br>0.7 | 17,859<br>44,240<br>80,369 | 125<br>316<br>649 |
| Human<br>(Cycle 2/Dose 6) | 0.81 | 211,555 | 4,963 |

## *Local Tolerance*

Perivenous toxicity of pralatrexate was studied in Sprague-Dawley rats. Five male and 5 female rats were dosed 40 mg/kg (240 mg/m$^2$) pralatrexate (2 ml/kg dosing volume) by bolus injection perivascular to the saphenous vein. Animals were observed for 8 days following injection. No systemic toxicities were observed during this observation period. Therefore, a single perivenous injection of pralatrexate at 40 mg/kg did not result in any local irritancy at the injection site in Sprague-Dawley rats.

Dermal tolerance of pralatrexate was studied in Sprague-Dawley rats. Five male and 5 female rats were dosed interscapular with 20 mg/kg (120 mg/m$^2$) pralatrexate (1 ml/kg dosing volume) by slow bolus injection. Animals were observed for 8 days following injection. No systemic toxicities were observed during this observation period. Minimal oedema and minimal to mild erythema were observed in both males and females from day 4 following administration of a single dose of pralatrexate. Therefore, intradermal administration of pralatrexate at 20 mg/kg produced minimal to mild irritancy in Sprague-Dawley rats.

## *Other toxicity studies*

### *Immunotoxicity*

Pralatrexate is a folate analogue having anti-inflammatory activity, and therefore pralatrexate may be immunosuppressive. Repeat-dose toxicity studies in dogs showed effects on parameters associated with the immune system, i.e. thymic atrophy and hematologic toxicities, including reduced absolute lymphocyte counts. No specific studies investigating pralatrexate immunotoxicity were performed.

### *Studies on impurities*

Three impurities are included in the drug substance specifications (4-OH-PDX, 10-CBM-PDX, Des-Glu-PDX). These specified impurities were qualified for safety by their exposure in toxicology and clinical studies.

The only degradation product observed in pralatrexate drug substance and drug product that significantly increased over time is 4-OH-PDX. Degradation of pralatrexate to 4-OH-PDX is both time- and temperature-dependent. 4-OH-PDX was found to be significantly less cytotoxic (IC50 ≥ 1.4 µM) against the NCI-H460 lung, and MDA-MB231, MDA-MB435, and SK-BR3 breast cancer cell lines than pralatrexate. The toxicity of 4-OH-PDX was evaluated in a six-week study where Beagle dogs

(4 dogs/sex/group) were treated IV once weekly. While renal toxicity, ataxia and lethargy were observed in males administered 30 mg/kg, 4-OH-PDX was found to be well-tolerated at doses up to 10 mg/kg (200 mg/m$^2$); mild transient emesis and salivation were the only observed effects at doses of 3 and 10 mg/kg. The NOAEL for 4-OH-PDX in these toxicology studies was 10 mg/kg.

Furthermore, a Multi-Computer Automated Structure Evaluation (MCASE) computational assessment of genetic toxicity potential of starting materials, process materials, intermediates, known and potential impurities, pralatrexate, and degradation products was carried out. 4-OH-PDX did not exhibit a consistent positive alert for genotoxic potential across the test battery and can thus be considered non-genotoxic. Of the structures tested, only the starting material IN0222 (2,4-diamino-6-chlormethylpteridine) exhibited a positive alert for genotoxic potential. A bacterial reverse mutation assay (Ames Test) confirmed the positive alert observed in the MCASE analysis. The manufacturing process controls the residual IN0222 to a level of 0.00013% in pralatrexate drug substance, which is equivalent to a daily dose of IN0222 of 0.0715 µg/day and is below the threshold of toxicological concern.

## 2.3.4. Ecotoxicity/environmental risk assessment

The log P value for pralatrexate is 0.025, which was determined experimentally by potentiometric titration in dual-phase n-octanol/water (0.15 M KCl) system. This is below the value of 4.5 indicated in the guideline as a trigger for further investigation of persistence, bioaccumulation and toxicity.

Folotyn is indicated for the treatment of adult patients with relapsed or refractory PTCL (nodal, extranodal and leukaemic/disseminated). Based on the incidence of this disease in the EU the maximum number of eligible patients would be 20,295. Based on a refinement of Fpen, the Applicant presented a number for $PEC_{surface\ water}$ which is below the trigger value for a phase II assessment.

**Table 6 Summary of main study results**

| | | | |
|---|---|---|---|
| **Substance (INN/Invented Name):** Pralatrexate/Folotyn | | | |
| **CAS-number (if available):** 146464-95-1 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | Draft OECD 122 guideline | Log P = 0.025 | No PBT Potential |
| ***Phase I*** | | | |
| **Calculation** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.00194 µg/L | µg/L | < 0.01 threshold |
| Other concerns (e.g. chemical class) | | | No |

## 2.3.5. Discussion on non-clinical aspects

Pralatrexate is a folate analogue which inhibits the enzyme dihydrofolate reductase (DHFR) with a Ki of 13.4 pM. DHFR is responsible for the reduction of folate to tetrahydrofolate, which is required for the synthesis and catabolism of several amino acids, formation of creatine and choline, synthesis of purines, methylation of RNAs, synthesis of deoxythymidine monophosphate (dTMP) and thus synthesis of DNA. DHFR inhibition results in disruption of DNA synthesis which causes necrosis or apoptosis of rapidly dividing cells such as some cancer cells and potentially normal cells of the gastric mucosa and

bone marrow. It was demonstrated in the human acute lymphoblastic leukaemia cell line CCRF-CEM, that pralatrexate is more efficiently transported into cancer cells than methotrexate. Moreover, pralatrexate is a more effective folylpolyglutamyl synthetase (FPGS) substrate than methotrexate (Sirotnak et al. 1998), which indicates that internalization and accumulation of polyglutamated pralatrexate within tumour cells is more favourable. The uptake of natural folates into the cell is known to involve several protein carriers, including the reduced folate carrier (RFC), membrane folate binding protein (FBP, also known as folate receptor) and most likely also additional transporter systems yet to be determined.

Currently, there are no non-clinical models for peripheral T-cell lymphoma but pralatrexate was found to have growth inhibitory activity in a broad range of cancer cell lines. Of the 56 cancer cell lines tested, 39 cell lines (70%) were highly sensitive to the growth inhibitory effect of pralatrexate with 50% growth inhibition concentrations (GI50) of < 0.1 µM. The highest frequency of pralatrexate-sensitivity was observed in cancer cell lines of leukaemia (4 of 4 tested), colon (7 of 7 tested), and CNS (5 of 6 tested). In comparative in vitro studies, pralatrexate consistently exhibited lower IC50 values than methotrexate in the tumour cell lines tested (acute lymphocytic leukaemia, breast carcinoma, and non-small cell lung carcinoma cell lines).

Racemic pralatrexate and the individual diastereomers PDX-10a and PDX-10b showed similar cytotoxic activity against the CWR22-RV1 human prostate cancer line.

Pralatrexate showed higher antitumor activity *in vitro* and *in vivo* in mouse xenograft models when compared to methotrexate. This appears to be due to an increased cellular uptake and a higher polyglutamation. Whether these findings will translate to a better antitumor activity in the clinical setting is not clear. The dose-limiting toxicity (gastrointestinal and haematological toxicity) is directly related to its pharmacology. It is not clear why the properties resulting in higher antitumor activity would not result in an equally stronger toxicity. The Applicant presented data showing minimal cytotoxicity with normal hepatocytes but these studies were not comparative, and the relevance of the cells studied is questionable. The Applicant also stated that there is no significant cytotoxicity to human PBMC, referring to an abstract where there were no data details and there was no comparison to methotrexate.

The stronger anti-tumour activity in the mouse xenograft models cannot be translated directly to predict stronger anti-tumour activity in humans. The xenograft model is poorly adapted to answer questions about therapeutic window. The anti-tumour activity is directed against human tumour cells, while toxicity is directed against the mouse tissue. It is clear that there are pronounced differences in the sensitivity to pralatrexate between mice and humans (no toxicity studies were performed in mice, but in the rat the exposure at the MTD was more than 10 times higher than at the MTD in patients). The determination of MTD in the mouse xenograft models is based on bodyweight increase which is of limited relevance for the human situation. The micronucleus genotoxicity study in mice (discussed further below) suggested that haematological toxicity may occur at doses magnitudes lower than those resulting in body weight loss.

It is concluded that non-clinical data have shown evidence of antitumor activity of pralatrexate and that there is activity at lower concentrations than with methotrexate. There are no data which would predict a stronger antitumor response in the clinical setting when the two compounds are given at the maximally tolerated dose.

The potential for pralatrexate to bind to secondary targets (receptor screening assay) has not been evaluated. Considering the indication and the serious adverse effects associated with pralatrexate treatment, this is acceptable.

The conducted safety pharmacology studies addressed cardiovascular, respiratory and central nervous system safety. The *in vitro* study on cardiovascular safety showed inhibition of hERG but this effect was observed only at concentrations substantially higher than clinical exposure. The *in vivo* study in dogs showed no cardiovascular effects. Since the dog is very sensitive to the toxicity of pralatrexate, this study was performed at an exposure much lower than the clinical exposure. Toxicokinetics data from repeat dose toxicity study at the same dose (0.7 mg/kg) showed a $C_{max}$ approximately three times lower than the clinical $C_{max}$ (1793 ng/ml vs. 4963 ng/ml). While there are no signals for cardiovascular effects from the nonclinical studies, the *in vivo* study provided only limited reassurance concerning cardiac safety, and clinical data are essential.

Pharmacokinetics studies were performed in rats and dogs. The data showed a similar pattern with an initial, rapid declined followed by a more gradual, terminal decline. The volume of distribution at steady state indicated extensive tissue distribution. No significant differences in PK parameters were observed for the two diasteroemers.

Tissue distribution of pralatrexate over time has not been studied. Tissue distribution at 168 hours after a single IV $^{14}$C-pralatrexate dose in a mass balance study in rats showed the highest measurable content in liver and kidney. The potential of pralatrexate to penetrate the blood-brain barrier was assessed in an in situ rat brain perfusion model. The uptake rate of pralatrexate was comparable to that of methotrexate. Binding to human plasma proteins was 67-86%.v Placental transfer and milk excretion was not investigated.

Metabolism studies have been performed by incubation with human hepatocytes and human liver microsomes. No significant metabolism was observed in these studies. No studies on *in vivo* metabolism have been performed in animals. A human mass balance study is ongoing. *In vitro* studies suggest limited metabolism of pralatrexate, and considering the indication and the toxicity of pralatrexate itself it is agreed that no animal *in vivo* metabolism studies are required.

In rats, the primary route of excretion was faecal (44-66%), followed by urine (21-31%) and expired $CO_2$ (6.4-10%). 70-92% of pralatrexate-related material was excreted in the first 24 hours following administration. In single-dose PK studies the renal excretion of the parent drug ranged from 3% to 20% in both rats and dogs. In ongoing clinical studies, the percentage of intact pralatrexate excreted in urine is 25-38% (range of the mean for PDX-10a and PDX-10b from studies PDX-007 and PDX-008). Biliary excretion or enterohepatic circulation was not investigated.

In competitive binding studies, pralatrexate did not significantly interfere with human plasma protein binding of 6 reference products, nor was pralatrexate displaced to a significant extent from human plasma proteins by 6 reference products. Further, pralatrexate did not significantly inhibit or induce CYP450 enzymes or P-glycoproteins.

Data from a dose-range finding study showed that a single IV dose 3 mg/kg (60 mg/m$^2$) was lethal to dogs. The dog is considered an appropriate non-clinical model for human anti-folate toxicity since dogs and humans have nearly identical serum folic acid and thymidine concentrations (Branda, 1981; Nottebrock and Then, 1977). However, the rat is relatively insensitive to anti-folates since the serum folate and thymidine levels are approximately 8.5 and 16-fold higher than in humans, respectively. The rabbit is reported to have a 7-fold higher serum folate level than in humans, while the thymidine concentration is 2.5-fold of the level in humans (Branda, 1981; Nottebrock and Then, 1977).

Toxicokinetic analysis showed that in rat the mean AUC at the NOAEL (5 mg/kg) was close to the clinical exposure and at the high dose (25 mg/kg) 10 times clinical exposure; in the dog, exposure at the highest dose (0.7 mg/kg) was only one third of the clinical exposure.

All adverse findings in the repeat-dose toxicity studies appear to be related to the pharmacology of pralatrexate and were primarily related to reversible gastrointestinal and haematological toxicities. The high sensitivity for pralatrexate of the dog results in exposure far below clinical exposure, while the rat appears to be much less sensitive than humans. Still, the toxicology data give sufficient reassurance that no other toxicity than the pharmacologically mediated toxicity is to be expected.

Pralatrexate was negative in a standard battery of genotoxicity tests. However, in the *in vitro* chromosomal aberration test, inhibition of mitosis resulted in that the test was performed at concentrations far below what is encountered *in vivo* in clinical use. In the mouse micronucleus study, an initial range-finding test was performed with doses of 5, 25, 100, 200 and 394 mg/kg IP. These doses were tolerated (based on body weight). Based on these results a micronucleus assay was performed with doses of 100, 200 and 394 mg/kg. However, with all doses the frequencies of polychromatic erythrocytes (PCE) were too low for evaluation, suggesting haematological toxicity. Following protocol amendment, new range-finding tests were performed and the final micronucleus assay was performed at the doses 0.5, 1, 2, and 3 mg/kg. While no toxicokinetics data were generated in mice, these doses are unlikely to result in exposures exceeding clinical exposure. No firm conclusions on the genotoxic potential of pralatrexate can be drawn from the studies on chromosomal aberrations *in vitro* and *in vivo*. The CHMP noted that other folate analogues were either shown to be negative in the *in vitro* chromosomal aberration test but positive in the mouse micronucleus assay or stated to be mutagenic *in vitro* and *in vivo*. Therefore, based on the pharmacology of pralatrexate as well as experience with other folate analogues an increased risk for genotoxicity from pralatrexate treatment cannot be excluded. This has been reflected in the proposed SmPC section 5.3.

No carcinogenicity studies have been performed with pralatrexate because it is intended to treat patients with serious, life threatening cancer.

In studies on embryo-foetal toxicity no significant maternal toxicity in rats and rabbits was recorded at the applied high-dose levels 0.06 and 1.0 mg/kg; however the high dose level of pralatrexate was embryo toxic in both species. Embryo toxicity was characterized by early resorptions, and post-implantation loss. Pralatrexate did not cause foetal malformations. The maternal/foetal no observed effect level (NOEL) was considered to be 0.03 mg/kg/day (0.18 mg/m$^2$/day) in rats and 0.1 mg/kg/day (1.2 mg/m$^2$/day) in rabbits. However, the studies on embryo-foetal toxicity were performed at much lower doses than used in the repeat-dose toxicity studies (maximum dose in rat embryo-foetal toxicity study: 0.6 mg/kg; lowest dose in rat repeat-dose toxicity study: 5 mg/kg). This is understandable since dosing in the embryo-foetal toxicity was daily, while the repeat-dose toxicity study was performed with once weekly dosing. However, this means that exposures in the embryo-foetal toxicity were below clinical exposure. No toxicokinetics were performed in the rat embryo-foetal toxicity study, but in a dose-range finding study, exposures at the high dose 2 mg/kg was $C_{max}$= 212 ng/ml and AUC= 277 ng•h/ml. These values are more than 10 times lower than clinical exposure. In the rabbit, toxicokinetics data from a dose range finding study showed exposures at 1 mg/kg (top dose in the pivotal study) to be $C_{max}$=2560 ng/ml and AUC=2410 ng•h/ml. These values are approximate ½ of the clinical exposure. There was no evidence for teratogenicity in any of the studies with pralatrexate. However, for other folate analogues a teratogenic potential has been reported. The CHMP considered it unlikely that pralatrexate does not share this property and it is likely that pralatrexate is embryotoxic in humans. The risk for teratogenicity is likely to be greater with a less intense dosing at higher doses (such as the once weekly dosing), which is likely to result in less embryolethality.

In accordance with ICH S9, pralatrexate has not been studied with respect to effects on fertility and pre- and post-natal development. Due to the genotoxic properties of the related folate analogues, a similar warning has been included in the proposed SmPC section 4.6 to inform that women of

childbearing potential must use effective contraception during treatment with pralatrexate. Pralatrexate may have genetically damaging effects. Sexually mature males are advised not father a child during treatment and up to 6 months thereafter. Barrier contraceptive measures or abstinence are recommended. Furthermore, Folotyn is not recommended during pregnancy and in women of childbearing potential not using contraception and it is contraindicated during breast-feeding.

Perivenous injection of pralatrexate at 40 mg/kg did not result in any local irritancy at the injection site in rats. Intradermal administration at 20 mg/kg produced minimal to mild irritancy in rats.

Nonclinical data on phototoxicity were not submitted. Pralatrexate absorbs light at 338 nm (hydrochloric acid conditions) and 372 nm (ammonium acetate conditions). Based on the calculated molar extension coefficients (11939 and 8118 $L.mol^{-1}.cm^{-1}$), it cannot be excluded that a phototoxic potential is present. However, a rat distribution study indicated that the distribution of pralatrexate to the skin and eyes is negligible (≤ 0.52% of the administered dose). Moreover, the Applicant pointed out that it is not feasible to conduct a 3T3-NRU phototoxicity test due to the cytotoxic properties of pralatrexate. In the mammalian cell genotoxicity assay the mitotic index was reduced from around 100% at 0.008 µg/ml to 16% at 2.5 µg/ml hence the cytotoxic properties of pralatrexate does not appear to preclude phototoxicity testing. Safety data are available from 689 patients treated with pralatrexate. Only two of the reported dermatological adverse events were considered related to treatment. Moreover, the most commonly reported ocular adverse events were reduced visual acuity and eye pain; adverse events which do not appear to be caused by phototoxicity. Hence, based on the clinical safety data, pralatrexate appears to have a low ocular and dermatological phototoxic potential. Considering the relative stability of pralatrexate, the limited and transient distribution of pralatrexate to skin and eyes in rats, the rarity and poor prognosis of the relapsed/refractory PTCL population, the rare clinical occurrence of mild AEs of phototoxicity and/or photosensitivity related to pralatrexate treatment, and the pharmacovigilance measures put in place around dermatologic reactions, non-clinical phototoxicity studies with pralatrexate are not warranted.

Pralatrexate is a folate analogue having anti-inflammatory activity, and therefore pralatrexate may be immunosuppressive. Repeat-dose toxicity studies in dogs showed effects on parameters associated with the immune system, i.e. thymic atrophy and hematologic toxicities, including reduced absolute lymphocyte counts. No specific studies investigating pralatrexate immunotoxicity were performed. A warning in SmPC section 4.4 reflects that pralatrexate can suppress bone marrow function.

In studies on impurities the starting material IN0222 (2,4-diamino-6-chlormethylpteridine) was mutagenic in the bacterial reverse mutation assay.The manufacturing process controls the residual starting material to such a level in pralatrexate drug substance, which is equivalent to a daily dose of IN0222 below the threshold of toxicological concern. Hence, the mutagenic property of IN0222 does not cause a safety concern.

Pralatrexate $PEC_{surface\ water}$ value is below the action limit of 0.01µg/L and is not a PBT substance as log $K_{ow}$ does not exceed 4.5.

## 2.3.6. Conclusion on non-clinical aspects

The non-clinical data submitted are considered adequate to support the marketing authorisation application. There are no outstanding non-clinical issues.

## *2.4. Clinical aspects*

## 2.4.1. Introduction

### *GCP*

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. Furthermore, the Applicant stated that the two main studies included in the PTCL clinical study programme of pralatrexate, PDX-02-078 and PDX-008, were conducted according to the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki.

**Table 7 - Tabular overview of clinical studies**

| Study ID | Design | Primary Objective | Study population | | | | Primary Endpoint |
|---|---|---|---|---|---|---|---|
| | | | Entered/ treated | Gender M/F | Median age | Diagnosis | |
| PDX-97-006 | Phase I, Non-randomised, open-label | Establish weekly i.v. dosage | 35/33 | 15/18 | 57 yrs (35-77) | NSCLC | |
| PDX-99-053 | Phase II, Non-randomised, open-label | Determine efficacy in 1st/2nd line | 39/39 | 13/26 | 57 yrs (40-71) | Advanced NSCLC | Response rate |
| PDX-99-083 | Phase I, Non-randomised, open-label | Dosage and safety in combination with a taxane | 51/48 | 27/21 | 61.5 yrs (37-78) | Advanced cancers | |
| PDX-01-014 | Phase I, Non-randomised, open-label | Establish bi-weekly dose, safety, activity; given with probenicid | 17/17 | 8/9 | 57 yrs (33-80) | Advanced solid tumours | |
| PDX-01-076 | Phase II, Non-randomised, open-label | Determine efficacy of Pralatrexate as 1st line therapy | 17/16 | 13/3 | 71. yrs (49-86) | Unresectable pleural mesothelioma | Response rate |
| PDX-02-078 | Phase I/II, Non-randomised, open-label | Determine efficacy + weekly dosage with vit. B12 and folic acid | 72/72 | 44/28 | 56.5 yrs (20-80) | Relapsed or refractory NHL or Hodgkin lymphoma | |
| PDX-008 | Phase II, Non-randomised, open-label | Determine efficacy of Pralatrexate with B12 and folic acid supplementation | 115/111 | 76/35 | 59 yrs (21-85) | Relapsed or refractory PTCL | Response rate |
| PDX-009 | Phase I/IIa, Non-randomised, open-label | Determine dose, safety and PK of Pralatrexate given with Gemcitabin | Ongoing 62 treated | | | Relapsed or refractory lymphoprol. Malignancies | |
| PDX-010 | Phase II, Non-randomised, open-label | Determine optimal dose with vitamin B12 and folic acid | 48 treated at data cut-off | | | Relapsed or refractory CTCL | |

## 2.4.2. Pharmacokinetics

The pharmacokinetics of pralatrexate in plasma and urine was primarily evaluated in two Phase 1 studies (PDX 99-083 and PDX-007) and in the pivotal Phase 2 study (PDX-008). In these studies, the individual R- and S-diasteromers at carbon 10 were analysed.

### *Absorption*

Not applicable as Folotyn is an aqueous solution for IV administration that contains standard pharmaceutical excipients.

### *Distribution*

In study PDX-008, the mean Vdss values (CV%) were 105 L (75%) and 37 L (53%) for PDX-10a and PDX-10b, respectively.

*In vitro* studies indicated moderately high plasma protein binding of pralatrexate in human plasma, about 67% as determined by equilibrium dialysis and about 86% as determined by ultracentrifugation, and that the major binding protein is albumin. Pralatrexate was found not to partition into red blood cells to any significant degree. No displacement interactions were seen with highly protein bound reference compounds, which is expected given that pralatrexate is only moderately bound to plasma proteins and is suggested to be a low hepatic-extraction ratio substance.

Based on a study in MDR1-MDCK cells, pralatrexate appeared to be a low-permeability compound that is not a substrate for Pgp.

*In vitro* studies have demonstrated that pralatrexate is a substrate to the uptake transporters OATP1B1 and OATP1B3, and to the efflux transporters BCRP, MRP2 and MRP3.

### *Elimination*

Pralatrexate demonstrated a multiphasic decline in plasma concentrations, with a slow terminal phase that is suggested not to substantially contribute to the total exposure or total clearance. The decline of both diastereomers was similar; however, PDX-10b plasma concentrations were about 50-100% higher than the PDX-10a concentrations at most time points. The data suggested that both pralatrexate diastereomers have relatively low clearance values, moderate volumes of distribution and relatively long terminal half-lives. PDX-10b had lower values for total clearance ($CL_{tot}$) and Vdss, while the terminal half-lives were relatively similar for the two diastereomers. After a 30 mg/m$^2$ dose, the mean $CL_{tot}$ was 417 and 191 ml/min for PDX-10a and PDX-10b, respectively. The mean terminal $t_{1/2}$ was 18 and 12 hours for PDX-10a and PDX-10b, respectively.

Both pralatrexate diastereomers were excreted unchanged in urine with mean $f_e$ values of 31% and 38% for PDX-10a and PDX-10b, respectively. Assuming a $f_u$ of ~0.33, the degree of renal clearance indicates that both diastereomers undergo net renal tubular secretion, i.e. via active transport.

The results of the different *in vitro* metabolism studies all indicated negligible phase I as well as phase II metabolism of pralatrexate. No metabolites have been structurally identified. It is considered unlikely that hepatic metabolism is an important route of elimination for pralatrexate. As there is no mass-balance data yet, extra-hepatic tissue metabolism cannot be completely ruled out. The related compound, methotrexate is, however, reported not to be significantly metabolised, either by hepatic or extra-hepatic mechanisms, but to be primarily excreted unchanged.

Overall, renal excretion of unchanged substance appeared to account for approximately one third of the total clearance of pralatrexate. The major part of the elimination, on average more than 60%, is therefore expected to be via non-renal routes. As there was no significant hepatic metabolism of pralatrexate, the non-renal elimination might be via biliary excretion of unchanged substance and/or extra-hepatic tissue metabolism. There is not yet any human mass-balance data, so the mechanisms for non-renal clearance, or their relative importance, cannot be evaluated. However, as both renal tubular secretion and, highly likely, biliary excretion of unchanged parent compound are important for the elimination of pralatrexate, renal and hepatic uptake and efflux transporters are expected to be involved to a significant degree. Based on *in vitro* transport studies, the Applicant suggested that the major elimination pathway for pralatrexate may be OATP1B1-mediated sinusoidal hepatocellular uptake and subsequent MRP2/BCRP-mediated canalicular efflux of pralatrexate, leading to biliary/faecal excretion.

A human mass-balance study is ongoing, but enrolment into the study has been put on hold while a more stable $^{14}$C-pralatrexate is being developed.

Due to the low degree of hepatic metabolism, genetic polymorphism in hepatic metabolising enzymes is not an issue. On the other hand, pralatrexate is substrate to transport proteins that are polymorphically expressed.

For example, the reduced folate carrier protein (RFC-1), responsible for uptake of folates into cells, is polymorphically expressed, which may lead to variation in pharmacodynamic response as well as, possibly, in renal elimination. However, currently available data do not allow for a recommendation of pre-treatment genotyping. The Applicant suggests that as that there are many important components in the pathway, changes in one component may be counteracted by changes in another pathway. For example, the effects of reduced expression of the reduced folate carrier (RFC-1) can be counteracted by increased expression of folylpolyglutamyl synthetase (FPGS) or reduced expression of dihydrofolate reductase (DHFR).

Hepatic transporters might potentially be involved in the development of pralatrexate-induced hepatotoxicity, although there is yet no data to support this assumption. As a speculative example, MRP2 is a transporter that transports bilirubin out of the hepatocyte and into the bile. In subjects with Dubin–Johnson syndrome (Rotor syndrome) MRP2 is defect or lacking. In these patients, MRP3, which transports certain compounds out of the hepatocyte into the blood, is upregulated and thereby compensates for the lack of MRP2. Inhibition of MRP3 by pralatrexate in these patients might possibly lead to accumulation of bilirubin in the hepatocytes.

### *Dose proportionality and time dependencies*

There was no obvious non-linearity in pralatrexate pharmacokinetics over the studied dose range, 30 mg/m$^2$ to 325 mg/m$^2$, although there was a large variability in the data. The pharmacokinetics of pralatrexate did not change significantly over multiple treatment cycles and no relevant accumulation of pralatrexate was observed at once weekly administration.

Pralatrexate pharmacokinetics display high inter-individual variability, with coefficients of variation for pharmacokinetic parameters often exceeding 50%. The variability seemed to be somewhat smaller for the PDX-10b than for the PDX-10a diastereomer. Normalisation of $CL_{tot}$ or $V_dss$ to body weight (BW) or body surface area (BSA) did not improve the population variability.

## *Special populations*

- **Impaired renal function**

There was no specific study of pralatrexate in patients with renal impairment. In the non-compartmental co-variate analysis including e.g. age, gender, bodyweight (BW), BSA, CLcrea and serum creatinine, only age and CLcrea were statistically significant covariates for pralatrexate CLtot. These co-variates accounted for only approximately 10% of the variability in CLtot for PDX-10a and PDX-10b, respectively, and the Applicant considered that a dose reduction is not necessary within the range of CLcrea and age included in the study.

Data in renal impairment is currently very limited, but a specific study is ongoing. Pharmacokinetic data from other studies including patients with mild-moderate impairment (creatinine clearance 53-130 ml/min), indicated that total clearance would be approximately 20% lower in a subject with creatinine clearance of 30 ml/min compared with a subject with creatinine clearance of 80 ml/min or above. At severe renal impairment, the non-renal elimination might also be affected, e.g. due to inhibition of hepatic transporters by urinary toxins, and a disproportionally larger effect on total clearance than that predicted from data on CLcrea > 30 ml/min might possibly be expected.

- **Impaired hepatic function**

There was no specific study in patients with hepatic impairment. In the non-compartmental co-variate analysis, the laboratory markers Albumin, Bilirubin and Hb were not statistically significant co-variates for pralatrexate clearance. The range of these co-variates was 2.7-4.5 g/dl for albumin, 0.2-1.6 mg/dl for bilirubin and 9.0-15.5 g/dl for Hb. There was no assessment of the hepatic function markers (AST, ALT and TBIL) in the population PK analysis.

Although non-renal mechanisms accounts for the major part of pralatrexate clearance, the lack of a specific study in hepatic impairment is currently acceptable, given that such a study would need to be performed in the target patient population, and recruitment would therefore likely be difficult. As biliary excretion is likely an important route of elimination for pralatrexate, and hepatic impairment therefore might be expected to lead to increased exposure, caution is advised in patients with hepatic impairment. A contraindication was not considered appropriate given the proposed indication. Data are currently not sufficient for evaluation of whether patients with pre-existing hepatic impairment have a higher risk of developing hepatotoxicity from pralatrexate treatment (see safety assessment).

- **Gender**

The integrated non-compartmental pharmacokinetic analysis (n=54) included 52% female and 48% male patients. There was no correlation between gender and pralatrexate clearance in this analysis.

The population pharmacokinetic analysis (n=154) included 61% males and 39% females and the estimated effect on pralatrexate clearance was small (15% lower clearance in women).

- **Race**

The integrated non-compartmental pharmacokinetic analysis (n=54) included 82% White, 15% Black, and 2% Asian patients. One patient (2 %) was of unknown ethnicity.

Covariate analysis did not reveal race as a significant covariate, however, data are not sufficient to draw any conclusions on potential ethnical differences.

- **Weight**

The patients included in the integrated non-compartmental pharmacokinetic analysis (n=54) had a weight range of 43 to 127 kg (mean 77 kg). Their creatinine clearance ranged from 53 to 130 ml/min (mean 89 ml/min). The population pharmacokinetic analysis (n=154) included patients up to 85 years.

Weight or BSA were not statistically significant co-variates for pralatrexate clearance in the non-compartmental analysis.

This analysis does therefore not support dosing based on BSA. Available data might indicate that BSA-based dosing to some extent will add to the overall variability, with higher exposure in larger patients and lower exposure in smaller patients. Differences in BSA would, however, only explain a part of the total pharmacokinetic variability. Potential overdosing will be handled by monitoring of side effects followed by dose reductions/interruptions. In addition, the Applicant presented data demonstrating no or only a weak relationship between BSA and effect of pralatrexate on different haematological parameters, which is considered to reassure that BSA-based dosing will not lead to significant underexposure in low-weight patients. There is, however, no or only limited data for BSA extremes.

- **Elderly**

The patients included in the integrated non-compartmental pharmacokinetic analysis (n=54) were within the age range 24-77 years (mean 60 years). The covariate analysis revealed age as a statistically significant covariate for pralatrexate clearance. However, this accounted for only approximately 10% of the observed population variability and the effect was relatively small and is suggested to reflect the decline in renal function with age.

The population PK analysis did not allow for an evaluation of the effect of age.

- **Children**

There was no data in children.

## *Pharmacokinetic interaction studies*

### *Effects of pralatrexate on concomitant medications*

*In vitro* studies demonstrated no relevant inhibition by pralatrexate of CYP1A2, CYP2A6, CYP2B6 CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.

The concentrations in the *in vitro* induction studies were a bit too low to completely rule out an induction potential of pralatrexate, however, clinically relevant induction is not expected at intermittent, once weekly administration.

*In vitro*, pralatrexate was a potent inhibitor of MRP3. The clinical importance of this inhibition is unclear. The Applicant proposed warnings against concomitant administration of the known MRP3 substrates etoposide, tenoposide and methotrexate. MRP3 transports certain substances from the hepatocyte into the blood. Theoretically, inhibition of MRP3 might lead to accumulation of potentially toxic substances in the hepatocyte.

Pralatrexate did not inhibit Pgp, BCRP, OTC2, OAT1 or OAT3 *in vitro*, and was only a weak inhibitor of OATP1B1 and OATP1B3.

### *Effects of concomitant medications on pralatrexate*

As pralatrexate is not subject to hepatic metabolism, clinically relevant effects of CYP inhibitors or inducers on pralatrexate pharmacokinetics are not expected.

At combination of pralatrexate with probenecid, tolerability was decreased and the AUC of pralatrexate increased, likely due to inhibition of renal tubular secretion and presumably also by inhibition of cellular efflux.

The Applicant also proposed warnings against concomitant administration of substances that affect glomerular filtration or renal secretion. As there is no such interaction data for pralatrexate, the Applicant based the proposal on warnings given for the previously approved methotrexate, pemetrexed and raltitrexed, which all have an even higher degree of renal clearance than pralatrexate.

Pralatrexate is a substrate to BCRP, OATP1B1, MRP2, MRP3 and OATP1B3, with highest affinity for OATP1B3. The Applicant suggested that the risk for a relevant effect on pralatrexate pharmacokinetics by an inhibitor of one of these transporters may be low as pralatrexate is a substrate for a number of different transporters. However, as the transporters have different functions and are part of a chain of event (e.g. uptake-efflux) it is not evident that inhibition of one transporter may be compensated by another transporter. Nevertheless, it is agreed that current knowledge is not sufficient to include specific warnings regarding transport inhibition, except for the warnings against probenecid and substances that are known to affect renal secretion.

### *Pharmacokinetics using human biomaterials*

Not applicable.

## 2.4.3. Pharmacodynamics

### *Mechanism of action*

Pralatrexate is a new anti-neoplastic folate analogue that *in vitro* was shown to be more efficiently transported into the cells and more efficiently polyglutamated than methotrexate.

Pralatrexate has high affinity for the reduced folate carrier 1 protein and is an efficient substrate for polyglutamation by the enzyme folylpolyglutamyl synthetase, resulting in extensive internalization and accumulation within tumour cells. Pralatrexate exerts antifolate activity via the inhibition of the enzyme dihydrofolate reductase (DHFR) in the folic acid metabolic pathway. Folate undergoes reduction to dihydrofolate, which in turn is then reduced to tetrahydrofolate (THF) by the action of DHFR. THF is required for the synthesis and catabolism of several amino acids, formation of creatine and choline, synthesis of purines, methylation of RNA, and synthesis of deoxythymidine monophosphate and thus synthesis of DNA. The inhibition of the metabolic pathways thus provides the basis for the cytotoxic activity of antifolate agents such as pralatrexate.

### *Primary and Secondary pharmacology*

No specific studies on primary pharmacology in humans were performed in addition to the *in vitro* PD studies discussed in section 2.3.2.

Cardiovascular safety assessment in in-vitro studies showed that pralatrexate does not inhibit the human ether-a-go-go-related gene (hERG) or affect dog Purkinje fiber action potential at concentrations well above the clinically observed Cmax. A QTc assessment was completed in a sub-group of 14 evaluable NSCLC patients in PDX-007. Patients were treated with pralatrexate doses of 190 or 230 mg/m$^2$ administered IV over 3 - 5 minutes or over 60 minutes. 12-lead electrocardiograms (ECGs) were performed at screening, at baseline (just prior to pralatrexate injection), at the end of infusion, and 1, 3 and 6 hours post-infusion in conjunction with pralatrexate plasma PK collections. Pralatrexate demonstrated only a minimal impact on cardiac repolarisation with no patient exhibiting a

QTc interval > 500 msec. There was no correlation observed between either maximum or mean QTc changes post-injection with pralatrexate exposures (Cmax or AUC∞). The mean Cmax and AUC∞ values observed in patients dosed at 190 mg/m$^2$ were approximately 5-fold higher than the mean values observed in PDX-008; these findings suggest that pralatrexate is unlikely to markedly delay cardiac repolarisation in PTCL patients treated with pralatrexate doses ≤ 30 mg/m$^2$.

## 2.4.4. Discussion on clinical pharmacology

The pharmacokinetic profile in plasma and urine of the two pralatrexate diastereomers is considered sufficiently studied in the target population, at the proposed clinical dose of 30 mg/m$^2$.

Protein binding, distribution to blood cells, permeability over Pgp-expressing cells, substrate specificity/inhibition potential for certain transport proteins and hepatic metabolism has been thoroughly investigated *in vitro*. No hepatic metabolism was observed. As it has not yet been possible to finalise the mass-balance study due to instability of the radiolabel, there is still some uncertainty regarding the non-renal metabolism pathways, which account for about 2/3 of the total clearance. Based on *in vitro* transport studies, the Applicant suggests that the major elimination pathway for pralatrexate may be OATP1B1-mediated sinusoidal hepatocellular uptake and subsequent MRP2/BCRP-mediated canalicular efflux of pralatrexate, leading to biliary/faecal excretion.

There is no specific data in patients with organ impairment. A study in renally impaired patients is planned. Some patients with mild to moderate renal impairment (CLcrea > 50 ml/min) were included in the pharmacokinetic studies, but for severe renal impairment and for hepatic impairment, recommendations will presently need to be based on theoretical considerations.

*In vitro* inhibition studies demonstrated no potential or pralatrexate to inhibit CYP450 metabolising enzymes. Pralatrexate was, however, a potent inhibitor of the efflux transporter MRP3. The clinical relevance of such inhibition is currently unclear.

Probenecid decreased clearance as well as tolerability of pralatrexate, likely by effecting renal secretion and possibly tissue distribution. Pralatrexate may interact also with other substances that are actively secreted or known to inhibit active renal secretion.

## 2.4.5. Conclusions on clinical pharmacology

At present, the *in vivo* data on pralatrexate pharmacokinetics are considered sufficient. The data from the ongoing mass-balance study and renal impairment study should be submitted when available.

Also the provided *in vitro* data on metabolism, transport proteins and CYP inhibition are considered sufficient, although the clinical implications of the transporter data are yet largely unknown.

*In vitro* studies in leukaemia cells have shown that pralatrexate is more efficiently transported into the cells and more efficiently polyglutamated than methotrexate. These improvements in cellular pharmacokinetics are suggested to lead to improved cytotoxic activity of pralatrexate compared with methotrexate. Whether toxicity is similarly affected is unknown.

# *2.5. Clinical efficacy*

## 2.5.1. Dose response study

No formal dose-response studies were reported. See Supportive Studies for a description of phase I-II studies.

## 2.5.2. Main study

**PDX-008:** A Multi-center, Phase 2, Open-label Study of (RS)-10-Propargyl-10-Deazaaminopterin (Pralatrexate) with Vitamin B12 and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma.

### *Methods*

### Study Participants

*Inclusion criteria, selected*

1. Patient recruited into the study had histologically/cytologically confirmed PTCL, using the Revised European American Lymphoma (REAL) WHO disease classification:
   - T/NK-cell leukaemia/lymphoma
   - Adult T-cell lymphoma/leukaemia (human T-cell leukaemia virus [HTLV] 1+)
   - Angioimmunoblastic T-cell lymphoma
   - Blastic NK lymphoma (with skin, lymph node, or visceral involvement)
   - Anaplastic large cell lymphoma (ALCL), primary systemic type
   - PTCL – unspecified
   - T/NK-cell lymphoma – nasal
   - Enteropathy-type intestinal lymphoma
   - Hepatosplenic T-cell lymphoma
   - Extranodal peripheral T/NK-cell lymphoma – unspecified
   - Subcutaneous panniculitis T-cell lymphoma
   - Transformed mycosis fungoides
2. Patient had documented PD after at least 1 prior treatment. Patients may not have received an experimental drug or biologic as their only prior therapy. Patient must have had clear PD after the last treatment received. Patient had at least 1 biopsy from initial diagnosis or in the relapsed setting to confirm the diagnosis of PTCL.
3. ECOG performance status ≤ 2.
4. At least 18 years of age.
5. Adequate haematological, hepatic, and renal function as defined by: absolute neutrophil count (ANC) ≥ 1000/µL, platelet count ≥ 100,000/µL (at both screening and within 3 days prior to dosing on cycle 1, day 1), total bilirubin ≤ 1.5 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN), (AST/ALT < 5 × ULN if documented hepatic involvement with lymphoma), creatinine ≤ 1.5 mg/dL (if the patient's creatinine was > 1.5 mg/dL, then the calculated creatinine clearance must have been ≥ 50 mL/minute).

*Exclusion criteria, selected*

1. Patient had:
   - Precursor T/NK neoplasms, with the exception of blastic NK lymphoma

- T-cell prolymphocytic leukaemia (T-PLL)
- T-cell large granular lymphocytic leukaemia
- Mycosis fungoides, other than transformed mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ disorders: ALCL and lymphomatoid papulosis

2. Congestive heart failure Class III/IV according to the NYHA Guidelines.
3. Uncontrolled hypertension.
4. Human immunodeficiency virus (HIV)-positive diagnosis and was receiving combination anti-retroviral therapy.
5. Patient had, or had history of, brain metastases or central nervous system (CNS) disease.
6. Patient had undergone an allogeneic SCT.
7. Patient had relapsed less than 75 days from time of an autologous SCT.
8. Receipt of any conventional chemotherapy or radiation therapy (RT) within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study treatment or planned use during the course of the study.
9. Receipt of corticosteroids within 7 days of study treatment, unless patient had been taking a continuous dose of no more than 10 mg/day of prednisone for at least 1 month.
10. Previous exposure to pralatrexate.

## Treatments

*Pralatrexate administration*

One cycle of pralatrexate therapy was 7 weeks in duration and consisted of 6 weekly doses of pralatrexate IV push over 3-5 minutes, followed by 1 week of rest. The dose of pralatrexate was 30 mg/$m^2$/week.

Dose reduction to 20 mg/$m^2$ due to toxicity was allowed per protocol-defined criteria for haematological toxicities, mucosal inflammation, and other treatment-related non-haematological toxicities. No further dose reductions were allowed. If the patient developed an AE indicating intolerance of this lower dose of 20 mg/$m^2$/week, the patient was to be discontinued from study treatment. Re-escalation of the pralatrexate dose once a dose reduction occurred was not allowed.

*Vitamin administration*

Vitamin supplementation began after a patient's blood has been collected for MMA and Hcy analysis at screening based on the following:

- If the patient's MMA level was > 200 nmol/L and/or Hcy was > 10 µmol/L at screening, vitamin supplementation was initiated at least 10 days prior to pralatrexate administration on cycle 1, dose 1.
- If, however, MMA and Hcy results were within normal range, pralatrexate dosing could be started immediately (it was not necessary to wait 10 days).

Vitamin supplementation consisted of vitamin B12 1 mg intramuscular (IM) every (q) 8-10 weeks, and folic acid 1.0-1.25 mg, orally (po) every day (qd). Once pralatrexate was permanently discontinued,

vitamin supplementation continued at least 1 month after the last pralatrexate dose, or longer at the discretion of the investigator.

*Therapies not permitted*

While on treatment with pralatrexate, steroids were not allowed for prophylaxis or treatment. Any form of additional therapy for T-cell lymphoma was not permitted during treatment with pralatrexate, including radiation therapy, other cytotoxic agents, biologic, or immune response modifiers.

*Duration of therapy*

Patients were treated with pralatrexate (6 weeks of treatment followed by 1 week of rest) for up to 24 months or until at least 1 of several pre-determined study treatment discontinuation criteria were met. Criteria for study treatment discontinuation were:

- Development of PD
- Initiation of radiotherapy or systemic chemo/biologic therapy for T-cell lymphoma
- Development of an AE indicating intolerance of the lowest study dose allowed (20 mg/$m^2$/week)
- Omission of 3 sequential doses of pralatrexate due to a treatment-related AE
- Development of an AE, intercurrent illness, condition, or procedural complication
- that may interfere with the patient's participation
- Withdrawal of consent
- Death of patient
- Investigator decision
- Sponsor decision
- Treatment with pralatrexate for 24 months

## Objectives

The primary objective was to determine the efficacy of pralatrexate with concurrent vitamin B12 and folic acid supplementation when administered to patients with relapsed or refractory PTCL.

Secondary objectives were to determine the safety of pralatrexate with concurrent vitamin B12 and folic acid supplementation when administered to patients with relapsed or refractory PTCL as well as to determine the PK profile of pralatrexate when administered with vitamin B12 and folic acid supplementation.

## Outcomes/endpoints

The primary efficacy endpoint in PDX-008 was response rate defined as the number of responders (CR + CRu + PR) divided by the number of evaluable patients.

The Secondary efficacy variables were:

- Duration of response; defined as the number of days between the date of first tumour response assessment of objective response (including CR, CRu, and PR) to the time of the first tumour response assessment of PD or death due to any cause

- PFS; number of days from study day 1 to the date of PD per central radiology review or death, regardless of cause
- OS; number of days from study day 1 to death

Exploratory analyses included:

- Evaluation of the correlation between response rate and survival.
- A retrospective analysis comparing the investigators' assessment of response rate and PFS with the same endpoints for the immediate prior therapy for patients entered into the study.
- Exploration of the effect of pralatrexate on progressive resistance to consecutive prior treatments.

*Response assessment*

Response was assessed on the basis of clinical, radiological, and pathological criteria. Response was assessed by independent central review according to IWC and by the treating investigator. Central review assessors were blinded to the response assessments by the treating investigator. The primary analysis was based on response assessed by central review.

As the IWC (Cheson et al., 1999) did not address incorporation of cutaneous disease into the assessment of response, the charter used by the independent central review established rules for incorporation of the cutaneous disease into response assessments. Positron-emission tomography (PET) scans were also collected throughout the study at the baseline and response assessment visits for the purpose of an exploratory analysis.

The following procedures/tests were performed for evaluation of response:

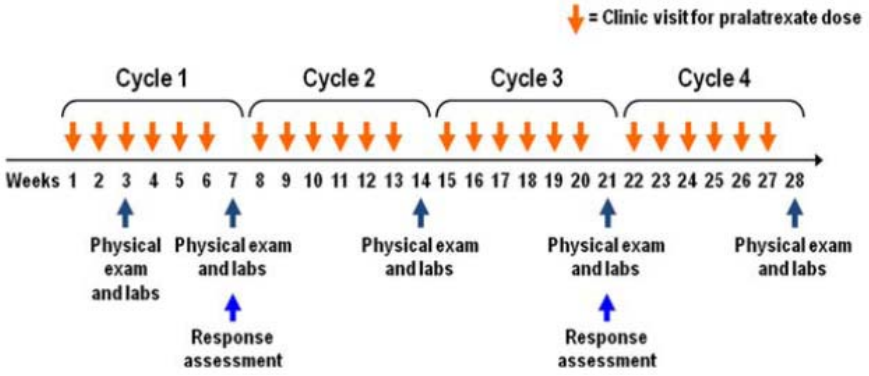
1. Radiographic imaging (using same imaging technique as screening):
   - CT of chest, neck, abdomen, and pelvis
   - Other imaging techniques documenting disease site(s) other than chest, neck, abdomen, or pelvis, if applicable.
   - Exploratory: Whole body PET (Note: PET imaging was not necessary if PD according to the IWC documented by clinical examination, CT or other imaging technique)
2. Physical examination to assess liver, spleen, lymph nodes, and skin (included medical photography with ruler measurements for documentation of any skin lesions).
3. LDH level determination.
4. If the patient's screening bone marrow biopsy/aspirate results were positive or indeterminate and the patient had a confirmed CR, a repeat bone marrow biopsy and aspirate assessment was to be performed. Prior to Amendment 4 (04 Oct 2006) of the protocol, if a patient's screening bone marrow biopsy/aspirate results were positive or indeterminate and the patient had a confirmed CR by imaging, a repeat bone marrow biopsy and aspirate assessment by flow cytometry were required per the protocol. Effective with Amendment 4, the bone marrow flow cytometry assessment was no longer required. If bone marrow aspirate flow cytometry was performed, results were to be sent to the central pathology reviewer. Once a patient's bone marrow was negative for lymphoma, the bone marrow biopsy was only repeated when clinically indicated unless it was the patient's only site of disease.
5. A tumour biopsy could be performed if needed to confirm a response evaluation.

6. If peripheral blood flow cytometry was performed, results were to be sent to the central pathology reviewer.

*On-study assessments*

Evaluation of response was to be performed within 7 days prior to the projected first dose of the second cycle and then within 7 days prior to the projected first dose of every even numbered subsequent cycle (i.e. prior to cycles 4, 6, 8, etc), see overview below.

**Figure 1**




*Post-treatment follow-up*

All patients who received at least 1 dose of pralatrexate were to attend routine follow-up visits every 3 months (± 2 weeks) after the safety follow-up visit (to occur 35 ± 5 days after the last dose of pralatrexate) until PD was determined or subsequent treatment for T-cell lymphoma was initiated. The frequency of response assessments for those patients who sustained a CR for at least 1 year was based on the institution's standard of care and was no longer required every 3 months. Once PD was documented or subsequent treatment for T-cell lymphoma was initiated, routine follow-up visits were no longer required. Patients were followed for survival and subsequent treatment for T-cell lymphoma every 6 months for a total duration of 2 years after the first dose of pralatrexate.

## Sample size

A 2-stage Simon design was employed for this study. A minimum of 100 patients were to be recruited based on a null hypothesis of a true response rate of 15% and an alternative hypothesis of a true response rate of 27%. Given response rates p0 and p1 of 15% and 27% respectively and error probabilities, α and 1-β, of 2.2% and 84.3% at least 4 out of 35 patients had to experience a response in Stage 1 for the trial to proceed to Stage 2. In Stage 2, 65 additional patients were to be enrolled where at least 23 out of the total 100 patients had to show response in order to exclude 15% with a 95% confidence interval for the response rate. Since the above properties are not explicitly stated in the Simon paper, they were derived using equation (1) under the "Optimal Two-Stage Designs" section of the Simon reference.

The levels of response rates p0 and p1 were chosen based on the assumption that a response rate of 20% was considered a good indicator of activity with any new treatment in the patient population comprised in the current protocol.

## Randomisation

Not applicable

## Blinding (masking)

Not applicable

## Statistical methods

Analyses of primary and secondary efficacy endpoints were based on all evaluable patients. A patient was considered evaluable if he/she received at least 1 dose of pralatrexate and had the diagnosis of eligible PTCL histopathological subtype confirmed by central pathology review. The presentation of safety endpoints were based on all enrolled patients who received at least 1 dose of pralatrexate.

Response rate was estimated using response data received from central review with a 95% confidence interval calculated using the binomial density function. Response rate based on investigators' assessments were also to be reported.

Duration of response was measured from the first day of documented response to disease progression or death. Patients receiving subsequent therapy (including transplant) before documentation of PD were censored. In addition to duration of response, duration of treatment for responding patients was to be presented.

PFS and OS were estimated using the Kaplan-Meier product-limit estimator.

Patients who were alive without a disease response assessment of PD were censored at the last disease assessment date or the date of first dose, whichever was later. Date of progression was not to be imputed for patients with missing tumour assessment(s) during treatment before an assessment of PD. These patients were considered as having PD on the date of the actual assessment of PD or they were censored at the date of their last assessment (at which there was no progression) or study day 1, whichever occurred later. Patients who withdraw consent to participate in the study prior to progression were censored at the date of their last disease assessment (or study day 1, whichever was later). Patients who withdraw from treatment prior to progression without withdrawing consent were followed for disease status and survival whenever possible. These patients were censored at their last tumour assessment or initiation of subsequent anti-cancer therapy, whichever came first, if they had not progressed by that time. Patients who did not have response assessments after baseline were censored at study day 1.

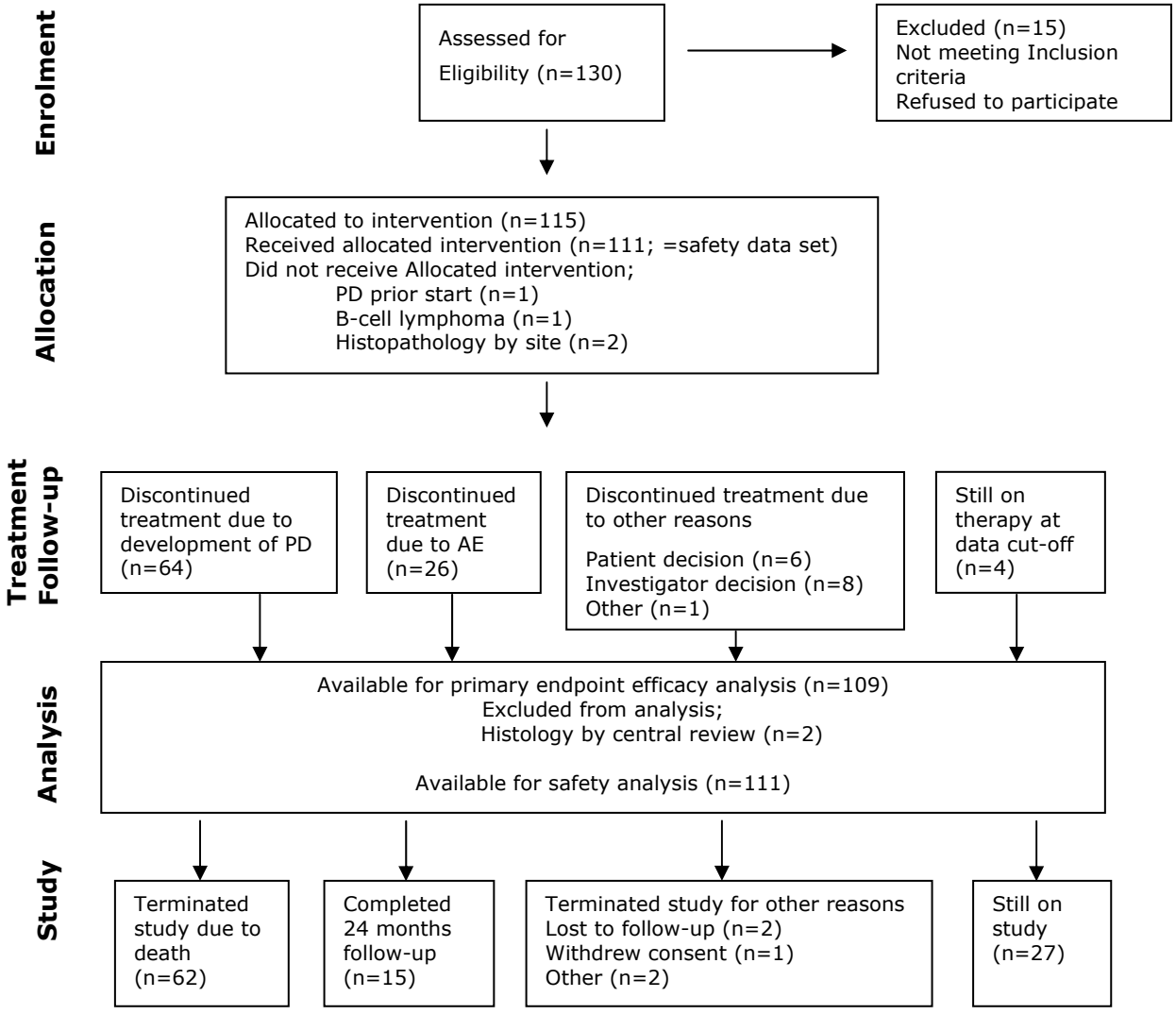
Patients who had not died (no record of death) or were lost to follow-up were censored at the date of last contact. Patients who withdraw consent to participate in the study, including consent to be followed, were censored on the date of withdrawal. Patients who withdraw from treatment without withdrawing consent were to be followed for survival status.

Additional efficacy analyses not described in the Statistical Analysis Plan were performed regarding the relationship between response and survival. Two main approaches were employed; a Cox model with a time-dependent covariate indicating each patient's responder status over time and a method referred to as "the landmark method". In the latter a time-point (landmark) was chosen post enrolment and all patients who were alive at that time-point were categorized as either responders or non-responders and responder status was included as a binary covariate in a Cox model.

In addition, in order to explore a hypothesis of progressive resistance with the objective to establish clinical benefit, retrospective analyses were performed where patients' response rates and PFS to prior therapies were analysed using patients as their own control.

## *Results*

## Participant flow




## Recruitment

Patients were enrolled between 24 August 2006 and 14 April 2008 across 25 study centres (out of 35 activated); 15 centres enrolled 80 patients in US, 8 centres enrolled 26 patients in Europe, and 2 centres enrolled 9 patients in Canada. The database cut-off was performed on 17 August 2009.

The DMC reviewed data tables on 21 September 2007 for the first 35 treated patients. The threshold for response rate for Stage 1 of the trial (at least 4 out of 35 patients responding) had been exceeded and the DMC recommended that the trial should continue as planned.

## Conduct of the study

Six amendments were made to the initial study protocol. Only one of these amendments, amendment 6, was made after the first patient inclusion. This amendment was made to allow patients to continue treatment with pralatrexate beyond 24 months after their initial dose if they were

experiencing clinical benefit per the investigator's judgment. In amendment 5 amongst other changes the eligibility criterion regarding platelets was increased from 50,000/µL to 100,000/µL.

Two different protocol deviations occurred: Receipt of a prohibited concomitant medication per the protocol (no=6, all due to corticosteroid therapy), and failure to adhere to protocol-specified dose modification rules (no=17).

## Baseline data

The majority of patients were male, white and ≥65 years old. The median age was 59 years. A male predominance has been described in PTCL.

**Table 8 Patient demographics**

| Parameter | Value | Efficacy Analysis Set (N = 109) |
|---|---|---|
| Gender n (%) | Male | 74 (68) |
| | Female | 35 (32) |
| Race n (%) | White | 79 (72) |
| | Black | 13 (12) |
| | Asian | 6 (6) |
| | Hispanic | 9 (8) |
| | Other | 1 (< 1) |
| | Unknown | 1 (< 1) |
| Age (years) n (%) | < 65 | 70 (64) |
| | ≥ 65 | 39 (36) |
| | Median | 59.0 |
| | Mean | 57.9 |
| | Std Dev | 14 |
| | Min - Max | 21 - 85 |
| | N Missing | 0 |

PTCL-unspecified was the most common entity enrolled, representing more than half of the patients, followed by ALCL, primary systemic type.

**Table 9 Histopathology per central review; efficacy analysis set**

| | (N=109) n | (%) |
|---|---|---|
| PTCL-unspecified | 59 | (54) |
| Anaplastic large cell lymphoma, primary systemic type | 17 | (16) |
| Angioimmunoblastic T-cell lymphoma | 13 | (12) |
| Transformed mycosis fungoides | 12 | (11) |
| Blastic NK lymphoma (with skin, lymph node, or visceral involvement) | 4 | (4) |
| T/NK-cell lymphoma-nasal | 2 | (2) |
| Extranodal peripheral T/NK-cell lymphoma unspecified | 1 | (<1) |
| Adult T-cell leukemia/lymphoma (HTLV 1+) | 1 | (<1) |

Median number of prior systemic regimens was 3, with almost 1/3 of patients having received 4 or more regimens. Twenty-four percent of patients had not responded (CR/PR) to any previous therapy and 64% of patients did not respond to the most recent prior therapy. Thus, a heavily pre-treated population with a high fraction of resistant patients was recruited to the study.

**Table 10 Disease characteristics; efficacy analysis set**

| | | (N=109) n (%) |
|---|---|---|
| Months Since Initial Diagnosis | Median | 15.4 |
| | Mean | 30.3 |
| | Std Dev | 43.1 |
| | Min - Max | 0.8 - 322.3 |
| | N Missing | 0 |
| Days Since Most Recent Progression | Median | 32 |
| | Mean | 58 |
| | Std Dev | 169 |
| | Min - Max | 2 - 1736 |
| | N Missing | 3 |
| Number of Prior Regimens n (%) | 1 | 18 (17) |
| | 2 | 26 (24) |
| | 3 | 23 (21) |
| | 4 | 16 (15) |
| | >=5 | 26 (24) |
| | Median | 3.0 |
| | Min - Max | 1 - 12 |
| Number of Prior Systemic Regimens n (%) | 1 | 23 (21) |
| | 2 | 29 (27) |
| | 3 | 23 (21) |
| | 4 | 14 (13) |
| | >=5 | 20 (18) |
| | Median | 3.0 |
| | Min - Max | 1 - 11 |
| Best Response to Any Prior Regimen | CR | 48 (44) |
| | PR | 35 (32) |
| | SD | 9 (8) |
| | PD | 12 (11) |
| | NA | 5 (5) |
| Response to Most Recent Prior Regimen | CR | 20 (18) |
| | PR | 20 (18) |
| | SD | 14 (13) |
| | PD | 43 (39) |
| | NA | 12 (11) |
| Baseline ECOG PS | 0 | 42 (39) |
| | 1 | 49 (45) |
| | 2 | 18 (17) |
| Baseline Cutaneous Involvement per Central Review [1] | Yes | 35 (32) |
| | No | 74 (68) |

Seventy-eight patients (70%) had previously received CHOP, which was the most common prior therapy. Twenty-five patients received CHOP as the most recent prior therapy, 10 of these without evidence of response. Eighteen patients had undergone ABMT before study entry, whereof 9 as the most recent therapy; 4 of these with no evidence of response.

**Table 11 Prior therapy for peripheral T-cell lymphoma**

| Prior Therapy for PTCL | Safety Analysis Set (N = 111) n (%) |
|---|---|
| Local Therapy | |
| Radiation therapy | 25 (23) |
| Photopheresis | 10 (9) |
| Topical nitrogen mustard | 4 (4) |
| Systemic Therapy | |
| CHOP | 78 (70) |
| Platinum-containing multi-agent chemotherapy | 45 (41) |
| Non platinum-containing multi-agent chemotherapy | 43 (39) |
| Single-agent chemotherapy | 36 (32) |
| Autologous stem cell transplant | 18 (16) |
| Bexarotene | 15 (14) |
| Other | 13 (12) |
| Steroids alone | 8 (7) |
| HyperCVAD | 8 (7) |
| Denileukin diftitox | 7 (6) |
| Systemic investigational agents | 7 (6) |

**Table 12 Most recent prior therapy for peripheral T-cell lymphoma**

| Most Recent Prior Therapy for PTCL | Safety Analysis Set (N = 111) n (%) |
|---|---|
| Local Therapy | |
| Radiation therapy | 6 (5) |
| Topical nitrogen mustard | 1 (< 1) |
| Systemic Therapy | |
| CHOP | 25 (23) |
| Non platinum-containing multi-agent chemotherapy | 21 (19) |
| Single-agent chemotherapy | 20 (18) |
| Platinum-containing multi-agent chemotherapy | 20 (18) |
| Autologous stem cell transplant | 9 (8) |
| Bexarotene | 8 (7) |
| Denileukin diftitox | 2 (2) |
| HyperCVAD | 2 (2) |
| Other | 2 (2) |
| Systemic investigational agents | 2 (2) |
| Steroids alone | 1 (< 1) |

**Table 13 Most recent prior therapy – with no evidence of response**

| | Safety Analysis Set - No Evidence of Response (N=70) n (%) |
|---|---|
| Local Therapy | |
| Radiation Therapy | 4 (6) |
| Topical nitrogen mustard | 1 (1) |
| Systemic Therapy | |
| Single agent chemotherapy | 17 (24) |
| Platinum-containing multi-agent chemotherapy | 13 (19) |
| Non platinum-containing multi-agent chemotherapy | 11 (16) |
| CHOP | 10 (14) |
| Bexarotene | 7 (10) |
| Autologous stem cell transplant | 4 (6) |
| Systemic investigational agents | 2 (3) |
| Steroids alone | 1 (1) |
| HyperCVAD | 1 (1) |
| Other | 1 (1) |

## Numbers analysed

109 patients were evaluable for the efficacy analyses, 111 patient for the safety analysis.

## Outcomes and estimation

- Primary endpoint, primary analysis with supportive analyses

**Table 14 Summary of best response**

| Efficacy Analysis Set (N = 109) | | | | | | |
|---|---|---|---|---|---|---|
| | Central review of IWC | | | Local Investigator Review | | |
| | n | (%) | (95% CI) | n | (%) | (95% CI) |
| CR+CRu+PR | 32 | (29) | (21, 39) | 43 | (39) | (30, 49) |
| CR | 11 | (10) | | 17 | (16) | |
| Cru | 1 | (1) | | 3 | (3) | |
| PR | 20 | (18) | | 23 | (21) | |
| SD | 21 | (19) | | 21 | (19) | |
| PD | 40 | (37) | | 40 | (37) | |
| UE | 2 | (2) | | - | - | |
| Missing: off-treatment in cycle 1 | 14 | (13) | | 5 | (5) | |

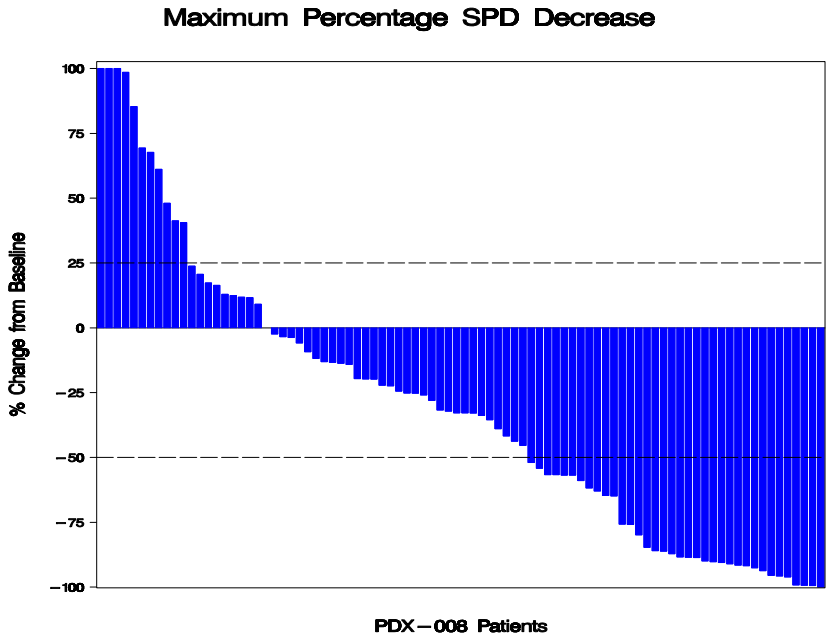
IWC = International Workshop Criteria
CI = confidence interval
CR = complete response
CRu = complete response unconfirmed
SD = stable disease
PR = partial response
PD = progressive disease
UE = unevaluable (insufficient materials for central review)

According to the primary analysis, independent central review using IWC, 32 patients responded to the treatment corresponding to an overall response rate of 29% with 95% CI 21-39%; 11, 1, and 20 patients reached CR, CRu, and PR, respectively. In the local investigator review, substantially more patients reached CR/CRu and overall 43 patients (39%) were judged as responders. The response rate according to IWC+PET was 26% (n=28) with 15 patients reaching CR.

Seventeen patients (25%) of the 69 patients in the overall efficacy analysis set that did not have evidence of response to their most recent prior therapy were stated to respond to pralatrexate per central review. Of the 26 patients in the efficacy analysis set that did not have evidence of response to any prior therapy, 5 patients (19%) responded to pralatrexate.

Response to pralatrexate was of relatively rapid onset, with 20 patients (63% of responders) observed to respond within 1 cycle of treatment as assessed by central review.

**Table 15 Waterfall-chart showing the maximum change from baseline in the sum of the products of the greatest diameter (SPD)**




Notable findings in the subset analyses include a slightly higher response rate in patients ≥65 years old than in younger patients, a slightly better response rate in methotrexate-naive patients, a lower response rate in patients diagnosed with angioimmunoblastic T-cell lymphoma as compared to the other entities included in the study, and, perhaps surprisingly, a slightly lower response rate in patients recruited at European centres as compared to North American centres (21% vs. 32%). However, the numbers of patients in the subgroups are generally low, and the results therefore have to be interpreted with caution.

**Table 16 Response rate by subsets per central assessment, efficacy analysis set (selected)**

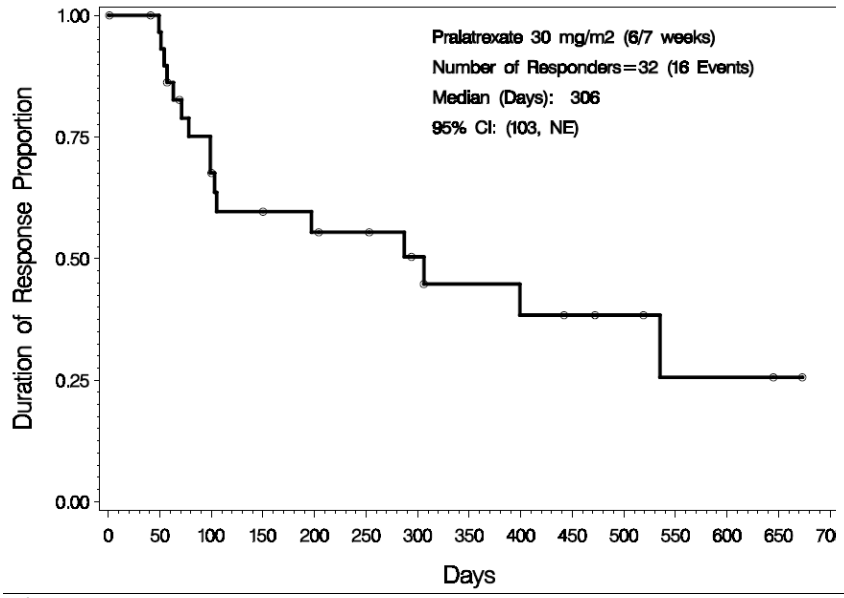
| | | Subset Incidence | | | | |
|---|---|---|---|---|---|---|
| | | N | (%) | Responders | Resp. Rate(%) | (95% CI) |
| Overall | | 109 | (100) | 32 | (29) | (21, 39) |
| Age | Age <65 | 70 | (64) | 19 | (27) | (17, 39) |
| | Age >=65 | 39 | (36) | 13 | (33) | (19, 50) |
| Prior Systemic Therapy for PTCL | 1 Regimen | 23 | (21) | 8 | (35) | (16, 57) |
| | 2 Regimens | 29 | (27) | 7 | (24) | (10, 44) |
| | >2 Regimens | 57 | (52) | 17 | (30) | (18, 43) |
| Histology | PTCL Unspecified | 59 | (54) | 19 | (32) | (21, 46) |
| | Angioimmunobl Tcl | 13 | (12) | 1 | (8) | (0, 36) |
| | Anaplastic LCL | 17 | (16) | 6 | (35) | (14, 62) |
| | Transformed MF | 12 | (11) | 3 | (25) | (5, 57) |
| | Other | 8 | (7) | 3 | (38) | (9, 76) |
| Best Response to Prior Therapy | CR or PR | 83 | (76) | 27 | (33) | (23, 44) |
| | SD or PD or Unknown | 26 | (24) | 5 | (19) | (7, 39) |
| Best Response to Most Recent Prior Therapy | CR/PR | 40 | (37) | 15 | (38) | (23, 54) |
| | SD/PD | 57 | (52) | 14 | (25) | (14, 38) |
| | NA | 12 | (11) | 3 | (25) | (5, 57) |
| Selected Prior Systemic Therapy for PTCL | 1 prior regimen - prior CHOP | 15 | (14) | 7 | (47) | (21, 73) |
| | 1 prior regimen - no prior CHOP | 8 | (7) | 1 | (12) | (0, 53) |
| | >1 prior regimens - prior CHOP | 61 | (56) | 15 | (25) | (14, 37) |
| | >1 prior regimens - no prior CHOP | 25 | (23) | 9 | (36) | (18, 57) |
| Prior Methotrexate | Yes | 21 | (19) | 5 | (24) | (8, 47) |
| | No | 88 | (81) | 27 | (31) | (21, 41) |
| Prior Transplant | Yes | 18 | (17) | 6 | (33) | (13, 59) |
| | No | 91 | (83) | 26 | (29) | (20, 39) |
| Global Region | North America | 85 | (78) | 27 | (32) | (22, 43) |
| | Europe | 24 | (22) | 5 | (21) | (7, 42) |

- Secondary endpoints with supportive analyses

  - Duration of response

The median duration of response assessed by IWC, based on 32 responding patients with 16 events, was 306 days (95% CI, 103-not estimable). Fourteen of the 32 responding patients had a duration of response in excess of 6 months. The 6-month and 12-month Kaplan-Meier estimates for duration of response were 60% and 45%, respectively. The calculation was based on 16 patients with event dates (14 PD, 2 death) and censored end dates for the remaining 16 responding patients.

**Table 17 Duration of response per central review; efficacy analysis set**



The criterion used for response was evidence of CR, CRu, or PR at one occasion. In 16 of the 32 responding patients, the response was confirmed at the next consecutive scheduled response assessment, corresponding to a confirmed response lasting at least ≥14 weeks; in 3 patients, the response was confirmed at unscheduled assessments less than 14 weeks later. The remaining 13 responders were either progressing or censored before the next consecutive scheduled assessment, meaning they did not have a confirmed response and a duration of response <14 weeks. If these figures are used in a conservative calculation of response rate, taking into account only responders with a confirmed duration ≥14 weeks, the response rate would be 16/109 patients (15%). Among these 16 patients with a confirmed duration ≥14 weeks, only 5 experienced events (4 PR, 1 death), the remaining being censored.

The median duration of response assessed by IWC plus PET based on 28 responding patients was 386 days (95% CI, 191-not estimable). The 6-month and 12-month estimates were 71% and 57%, respectively. Median duration of response per local investigator was 246 days (95% CI, 154-379), based on 43 responders with 25 events. The 6-month and 12-month estimates were 59% and 39%, respectively.

Sensitivity analyses were conducted to investigate the robustness of the Kaplan-Meier estimates for duration of response. These analyses compared the duration of response: 1) per the protocol specification; 2) if patients were censored for transplant at the time of last contact (rather than at time of transplant); 3) based on response assessment by independent central review using IWC + PET; and 4) based on response assessment by the investigator.

**Table 18 Duration of response – sensitivity analyses**

| Analysis | No. Responders/Events | Median (months) | 6-Month Estimate |
|---|---|---|---|
| Per protocol/statistical analysis plan | 32/16 | 10.1 | 60% |
| Censor transplant at last contact[a] | 32/16 | 13.1 | 62% |
| Per protocol/statistical analysis plan – using IWC + PET response assessment | 28/11 | 12.7 | 71% |
| Per investigator response assessment | 43/25 | 8.1 | 59% |

[a]4 patients censored due to transplant remained free of subsequent therapy at last contact, extending duration of response from 41 to 593 days, 69 to 461 days, 150 to 460 days, and 100 to 344 days.

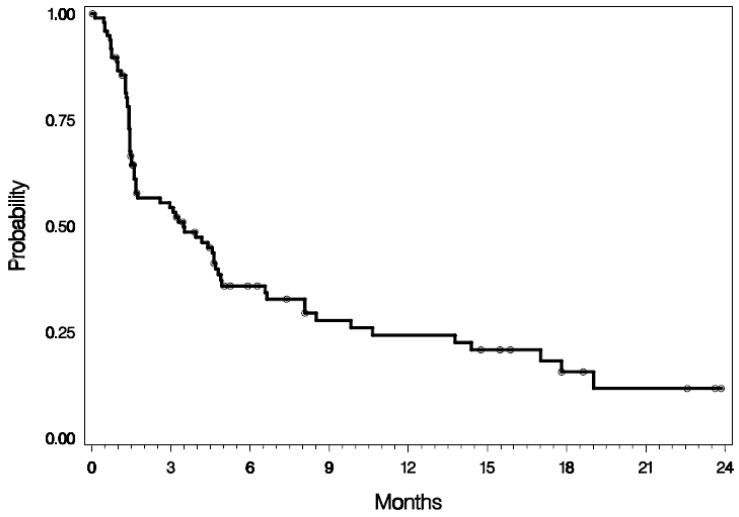
- Progression-free survival

Seventy patients (64%) had an event of either PD (n = 63, 58%) or death (n = 7, 6%) that was used to calculate their PFS.

Thirty-nine patients (36%) in the efficacy analysis population were censored for PFS (based on response assessed by central review using IWC) because they had not yet progressed at the time of the data cut-off date (n = 5, 5%) or they received anti-cancer therapy before PD was assessed (n = 26, 24%), and 4 patients (4%) terminated study follow-up for response. Four patients (4%) were censored due to transplant.

The median PFS based on response assessed by IWC was 106 days (95% CI, 51-146) with a range of 1-726 days.

**Table 19 Progression-free survival per central review (IWC)**




The median PFS based on response assessed by IWC plus PET was 141 days (95% CI, 79-243) or 4.6 months, with a range of 1-726 days. The median PFS based on response assessed by local investigator was 121 days (95% CI, 77-148 days) or 4.0 months, with a range of 1-726 days.

- Overall survival

Forty-seven patients (43%) were censored for OS because they were still alive at the time of the data cut-off date.

The median OS for the efficacy analysis set was 14.5 months (95% CI, 10.6- 22.5), with a range of 1.0-24.1 months.

- Updated PDX-008 Response and Survival Data

Since the cut-off of 17 August 2009, several PDX-008 investigational sites have provided additional survival data (n = 17) and/or response data (n = 7) for patients who were censored for one or more efficacy endpoint in the original analysis.

**Table 20 Survival Rates following pralatrexate initiation**

| | 1 year (%) | 2 years (%) | 3 years (%) | 4 years (%) |
|---|---|---|---|---|
| **Original PDX-008 Data** | 55.3 (45.2-64.3) | 33.7 (23.3-44.5) | --- | --- |
| **Updated PDX-008 Data** | 56.0 (46.1-64.9) | 34.8 (25.8-43.9) | 28.5 (19.1-38.6) | 24.9 (15.0-36.2) |

## Ancillary analyses

- Comparison of PFS and response rate with previous treatments of PTCL

It was hypothesised that the response rates and PFS would be lower with each subsequent line of therapy (hypothesis #1). Analyses were conducted on those patients who received at least 3 prior therapies. PFS and response rate of third prior therapy (-3) were compared with those of the second prior therapy (-2), PFS and response rate of second prior therapy (-2) were compared with those last line of therapy (-1) prior to pralatrexate, and PFS and response rate of last line of therapy (-1) were compared with pralatrexate therapy for these patients. These analyses utilised investigator assessment of PFS, and response since central review of tumour assessments on prior therapies was not available.

It was further hypothesised (hypothesis #2) that if progressive resistance was demonstrated, then pralatrexate may reverse or slow this trend, consistent with a clinical benefit for the drug. Therefore, an analysis was conducted on all patients comparing PFS and response rate of last line of therapy with those of pralatrexate therapy.

**Table 21 Comparison of median progression-free survival with previous treatments of PTCL: Patients with ≥2 previous treatments**

| Prior Systemic Treatment | Comparison | N | Progression-free Survival | | Response Rate |
|---|---|---|---|---|---|
| | | | Median (Days ) 95% CI | Hazard Ratio 95% CI | |
| Pralatrexate | | 86 | 119.00 (77.00, 146.00) | | 40 |
| -1 | -1 vs pralatrexate | 86 | 89.50 (72.00, 123.00) | 1.201 (0.868, 1.661) | 29 |
| -2 | -2 vs -1 | 86 | 144.00 (91.00, 188.00) | 0.785 (0.579, 1.063) | 38 |

**Table 22 Comparison of median progression-free survival and response rate between pralatrexate and the immediate prior treatment**

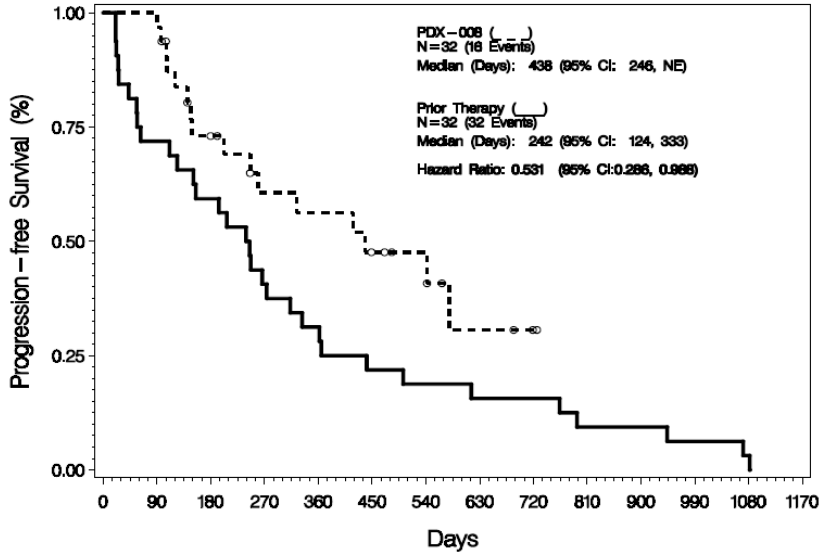
| Prior Systemic Treatment | Comparison | N | Progression-free Survival | | Response Rate |
|---|---|---|---|---|---|
| | | | Median (Days ) 95% CI | Hazard Ratio 95% CI | |
| Pralatrexate | | 109 | 121.00 (77.00, 148.00) | | 39 |
| -1 | -1 vs pralatrexate | 109 | 114.00 (89.00, 151.00) | 1.051 (0.785, 1.407) | 38 |

The retrospective analyses presented indicate that pralatrexate induces longer PFS and, in certain analyses, higher response rate than the previous lymphoma treatment(s).

- Additional intra-individual PFS analyses

The Applicant has undertaken further analyses to evaluate the impact of an objective response to pralatrexate on patient outcomes. In order to determine whether patients who responded to pralatrexate on PDX-008 were more likely to respond due to a superior disease prognosis at study entry, a retrospective analysis was conducted comparing the PFS of the pralatrexate responders with the PFS of the same patients' most recent prior therapies.

**Figure 2 Comparison of PFS for pralatrexate responders by central review on PDX-008 vs. most recent prior therapy**




- PFS and OS According to Best Response to Pralatrexate

**Table 23**

| | Outcome to Pralatrexate Therapy | | |
|---|---|---|---|
| | Response (n = 32) | Progressive Disease (n = 40) | Stable Disease (n = 21) |
| Median OS | 711 | 275 | 517 |
| Median PFS | 438 | 43 | 143 |
| Difference (Median OS - Median PFS) | 273 | 232 | 374 |

- PFS on pralatrexate compared to TTP on prior therapy

**Table 24 Comparison of Median PFS* and Response Rates between Pralatrexate and the Immediate Prior Systemic Regimens for Patients with At Least 2** Prior Systemic Regimens**

| Regimen | Prior Systemic | N | PFS Median (days) | HR | Response Rate |
|---|---|---|---|---|---|
| Overall | Pralatrexate | 86 | 119.0 | 1.20 | 40% |
| | -1 | 86 | 89.5 | | 29% |
| Single-agent Chemotherapy | Pralatrexate | 18 | 68.5 | 1.25 | 44% |
| | -1 | 18 | 81.5 | | 11% |
| CHOP | Pralatrexate | 15 | 97.0 | 0.92 | 33% |
| | -1 | 15 | 114.0 | | 40% |
| Bexarotene/Denileukin diftitox | Pralatrexate | 9 | 178.0 | 1.36 | 67% |
| | -1 | 9 | 56.0 | | 33% |
| Platinum-based Multi-agent Chemotherapy | Pralatrexate | 16 | 77.0 | 1.29 | 25% |
| | -1 | 16 | 62.0 | | 19% |

| | | | | | |
|---|---|---|---|---|---|
| Non-platinum, Non-CHOP Multi-agent Chemotherapy | Pralatrexate | 12 | 121.0 | 1.17 | 33% |
| | -1 | 12 | 87.5 | | 42% |
| Stem Cell Transplant | Pralatrexate | 9 | 324.0 | 2.38 | 56% |
| | -1 | 9 | 274.0 | | 56% |

*progression free survival on pralatrexate compared to time to progression on prior therapy
** This is the setting where all patients were known to be relapsed/refractory at the time of prior treatment.

- Responses to Pralatrexate in Patients Who Progressed Following CHOP or ICE

**Table 25 Responses to Pralatrexate in Patients Who Received First-line CHOP or Any Prior ICE**

| Prior Treatment | Investigator Assessment | | | Central Review | |
|---|---|---|---|---|---|
| | ORR to Prior Treatment | ORR to Pralatrexate | Median Duration of Response to Pralatrexate | ORR to Pralatrexate | Median Duration of Response to Pralatrexate |
| First-line CHOP (n = 16) | 75% (37.5% CR, 37.5% PR) | 38% (25% CR, 6% CRu, 6% PR) | 12.5 months | 44% (19% CR 25% PR) | NE |
| Any Prior ICE (n = 20) | 25% (15% CR, 10% PR) | 40% (25% CR, 15% PR) | 16.2 months | 40% (15% CR, 25% PR) | 13.1 months |

NE = not estimable due to insufficient PD events

Four patients who responded to second-line pralatrexate following CHOP (n=2) or ICE (n=2) proceeded to SCT (and were thus censored for duration of response).

- Decreased Risk of Death in Patients Who Responded to Pralatrexate

Landmark and time-dependent covariate analyses were applied, adjusted for the following baseline factors that could be potentially predictive chosen by clinicians: age (< 60 vs. age ≥ 60), extranodal growth (yes vs no), ECOG performance status (0,1 vs. 2), and number of prior therapies (< 3, ≥ 3).

**Table 26 Summary of Analyses of Survival by Tumour Response, Adjusting For Baseline Factors**

| Evaluation Method | Statistical Method | No. Patients in Analysis (Responders) | HR (95% CI) |
|---|---|---|---|
| Per central review | Landmark at cycle 1[a] | 93 (20) | 0.80 (0.38, 1.68) |
| | Time-dependent covariate | 109 (32) | 0.60 (0.32, 1.14) |
| Per investigator | Landmark at cycle 1[a] | 91 (32) | 0.49 (0.26, 0.93) |
| | Time-dependent covariate | 109 (43) | 0.39 (0.22, 0.71) |

[a]Deaths occurring or patients without any tumour response evaluations prior to day 53 were excluded.

The only baseline factor statistically significant at the 0.05 level was ECOG performance status, which was statistically significant in both methods. Extranodal growth was found to be marginally significant with either method.

- Historic Controls/Registry Data

Data from three registries, one from Europe and two from the US, were provided.

o European registry

This Registry has provided data on all PTCL patients diagnosed between 1997 and 2007. One hundred and four patients have been identified as having a diagnosis with histological subtypes of PTCL that were included in the PDX-008 study; the OS from diagnosis in this patient group showed a median of just 10 months, with a 5-year OS rate of 34.9%.

Fifty-five patients (53%) had a progression event, including 24 who progressed or died during initial therapy, 14 who progressed from PR or SD following initial therapy, and 14 who relapsed after a CR. A further 3 patients died while still in CR.

The median OS after failure of treatment was less than 1 month, with a 12-month survival of 10.7%. The majority of these patients would not have been eligible for inclusion in PDX-008, as 4 weeks needed to have lapsed between prior chemotherapy and pralatrexate initiation.

o US registries

Data was obtained a US registry and compared to the outcomes in PDX-008. Fifty patients were identified for inclusion in this dataset as follows: Histologies consistent with the inclusion criteria of PDX-008, and patients with at least 2 therapies. In comparison to the PDX-008 population, the registry dataset population was younger and less heavily pretreated. There was a 66% response rate to the most recent therapy and an 88% response rate to any therapy by investigator assessment.

The median OS (censored at 24.1 months) for the registry patients was 8.7 months (95% CI, 7.2-not estimable), with a range of 0.4-144.0 months; the median OS for the PDX-008 study was 14.5 months (95% CI, 10.6- 22.5), with a range of 1.0-24.1* months.

Comparisons between pralatrexate and a concurrent second database of comparable patients with PTCL were performed. Data on 70 patients treated between June 1997 and July 2011 was used for analysis.

The median OS (censored at 24.1 months) for the registry patients was 6.1 months (95% CI, 4.0 – 11.0; the median OS for the PDX-008 study was 14.5 months (95% CI, 10.6- 22.5

## Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 28 Summary of Efficacy for trial PDX-008**

| | | |
|---|---|---|
| **Title**: A Multi-center, Phase 2, Open-label Study of (RS)-10-Propargyl-10-Deazaaminopterin (Pralatrexate) with Vitamin B12 and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma | | |
| Study identifier | PDX-008 | |
| Design | Open-label, non-randomized, multi-center | |
| | Duration of main phase: | 24 August 2006 – 17 August 2009 |
| Hypothesis | Not applicable | |
| Treatments group | Pralatrexate, 6 weekly doses of pralatrexate IV (30mg/m2/week) over 3-5 minutes, followed by 1 week rest | |

<table>
<tr><td rowspan="4">Endpoints and definitions</td><td>Primary endpoint</td><td>Response rate</td><td>Response rate was defined as number of responders (CR+CRu+PR) and assessed by independent central review</td></tr>
<tr><td>Secondary endpoint</td><td>Duration of response</td><td>Number of days between the date of first tumour response assessment of objective response (including CR, CRu, and PR) to the time of the first tumour response assessment of PD or death due to any cause</td></tr>
<tr><td>Secondary endpoint</td><td>PFS</td><td></td></tr>
<tr><td>Secondary endpoint</td><td>OS</td><td></td></tr>
<tr><td>Database lock</td><td colspan="3">17 August 2009</td></tr>
<tr><td colspan="4"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Efficacy analysis set consists of all evaluable patients (n = 109); a patient was considered evaluable if he/she received at least 1 dose of pralatrexate and had a diagnosis of eligible PTCL histopathological subtype confirmed by central pathology review.</td></tr>
<tr><td rowspan="5">Descriptive statistics and estimate variability</td><td>Treatment group</td><td colspan="2">Pralatrexate</td></tr>
<tr><td>Number of subject</td><td colspan="2">109</td></tr>
<tr><td>Response rate</td><td colspan="2">
<table>
<tr><td></td><td colspan="3">Central review of IWC</td></tr>
<tr><td></td><td>n</td><td>(%)</td><td>(95% CI)</td></tr>
<tr><td>CR+CRu+PR</td><td>32</td><td>(29)</td><td>(21, 39)</td></tr>
<tr><td>CR</td><td>11</td><td>(10)</td><td></td></tr>
<tr><td>CRu</td><td>1</td><td>(1)</td><td></td></tr>
<tr><td>PR</td><td>20</td><td>(18)</td><td></td></tr>
</table>
<table>
<tr><td></td><td colspan="3">Local Investigator Review</td></tr>
<tr><td></td><td>n</td><td>(%)</td><td>(95% CI)</td></tr>
<tr><td>CR+CRu+PR</td><td>43</td><td>(39)</td><td>(30, 49)</td></tr>
<tr><td>CR</td><td>17</td><td>(16)</td><td></td></tr>
<tr><td>CRu</td><td>3</td><td>(3)</td><td></td></tr>
<tr><td>PR</td><td>23</td><td>(21)</td><td></td></tr>
</table>
</td></tr>
<tr><td>Duration of response</td><td colspan="2">Median 10.1 mos, range 1*-673 days (95% CI, 3.4 mos-not estimable)</td></tr>
<tr><td>PFS</td><td colspan="2">Median 3.5 mos, range 1*-726 days (95% CI, 1.7-4.8 mos)</td></tr>
<tr><td>OS</td><td colspan="2">Median 14.5 mos, range 1.0*-24.1 mos (95% CI, 10.6-22.5 mos)</td></tr>
</table>

*Indicates censoring

## Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy data across studies were not provided as pooled analyses due to the differences in tumour types, doses and schedules of administration of pralatrexate, and methods for efficacy assessments.

## Clinical studies in special populations

No clinical study in children or other special populations has been performed. Patients with renal or hepatic impairment were not eligible for the PDX-008 study.

## Supportive studies

*PDX-02-078*

PDX-02-078 was a non-randomised, open-label Phase I/II study in patients with relapsed or refractory aggressive NHL or HL. The primary objectives were to determine the efficacy of pralatrexate, determine impact of PK on AEs and drug elimination, and optimize a weekly schedule of pralatrexate with vitamin B12 and folic acid supplementation. Seventy-two patients were treated in the study. In the initial version of the study protocol, the starting dose of pralatrexate was 135 mg/m$^2$ administered every other week with intra-patient dose escalation. A higher than anticipated incidence of Grade 3 or 4 stomatitis occurred at this dose in patients. In addition, many patients with palpable disease experienced marked reductions in their disease by day 7, which grew back to baseline levels by day 15, suggesting cytokinetic failures. The protocol was then amended to become a Phase 1/2 study with an inter-patient dose-escalation scheme starting at 30 mg/m$^2$ weekly for 3 weeks of a 4-week cycle with subsequent increases in number of consecutive doses and dose amount. An amendment to the protocol included addition of vitamin B12 and folic acid supplementation. When dose-limiting toxicities (DLTs) occurred at the dose of 45 mg/m$^2$ for 6 weeks of a 7-week cycle, the maximum tolerated dose (MTD) was determined to be 30 mg/m$^2$/week for 6 weeks on a 7-week cycle.

Of the 39 evaluable patients, 13 patients had a response (6 CRs, 1 CRu, and 6 PRs) by investigator assessment (RR 33%), 15 had SD, and 11 had PD. Of the 13 patients who responded, 12 patients had T-cell lymphoma and 1 had B-cell lymphoma. Overall, there were 36 patients in PDX-02-078 with T-cell lymphoma, of whom 20 were evaluable per the protocol (must have completed 2 cycles of therapy) resulting in a response rate in T-cell lymphoma of 60%, based on investigator assessment. The median duration of response for the 13 responding patients was 5 months, with a range of < 1-18 months. However, the presentation and discussion of data was difficult to follow, and the real number of true responders fulfilling the criteria for evaluation is not entirely clear to the CHMP. It appears that 7/15 recruited patients, with histological entities included in the pivotal PDX-008 study and treated with the same dose regimen, responded to the treatment.

*Study PDX-010*

Study PDX-010 is an ongoing Phase I, open-label, multi-centre study of single agent pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). The objectives of the study are to determine an effective and well-tolerated dose and schedule of single-agent pralatrexate with vitamin B12 and folic acid supplementation that can be administered safely and to characterize the safety profile of pralatrexate in this group of patients. The 15 mg/m$^2$ dose given for 3 of 4 weeks was determined as the optimal dose/schedule and has been expanded with up to a total of 20 evaluable patients enrolled at this dose/schedule. Enrolment was completed after the data cut-off with a total of 54 treated patients, including 23 enrolled in the expanded cohort treated with pralatrexate at 15 mg/m$^2$ for 3 of 4 weeks.

Interim efficacy analyses showed that the overall response rate per investigator assessment using the modified severity-weighted assessment tool (mSWAT) was 40% (19/47 patients). Two patients had a best response of CR, 17 had PR, 18 had SD, 7 had PD, 3 patients did not have a response assessment prior to study treatment discontinuation, and response was pending for 1 patient. The 19 responders were heavily pretreated, with a median of 6 (range 3-18) prior treatment regimens and a median of 4 (range 1-11) prior systemic regimens. The overall response rate for the 22 patients treated at the determined recommended dosing regimen for CTCL patients (15 mg/m2 given weekly for 3/4 weeks) was 43%, with all 10 of the responding patients experiencing PR. In the 35 patients treated at the dose intensity of 15 mg/m2 given weekly for 3/4 weeks or higher, the overall response rate was 51% (18/35), with 17 PRs and 1 CR.

*Study PDX-009*

PDX-009 is a Phase I/IIa, open-label, multi-centre study of pralatrexate and gemcitabine administered on sequential days, or the same day depending on cohort, with vitamin B12 and folic acid supplementation to patients with relapsed or refractory lymphoproliferative malignancies. The data for PDX-009 were analyzed separately based on the phase of the study. In the phase 1 portion of the study, 3 to 6 patients in sequential cohorts were enrolled into each treatment group until the MTD was determined. Eight of 34 evaluable patients in this phase of the study had a response (24%), all of whom had PRs. Six additional patients (18%) had SD. One patient was considered evaluable but withdrew consent. The overall disease control rate (CR + CRu + PR + SD) for the phase 1 portion of the study was 41%. The median time to PD for the patients in the phase 1 part of the study was 51 days (range 1-379 days). According to the study report there were 8 evaluable patients with PTCL in this cohort, with 6 PDs and 2 PRs (by investigator).

Patients are currently being randomized in the phase 2a component of the study to receive either sequential dosing (pralatrexate 10 mg/m2 and gemcitabine 400 mg/$m^2$) or same-day dosing (pralatrexate 15 mg/m2 and gemcitabine 600 mg/$m^2$) to confirm the tolerability of the combination dose regimen and to obtain preliminary efficacy data to support later phase clinical trials. As of the data cut-off of 17 February 2010 for this ongoing study, 62 patients had been treated and had data available.

Of 27 evaluable patients in the phase 2a component of the study, 5 patients (19%) have achieved a response including 2 CRs and 3 PRs. These responses have been observed in both dosing schedules: 2 of 14 evaluable patients in the sequential-day dosing group and 3 of 13 patients in the same-day dosing group. Four patients (15%) in the phase 2a component had SD. The overall disease control rate for the phase 2a portion of the study to date was 33%. As enrolment in this phase of the study is ongoing, time-to-event analyses have not yet been performed. According to the study report there were 8 evaluable patients with PTCL in this cohort, with 4 PDs, 2 SDs, and 2 patients apparently unevaluable by IWC but with a metabolic response by PET (by investigator).

### *Proposed confirmatory study*

The Applicant proposed to perform as a specific obligation a randomised study with pralatrexate versus single-agent systemic treatment of physician's choice. The Applicant considers it unlikely that patients in the post-approval study will be those considered to be eligible for transplant in the second-line relapsed setting and suggests a choice of commercially available, single-agent chemotherapeutics and biologicals as comparator.

The Applicant has performed an international feasibility survey and an analysis of the competitive landscape and concluded that the proposed confirmatory study with its presently suggested design and a 3 years recruitment period including EU as well as non-EU sites would be feasible.

## 2.5.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

The main efficacy results are derived from the pivotal PDX-008 study (n=109 evaluable patients), with some support from the preceding phase I/II dose-finding PDX-02-078 study (n=15 evaluable patients with PTCL as defined in the PDX-008 study and treated with the same dose regimen).

Contrary to the CHMP/EMA advice, forwarded to the Sponsor in the setting of a protocol assistance, the pivotal study was designed as a single-arm trial with response rate constituting the primary endpoint.

As will be discussed below, lack of a randomised controlled study, in the absence of dramatic activity, hampers a conclusive assessment of the benefit-risk balance.

According to the Applicant, reasons for choosing a single-arm approach included the rarity of the studied disorders and the lack of treatment consensus in the refractory/relapse setting, that is, an obvious control arm. The Applicant furthermore stated that "..., the observation of objective responses – particularly durable responses – is generally accepted as a clinically meaningful endpoint by haematologists and oncologists, and this endpoint can be robustly assessed in non-comparative studies". Although the facts regarding the rarity of the disease(s) and the lack of a treatment consensus in refractory/relapsing PTCL are acknowledged, the clinical benefit of objective response *per se* has not been established in this clinical setting and in the absence of dramatic activity, the clinical benefit cannot be considered established. Additionally, a single arm design does not allow estimation of clinical benefit in terms of clinical benefit endpoints such as PFS or OS.

## Efficacy data and additional analyses

The response rate in PDX-008 study was 29%. Only 15% of patients in the efficacy set obtained a confirmed response duration of ≥14 weeks. The significance of PFS and OS is not possible to assess with this study design.

The intra-individual analyses comparing efficacy of pralatrexate with that of previous therapies were non-prespecified. These analyses are associated with the corresponding pitfalls, e.g. historical comparisons, investigator-derived PFS data and the risk of underestimated response duration of previous therapy.

The presented historical registry data are of general interest but of limited value for a direct comparison with data obtained with pralatrexate. The validity of the historical control as a comparator for PDX-008 is questioned by CHMP. It is not clear how selection bias was avoided and therefore, the historical comparison presented considered not acceptable.

The preliminary results of studies PDX-010 and PDX-009 did not add any substantial information to the assessment of pralatrexate's efficacy within the proposed indication. Study PDX-010 is a Phase I study of patients with CTCL, a very different patient group than those with PTCL. In study PDX-009, 16 evaluable PTCL patients show 10 PDs, 2 SDs, 2PRs, and 2 patients unevaluable by IWC but with a metabolic response by PET (by investigator).

## Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 1 December 2011 to provide advice on the following list of questions adopted by the CHMP at its November 2011 meeting.

1. **The SAG is asked to describe how impressive they view the efficacy data to be (based on response rate, duration of response, PFS, OS) in light of the methodological limitations of the study, in particular the absence of a randomised control group.**

Pralatrexate has shown antitumor activity in patients with relapsed PTCL. Based on indirect comparisons, the activity in terms of response rate appears to be in the same range of other single-agent or combination regimens which are currently used in this setting, although the efficacy of such treatment options cannot be considered established according to conventional scientific or regulatory standards. The antitumor activity observed for pralatrexate cannot be considered impressive or otherwise outstanding, and based on this the activity it is not possible to establish the clinical efficacy of this agent in the proposed indication.

There are serious concerns from the point of view of external validity in view of the design of the pivotal study, especially the non-randomised design of the study. Such design does not allow establishing the efficacy of pralatrexate in terms of relevant clinical benefit endpoints such as PFS or OS in this population. Overall, the clinical benefit cannot be considered established and therefore the benefit cannot be considered to outweigh the risks.

**2. Does the SAG consider the proposed confirmatory study feasible in the EU after the medicinal product would have obtained a marketing authorisation in the EU?**

Overall, the proposed trial is feasible (before or after a marketing authorisation). From an ethical point of view there are in principle no major issues, due to the fact that benefits have not been established.

Due to the rare disease, an underpowered study may be the only possible option. Such trial could still generate useful data, particularly in terms of PFS or OS, and to assess the proportion of patients that can undergo BMT (as a secondary endpoint). The feasibility of the study in terms of recruitment will also be affected also by practical issues (e.g., treatment options made available for the control arm).

Due to the long expected time lag between progression and death, PFS seems to be a more sensitive endpoint and this could allow a cross-over option after progression if this is deemed necessary. However, if the trial aims to detect a difference in terms of OS then cross-over is likely to be a problem.

**3. Does the SAG consider the results of the ongoing PDX-017 study of value and supportive/confirmatory in terms of efficacy for the current indication applied for?**

This trial is in a different indication and would not contribute useful information to support the proposed indication.

**4. Referring to Q2 and Q3 is there another patient group which is considered relevant for the indication applied for where a controlled study would be considered feasible to conduct.**

The proposed study is considered feasible (see answer to Q2). No other patient group was identified.

**5. The SAG is asked to discuss the severity of the side effects, in particular regarding mucositis and other skin reactions, and whether these can be managed in clinical practice.**

Overall the toxicity is considered to be significant, in particular concerning mucositis, skin reactions. Although in many cases such toxicity can be managed, as there is vast experience on managing similar toxicity with other agents such as methotrexate, drug-related deaths associated with pralatrexate have been observed. In the absence of established benefits, even if mostly manageable, the toxicity remains a concern.

Patients with existing cutaneous involvement are likely to be at a higher risk of cutaneous toxicity. In addition, there are too few data in patients with "third space" distribution of the drug and these uncertainties should be part of a risk minimisation plan.

## 2.5.4. Conclusions on the clinical efficacy

Pralatrexate showed antitumor activity in terms of response rate. However, the extent to which antitumor activity reflects clinical benefit is unknown. Therefore, the clinical efficacy of this agent cannot be considered established in the proposed indication.

## *2.6. Clinical safety*

### Patient exposure

Based on the data cut-off (31 January 2011) of the last update submitted by the Applicant, the clinical study safety database included data on 689 patients who were treated with pralatrexate across all clinical studies, of which 141 patients with relapsed/refractory PTCL who received single-agent pralatrexate (PDX-008 = 111 patients; PDX-02-078 = 30 patients). In addition, post-marketing experience in the USA is estimated include 1,157 to 2,025 patients. Overall, the total exposure of pralatrexate is approximately 1,298 to 2,166 patients in the requested indication.

In study PDX-008 the protocol allowed for dose omission or dose reduction to 20 mg/m$^2$/week if a patient experienced protocol-defined Adverse Events. Dose reduction below 20 mg/m$^2$ was not allowed. 76 patients (68%) remained at the target dose for the duration of treatment. The pralatrexate dose was reduced from 30 mg/m$^2$ to 20 mg/m$^2$ for 35 patients (32%).

The majority of patients received 1-3 cycles of treatment. The median total dose administered over the course of treatment was 208 mg/m$^2$ (range 27-2109 mg/m$^2$) and the mean was 384 mg/m$^2$. The median duration of treatment was 70 days and the mean was 121 days (range 1-696 days) for all treated patients The median number of pralatrexate doses administered to patients was 7 and the mean was 14 (range 1-74 doses).

Concerning long term treatment, nineteen patients (17%) were treated with pralatrexate for ≥ 6 months and 10 patients (9%) were treated for ≥ 1 year.

### Adverse events

The safety of pralatrexate was evaluated in 111 peripheral T-cell lymphoma (PTCL) patients in one single-arm pivotal clinical study, PDX-008, in which patients received 30 mg/m$^2$ once weekly for 6 weeks in 7-week cycles.

The most common adverse drug reactions reported in the PDX-008 study were mucosal inflammation (68% of patients), thrombocytopenia (40%), nausea (33%) and anaemia (32%). Neutropenia of any grade occurred in 24% of patients.

The most common AEs ≥grade 3 were thrombocytopenia, mucosal inflammation, neutropenia, anaemia and leucopoenia (32%, 22%, 22%, 16% and 8%, respectively). Other common Grade 3 and 4 adverse reactions included skin ulcer, infection, anorexia, dyspnoea, vomiting, nausea, pain, and fatigue.

The median time to onset of AEs ≥ Grade 3 was 15 days for thrombocytopenia, 19 days for mucosal inflammation, and 22 days for neutropenia. The median duration of AEs ≥ Grade 3 was 16 days for thrombocytopenia, 13 days for mucosal inflammation, and 8 days for neutropenia.

In the pivotal study the median onset of ≥ grade 3 mucosal inflammation, thrombocytopenia and neutropenia was between day 15-19 and the median duration was 8-16 days.

Bleeding complications coincident with the low platelet counts were generally mild in severity and predominantly presented clinically as epistaxis. Infection complications coincident with the low neutrophil counts were mostly Grade 1-2 in severity.

**Table 29 Treatment-Related Adverse Events by System Organ Class and Preferred Terms. All Grades population 1 – pivotal study, all treated patients**

| System Organ Class<br>Preferred Term | PDX-008 (N=111) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | | Total | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| ALL | 11 | (10) | 24 | (22) | 42 | (38) | 29 | (26) | 106 | (95) |
| GASTROINTESTINAL DISORDERS | 22 | (20) | 42 | (38) | 22 | (20) | 4 | (4) | 90 | (81) |
| STOMATITIS | 20 | (18) | 32 | (29) | 18 | (16) | 4 | (4) | 74 | (67) |
| NAUSEA | 22 | (20) | 12 | (11) | 4 | (4) | 0 | (0) | 38 | (34) |
| CONSTIPATION | 17 | (15) | 6 | (5) | 0 | (0) | 0 | (0) | 23 | (21) |
| VOMITING | 15 | (14) | 6 | (5) | 2 | (2) | 0 | (0) | 23 | (21) |
| DIARRHOEA | 12 | (11) | 6 | (5) | 1 | (1) | 0 | (0) | 19 | (17) |
| ABDOMINAL PAIN UPPER | 4 | (4) | 2 | (2) | 0 | (0) | 0 | (0) | 6 | (5) |
| APHTHOUS STOMATITIS | 5 | (5) | 0 | (0) | 0 | (0) | 0 | (0) | 5 | (5) |
| GASTROOESOPHAGEAL REFLUX DISEASE | 4 | (4) | 1 | (1) | 0 | (0) | 0 | (0) | 5 | (5) |
| ORAL PAIN | 5 | (5) | 0 | (0) | 0 | (0) | 0 | (0) | 5 | (5) |
| ABDOMINAL DISCOMFORT | 3 | (3) | 0 | (0) | 0 | (0) | 0 | (0) | 3 | (3) |
| ABDOMINAL PAIN | 2 | (2) | 1 | (1) | 0 | (0) | 0 | (0) | 3 | (3) |
| DRY MOUTH | 3 | (3) | 0 | (0) | 0 | (0) | 0 | (0) | 3 | (3) |
| DYSPEPSIA | 3 | (3) | 0 | (0) | 0 | (0) | 0 | (0) | 3 | (3) |
| HAEMORRHOIDS | 2 | (2) | 0 | (0) | 1 | (1) | 0 | (0) | 3 | (3) |
| FLATULENCE | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| GASTRITIS | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) |
| LIP DRY | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| OESOPHAGITIS | 0 | (0) | 0 | (0) | 1 | (1) | 1 | (1) | 2 | (2) |
| ANAL INFLAMMATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| CHEILITIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| CHEILOSIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| DYSPHAGIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| GINGIVAL OEDEMA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| GINGIVAL PAIN | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| HAEMORRHOIDAL HAEMORRHAGE | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| HYPOAESTHESIA ORAL | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| LIP DISORDER | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| LIP PAIN | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| LIP ULCERATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| MOUTH ULCERATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| ODYNOPHAGIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| OESOPHAGEAL PAIN | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| ORAL DISORDER | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| ORAL MUCOSAL ERYTHEMA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| PANCREATITIS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| PARAESTHESIA ORAL | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| PERIANAL ERYTHEMA | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| RECTAL HAEMORRHAGE | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| TONGUE DISCOLOURATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| TONGUE ULCERATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| TOOTHACHE | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 29 | (26) | 19 | (17) | 10 | (9) | 2 | (2) | 60 | (54) |
| FATIGUE | 17 | (15) | 11 | (10) | 5 | (5) | 1 | (1) | 34 | (31) |
| PYREXIA | 17 | (15) | 4 | (4) | 0 | (0) | 0 | (0) | 21 | (19) |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| OEDEMA PERIPHERAL | 13 | (12) | 7 | (6) | 0 | (0) | 0 | (0) | 20 | (18) | | | | | |
| MUCOSAL INFLAMMATION | 2 | (2) | 4 | (4) | 2 | (2) | 1 | (1) | 9 | (8) | | | | | |
| ASTHENIA | 2 | (2) | 3 | (3) | 1 | (1) | 0 | (0) | 6 | (5) | | | | | |
| FACE OEDEMA | 3 | (3) | 1 | (1) | 1 | (1) | 0 | (0) | 5 | (5) | | | | | |
| PAIN | 2 | (2) | 0 | (0) | 2 | (2) | 0 | (0) | 4 | (4) | | | | | |
| AXILLARY PAIN | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| CHEST PAIN | 0 | (0) | 2 | (2) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| CHILLS | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| INFLUENZA LIKE ILLNESS | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| LOCALISED OEDEMA | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| EARLY SATIETY | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| INFUSION RELATED REACTION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| LOCAL SWELLING | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| MUCOSAL DRYNESS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 40 | (36) | 8 | (7) | 5 | (5) | 1 | (1) | 54 | (49) | | | | | |
| EPISTAXIS | 24 | (22) | 2 | (2) | 0 | (0) | 0 | (0) | 26 | (23) | | | | | |
| DYSPNOEA | 8 | (7) | 0 | (0) | 3 | (3) | 0 | (0) | 11 | (10) | | | | | |
| PHARYNGOLARYNGEAL PAIN | 8 | (7) | 1 | (1) | 1 | (1) | 0 | (0) | 10 | (9) | | | | | |
| COUGH | 8 | (7) | 0 | (0) | 0 | (0) | 0 | (0) | 8 | (7) | | | | | |
| DYSPHONIA | 5 | (5) | 0 | (0) | 0 | (0) | 0 | (0) | 5 | (5) | | | | | |
| PHARYNGEAL INFLAMMATION | 1 | (1) | 2 | (2) | 1 | (1) | 0 | (0) | 4 | (4) | | | | | |
| DRY THROAT | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| PLEURAL EFFUSION | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| PNEUMONITIS | 0 | (0) | 2 | (2) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| PRODUCTIVE COUGH | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| HICCUPS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| HYPOXIA | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| LUNG CONSOLIDATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| NASAL CONGESTION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| PLEURITIC PAIN | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| PULMONARY CONGESTION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| PULMONARY EMBOLISM | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | 1 | (1) | | | | | |
| REFLUX LARYNGITIS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| RHINORRHOEA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| TACHYPNOEA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| THROAT TIGHTNESS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 3 | (3) | 9 | (8) | 22 | (20) | 19 | (17) | 53 | (48) | | | | | |
| THROMBOCYTOPENIA | 0 | (0) | 5 | (5) | 13 | (12) | 15 | (14) | 33 | (30) | | | | | |
| ANAEMIA | 1 | (1) | 15 | (14) | 13 | (12) | 1 | (1) | 30 | (27) | | | | | |
| NEUTROPENIA | 0 | (0) | 3 | (3) | 12 | (11) | 7 | (6) | 22 | (20) | | | | | |
| LEUKOPENIA | 1 | (1) | 0 | (0) | 1 | (1) | 3 | (3) | 5 | (5) | | | | | |
| FEBRILE NEUTROPENIA | 0 | (0) | 0 | (0) | 4 | (4) | 0 | (0) | 4 | (4) | | | | | |
| LYMPHOPENIA | 1 | (1) | 0 | (0) | 1 | (1) | 0 | (0) | 2 | (2) | | | | | |
| PANCYTOPENIA | 0 | (0) | 0 | (0) | 1 | (1) | 1 | (1) | 2 | (2) | | | | | |
| HAEMOLYTIC ANAEMIA | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| LYMPH NODE PAIN | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| SPLENOMEGALY | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 23 | (21) | 11 | (10) | 6 | (5) | 0 | (0) | 40 | (36) | | | | | |
| RASH | 10 | (9) | 2 | (2) | 0 | (0) | 0 | (0) | 12 | (11) | | | | | |
| PRURITUS | 4 | (4) | 3 | (3) | 1 | (1) | 0 | (0) | 8 | (7) | | | | | |
| SKIN ULCER | 2 | (2) | 2 | (2) | 2 | (2) | 0 | (0) | 6 | (5) | | | | | |
| ALOPECIA | 4 | (4) | 0 | (0) | 0 | (0) | 0 | (0) | 4 | (4) | | | | | |
| BLISTER | 2 | (2) | 2 | (2) | 0 | (0) | 0 | (0) | 4 | (4) | | | | | |
| SKIN LESION | 1 | (1) | 2 | (2) | 1 | (1) | 0 | (0) | 4 | (4) | | | | | |
| DRY SKIN | 3 | (3) | 0 | (0) | 0 | (0) | 0 | (0) | 3 | (3) | | | | | |
| ERYTHEMA | 3 | (3) | 0 | (0) | 0 | (0) | 0 | (0) | 3 | (3) | | | | | |
| PERIORBITAL OEDEMA | 1 | (1) | 2 | (2) | 0 | (0) | 0 | (0) | 3 | (3) | | | | | |
| PETECHIAE | 3 | (3) | 0 | (0) | 0 | (0) | 0 | (0) | 3 | (3) | | | | | |
| URTICARIA | 2 | (2) | 0 | (0) | 1 | (1) | 0 | (0) | 3 | (3) | | | | | |
| RASH GENERALISED | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) | | | | | |
| ECCHYMOSIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| GENERALISED ERYTHEMA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| NIGHT SWEATS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| PAIN OF SKIN | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| PENILE ULCERATION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| RASH ERYTHEMATOUS | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) | | | | | |
| RASH MACULAR | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| RASH MACULO-PAPULAR | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |
| RASH PAPULAR | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RASH PRURITIC | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| SCAB | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| SKIN DISORDER | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| SKIN EXFOLIATION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| SKIN HAEMORRHAGE | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| SKIN TOXICITY | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| INFECTIONS AND INFESTATIONS | 9 | (8) | 19 | (17) | 9 | (8) | 2 | (2) | 39 | (35) |
| SINUSITIS | 1 | (1) | 5 | (5) | 0 | (0) | 0 | (0) | 6 | (5) |
| FOLLICULITIS | 4 | (4) | 0 | (0) | 1 | (1) | 0 | (0) | 5 | (5) |
| ORAL HERPES | 5 | (5) | 0 | (0) | 0 | (0) | 0 | (0) | 5 | (5) |
| CANDIDIASIS | 2 | (2) | 1 | (1) | 1 | (1) | 0 | (0) | 4 | (4) |
| ORAL CANDIDIASIS | 4 | (4) | 0 | (0) | 0 | (0) | 0 | (0) | 4 | (4) |
| UPPER RESPIRATORY TRACT INFECTION | 2 | (2) | 1 | (1) | 1 | (1) | 0 | (0) | 4 | (4) |
| URINARY TRACT INFECTION | 0 | (0) | 3 | (3) | 1 | (1) | 0 | (0) | 4 | (4) |
| HERPES ZOSTER | 1 | (1) | 0 | (0) | 2 | (2) | 0 | (0) | 3 | (3) |
| LOCALISED INFECTION | 0 | (0) | 3 | (3) | 0 | (0) | 0 | (0) | 3 | (3) |
| PNEUMONIA | 0 | (0) | 2 | (2) | 1 | (1) | 0 | (0) | 3 | (3) |
| SEPSIS | 0 | (0) | 0 | (0) | 1 | (1) | 2 | (2) | 3 | (3) |
| BRONCHITIS | 0 | (0) | 2 | (2) | 0 | (0) | 0 | (0) | 2 | (2) |
| CELLULITIS | 0 | (0) | 2 | (2) | 0 | (0) | 0 | (0) | 2 | (2) |
| INFECTION | 0 | (0) | 1 | (1) | 1 | (1) | 0 | (0) | 2 | (2) |
| SUBCUTANEOUS ABSCESS | 0 | (0) | 2 | (2) | 0 | (0) | 0 | (0) | 2 | (2) |
| ABSCESS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| BACTERIAL INFECTION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| CHRONIC SINUSITIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| CLOSTRIDIUM DIFFICILE COLITIS | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| CYTOMEGALOVIRUS COLITIS | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| FUNGAL INFECTION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| FUNGAL SKIN INFECTION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| HERPES SIMPLEX | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| HERPES VIRUS INFECTION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| LUNG INFECTION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| NAIL INFECTION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| NASOPHARYNGITIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| OESOPHAGEAL CANDIDIASIS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| PHARYNGITIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| PILONIDAL CYST | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| SINUSITIS BACTERIAL | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| STAPHYLOCOCCAL INFECTION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| TOOTH INFECTION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| VULVOVAGINAL MYCOTIC INFECTION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| INVESTIGATIONS | 6 | (5) | 11 | (10) | 12 | (11) | 7 | (6) | 36 | (32) |
| PLATELET COUNT DECREASED | 1 | (1) | 3 | (3) | 4 | (4) | 4 | (4) | 12 | (11) |
| ALANINE AMINOTRANSFERASE INCREASED | 3 | (3) | 3 | (3) | 4 | (4) | 0 | (0) | 10 | (9) |
| HAEMOGLOBIN DECREASED | 2 | (2) | 3 | (3) | 3 | (3) | 1 | (1) | 9 | (8) |
| WHITE BLOOD CELL COUNT DECREASED | 1 | (1) | 2 | (2) | 3 | (3) | 1 | (1) | 7 | (6) |
| NEUTROPHIL COUNT DECREASED | 0 | (0) | 1 | (1) | 4 | (4) | 1 | (1) | 6 | (5) |
| WEIGHT DECREASED | 4 | (4) | 2 | (2) | 0 | (0) | 0 | (0) | 6 | (5) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 2 | (2) | 1 | (1) | 2 | (2) | 0 | (0) | 5 | (5) |
| ALANINE AMINOTRANSFERASE | 0 | (0) | 1 | (1) | 2 | (2) | 0 | (0) | 3 | (3) |
| ASPARTATE AMINOTRANSFERASE | 0 | (0) | 2 | (2) | 1 | (1) | 0 | (0) | 3 | (3) |
| BLOOD ALKALINE PHOSPHATASE INCREASED | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) |
| BLOOD BILIRUBIN INCREASED | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) |
| BLOOD CREATINE INCREASED | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| BLOOD CREATININE | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| BLOOD GLUCOSE INCREASED | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| BLOOD PHOSPHORUS INCREASED | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| BLOOD POTASSIUM DECREASED | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| BLOOD URIC ACID INCREASED | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| EJECTION FRACTION DECREASED | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| LIVER FUNCTION TEST ABNORMAL | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| METABOLISM AND NUTRITION DISORDERS | 17 | (15) | 6 | (5) | 4 | (4) | 0 | (0) | 27 | (24) |
| HYPOKALAEMIA | 8 | (7) | 2 | (2) | 0 | (0) | 0 | (0) | 10 | (9) |
| DECREASED APPETITE | 7 | (6) | 0 | (0) | 0 | (0) | 0 | (0) | 7 | (6) |
| ANOREXIA | 3 | (3) | 1 | (1) | 2 | (2) | 0 | (0) | 6 | (5) |
| HYPOMAGNESAEMIA | 5 | (5) | 0 | (0) | 0 | (0) | 0 | (0) | 5 | (5) |
| DEHYDRATION | 0 | (0) | 2 | (2) | 1 | (1) | 0 | (0) | 3 | (3) |
| HYPERKALAEMIA | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) |
| HYPERURICAEMIA | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HYPOPHOSPHATAEMIA | 1 | (1) | 0 | (0) | 1 | (1) | 0 | (0) | 2 | (2) |
| CELL DEATH | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| HYPERCALCAEMIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| HYPERGLYCAEMIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| HYPOGLYCAEMIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 11 | (10) | 13 | (12) | 3 | (3) | 0 | (0) | 27 | (24) |
| PAIN IN EXTREMITY | 5 | (5) | 4 | (4) | 0 | (0) | 0 | (0) | 9 | (8) |
| MUSCLE SPASMS | 5 | (5) | 1 | (1) | 0 | (0) | 0 | (0) | 6 | (5) |
| MYALGIA | 5 | (5) | 0 | (0) | 1 | (1) | 0 | (0) | 6 | (5) |
| ARTHRALGIA | 1 | (1) | 4 | (4) | 0 | (0) | 0 | (0) | 5 | (5) |
| BACK PAIN | 1 | (1) | 2 | (2) | 1 | (1) | 0 | (0) | 4 | (4) |
| MUSCULOSKELETAL PAIN | 1 | (1) | 2 | (2) | 0 | (0) | 0 | (0) | 3 | (3) |
| NECK PAIN | 0 | (0) | 3 | (3) | 0 | (0) | 0 | (0) | 3 | (3) |
| COSTOCHONDRITIS | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| JOINT STIFFNESS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| JOINT SWELLING | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| MUSCULOSKELETAL CHEST PAIN | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| MUSCULOSKELETAL DISCOMFORT | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| MUSCULOSKELETAL STIFFNESS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| NERVOUS SYSTEM DISORDERS | 15 | (14) | 5 | (5) | 2 | (2) | 0 | (0) | 22 | (20) |
| HEADACHE | 6 | (5) | 2 | (2) | 0 | (0) | 0 | (0) | 8 | (7) |
| DIZZINESS | 5 | (5) | 0 | (0) | 1 | (1) | 0 | (0) | 6 | (5) |
| PARAESTHESIA | 2 | (2) | 3 | (3) | 0 | (0) | 0 | (0) | 5 | (5) |
| HYPOAESTHESIA | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| NEUROPATHY PERIPHERAL | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| DYSGEUSIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| FORMICATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| MEMORY IMPAIRMENT | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| NEURALGIA | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| PERIPHERAL SENSORY NEUROPATHY | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| SENSORY LOSS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| SYNCOPE | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| EYE DISORDERS | 18 | (16) | 0 | (0) | 0 | (0) | 0 | (0) | 18 | (16) |
| EYE IRRITATION | 6 | (5) | 0 | (0) | 0 | (0) | 0 | (0) | 6 | (5) |
| OCULAR HYPERAEMIA | 5 | (5) | 0 | (0) | 0 | (0) | 0 | (0) | 5 | (5) |
| LACRIMATION INCREASED | 4 | (4) | 0 | (0) | 0 | (0) | 0 | (0) | 4 | (4) |
| CONJUNCTIVAL HYPERAEMIA | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| VISION BLURRED | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| CONJUNCTIVITIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| DRY EYE | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| ERYTHEMA OF EYELID | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| EYE PRURITUS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| EYELID OEDEMA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| EYELID PTOSIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| EYELIDS PRURITUS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| PHOTOPSIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| SCLERAL HYPERAEMIA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| UVEITIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| VISUAL ACUITY REDUCED | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| PSYCHIATRIC DISORDERS | 4 | (4) | 2 | (2) | 0 | (0) | 0 | (0) | 6 | (5) |
| ANXIETY | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) |
| INSOMNIA | 1 | (1) | 1 | (1) | 0 | (0) | 0 | (0) | 2 | (2) |
| AGITATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| CONFUSIONAL STATE | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| DELUSION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| DEPRESSION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| EAR AND LABYRINTH DISORDERS | 4 | (4) | 1 | (1) | 0 | (0) | 0 | (0) | 5 | (5) |
| TINNITUS | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| DEAFNESS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| HYPOACUSIS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| VERTIGO | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 4 | (4) | 1 | (1) | 0 | (0) | 0 | (0) | 5 | (5) |
| CONTUSION | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| EXCORIATION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| MUSCLE STRAIN | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| PROCEDURAL NAUSEA | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| CARDIAC DISORDERS | 3 | (3) | 0 | (0) | 0 | (0) | 1 | (1) | 4 | (4) |
| TACHYCARDIA | 2 | (2) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2) |
| CARDIO-RESPIRATORY ARREST | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) | 1 | (1) |
| CARDIOMEGALY | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| SUPRAVENTRICULAR TACHYCARDIA | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 3 | (3) | 1 | (1) | 0 | (0) | 0 | (0) | 4 | (4) |
| BALANOPOSTHITIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| GENITAL RASH | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| GENITAL ULCERATION | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| VULVOVAGINAL PRURITUS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| VASCULAR DISORDERS | 1 | (1) | 1 | (1) | 0 | (0) | 1 | (1) | 3 | (3) |
| HYPOTENSION | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) | 2 | (2) |
| JUGULAR VEIN THROMBOSIS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| SUBCLAVIAN VEIN THROMBOSIS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| HEPATOBILIARY DISORDERS | 0 | (0) | 2 | (2) | 0 | (0) | 0 | (0) | 2 | (2) |
| HYPERBILIRUBINAEMIA | 0 | (0) | 2 | (2) | 0 | (0) | 0 | (0) | 2 | (2) |
| CHOLANGITIS | 0 | (0) | 1 | (1) | 0 | (0) | 0 | (0) | 1 | (1) |
| HEPATOSPLENOMEGALY | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| RENAL AND URINARY DISORDERS | 1 | (1) | 0 | (0) | 1 | (1) | 0 | (0) | 2 | (2) |
| RENAL FAILURE | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| URINARY HESITATION | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| CONGENITAL, FAMILIAL AND GENETIC DISORDERS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| PHIMOSIS | 1 | (1) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |
| TUMOUR LYSIS SYNDROME | 0 | (0) | 0 | (0) | 1 | (1) | 0 | (0) | 1 | (1) |

## Serious adverse event/deaths/other significant events

*Serious adverse events*

SAEs that occurred in ≥ 2% of patients in the PDX-008 clinical trial are presented in descending order and by grade (all grades and ≥ Grade 3) in the table below.

**Table 30 PDX-008: SAEs ≥2% incidence**

| | PDX-008 (N = 111) | | | |
|---|---|---|---|---|
| | All Grades | | ≥ Grade 3 | |
| **Serious Adverse Events** | **n** | **(%)** | **n** | **(%)** |
| Pyrexia | 8 | (7) | 1 | (1) |
| Mucosal inflammation (grouped) | 6 | (5) | 6 | (5) |
| Febrile neutropenia | 5 | (5) | 5 | (5) |
| Sepsis | 5 | (5) | 4 | (4) |
| Dehydration | 4 | (4) | 2 | (2) |
| Dyspnoea | 4 | (4) | 4 | (4) |
| Herpes zoster | 3 | (3) | 3 | (3) |
| Neutropenia (grouped) | 3 | (3) | 2 | (2) |
| Pneumonia | 3 | (3) | 2 | (2) |
| Thrombocytopenia (grouped) | 3 | (3) | 3 | (3) |
| Abdominal pain | 2 | (2) | 1 | (1) |
| Cerebral infarction | 2 | (2) | 2 | (2) |
| Fatigue | 2 | (2) | 2 | (2) |
| Hypotension | 2 | (2) | 2 | (2) |
| Renal failure acute | 2 | (2) | 2 | (2) |
| Skin ulcer | 2 | (2) | 0 | (0) |
| Urinary tract infection | 2 | (2) | 2 | (2) |

The most common treatment-related SAEs reported in the PDX-008 study were mucosal inflammation and pyrexia (both 5%), and febrile neutropenia (4%). Treatment-related SAEs of grade 4 were reported due to thrombocytopenia (3%), mucosal inflammation and sepsis (both 2%).

In all studies (n=574), treatment-related SAEs of any grade were reported in 117 patients (20%); the most commonly reported were mucosal inflammation (9%), febrile neutropenia, pyrexia, and thrombocytopenia (all 2%). Tumour lysis syndrome occurred in 4 patients in the clinical trials of pralatrexate, whereof 3 patients with PTCL.

*Deaths*

In the pivotal study there were 8 deaths (7%), during the study or within 30 days of treatment. Seven deaths were due to disease progression and one (<1%) due to cardiopulmonary arrest.

In the entire safety population, 6 deaths were considered to be at least possibly related to study treatment, including 3 in patients with PTCL: Two related to neutropenia and one due to whole body desquamation.

*Serious dermatological reactions*

Among the 689 patients who received at least 1 dose of pralatrexate across all clinical studies, 346 patients (50%) experienced at least 1 AE regardless of causality within the skin and subcutaneous tissue disorders SOC. The most common of these dermatological AEs include alopecia (12%), pruritus (7%), and rash (7%).

Six cases in both clinical study and post-approval environments resulted in a fatal outcome. These severe events generally occurred after the first dose in patients with extensive skin disease and were generally associated with other adverse events including mucositis, neutropenia, and/or infection and included extensive skin involvement with both lymphoma and the subsequent dermatological reaction. These dermatological events included skin exfoliation, ulceration, and toxic epidermal necrolysis.

Twenty seven patients (4%) reported a grade 3-5 AE in the skin and subcutaneous tissue disorders SOC; grade 3-5 treatment-related dermatological AEs occurred in 23 patients overall (3%), those that occurred in > 1 patient included pain of skin, pruritus, and skin ulcer in 3 patients each (< 1%), and exfoliative rash, palmar-plantar erythrodysaesthesia syndrome, skin lesion, and toxic skin eruption in 2 patients each (< 1%). Fifteen patients across all studies reported dermatological SAEs and an additional 2 patients reported nonserious dermatological AEs that were discussed in the context of nondermatological SAEs. Thus, 17 patients in a total of 689 patients across all studies were considered as having experienced important dermatological reactions which corresponds to an incidence of approximately 2.5%.

In PDX-008, 7 patients (6%) reported Grade 3 events and no patients reported Grade 4-5 dermatological AEs. Grade 3 treatment-related dermatological AEs occurred in 6 patients (5%), including 2 patients with skin ulcer, 1 patient with erythematous rash and pruritic rash, and 1 patient each with pruritus, skin lesion, and urticaria. Two patients (2%) reported dermatological SAEs; both were hospitalisations for skin ulcer management (one was a Grade 1 treatment-related report and the other was a Grade 2 non-treatment-related reported).

*Thromboembolic cases*

Five thromboembolic SAEs were reported in PDX-008. All 5 SAEs were Grade 3-4 in severity, and 4 of 5 were assessed by the investigator as not related to pralatrexate. The SAE of pulmonary embolus was assessed by the investigator as possibly related to pralatrexate.

Based on the information provided, 1 patient had complete SAE resolution, 1 patient's condition improved, and the other 3 patients were discharged. One patient had a cerebral infarction that was treated with aspirin, resulting in resolution of all symptoms, and one patient had a subclavian thrombosis that was treated with heparin and warfarin, and the condition subsequently improved and the patient was discharged.

Two patients were reported as continuing on pralatrexate treatment, 2 patients were noted as having pralatrexate discontinued, and 1 patient had been previously discontinued from pralatrexate for progression of disease (PD). This patient received the last dose of pralatrexate 22 days prior to SAE onset, was permanently discontinued from the study 8 days prior to SAE onset, and had received subsequent therapy for the lymphoma (gemcitabine) 2 days prior to SAE onset.

*Respiratory disorders*

The SAEs of special interest involving respiratory disorders identified from the PDX-008 study included dyspnoea, exertional dyspnoea, and pneumonitis. There were 6 SAEs identified occurring in 5 patients, including 4 events of dyspnoea, all ≥ grade 3, considered not related to pralatrexate, 1 event of exertional dyspnoea considered possibly related to pralatrexate but likely due to lymphomatous infiltration of the lung, and 1 event of pneumonitis with suspicion of hypersensitivity aetiology. There were no reported findings of peripheral blood eosinophilia in any of these patients associated with the SAEs of dyspnoea, exertional dyspnoea, or pneumonitis.

However, there were insufficient data provided in the reporting of the SAEs to thoroughly evaluate specific diagnostic criteria for acute or chronic interstitial pneumonitis.

*Renal Failure*

There were 2 renal failure serious adverse events (SAEs) of special interest identified from the pivotal study PDX-008. Both cases were Grade 3-4 in severity and were assessed by the investigator as not related to pralatrexate. One case resulted in death and the other resulted in discontinuation of pralatrexate treatment due to disease progression (PD). In neither case was there any evidence of acute renal failure due to a renal toxic effect of pralatrexate.

## Laboratory findings

*Haematology*

In the PDX-008 study, clinically significantly reduced (defined as those ≥ grade 2 and represented a shift of ≥ 1 grade from the baseline value) neutrophil and platelet counts were reported for 49 (44%) and 53 (48%) patients, respectively. In total, 21 patients (19%) had Grade 3 neutrophil counts and 10 patients (9%) had Grade 4 counts; 17 patients (15%) had Grade 3 platelet counts and 25 patients (23%) had Grade 4 counts.

Five patients (5%) had platelet counts at some point during the study of < 10,000 µL. Two of these 5 patients discontinued study treatment due to thrombocytopenia. Two patients had their dose reduced to 20 mg/m$^2$, yet continued to experience Grade 3-4 thrombocytopenia, 1 patient had his dose reduced to 20 mg/m$^2$ and never experienced > Grade 2 thrombocytopenia with subsequent dosing, and 1 patient discontinued study treatment due to PD during the thrombocytopenia occurrence. Clinically significantly reduced haemoglobin levels were reported in 41% of the patients.

Overall, the frequency of decreased blood cell counts was higher in patients with lymphoproliferative malignancies than in patients with solid tumours.

*Clinical chemistry*

The clinical chemistry abnormality profile suggests a hepatotoxic potential of pralatrexate. The most frequent was increased aspartate aminotransferase (AST) in 19 patients (17%) and alanine aminotransferase (ALT) in 18 patients (16%). In total, 7 patients (6%) had Grade 3 ALT values. However, no grade 4 liver enzyme abnormalities were reported in the PDX-008 study. AST changes were very similar. In total, 3 patients (3%) had Grade 3 bilirubin values and 1 patient (1%) had Grade 4.

Elevated creatinine levels were reported in all studies, but at low frequencies. In total, 2 patients (2%) had Grade 3 creatinine values and 1 patient (1%) had Grade 4. Hypocalcaemia was reported in 23% of the combined PDX-02-078 and PDX-010 safety population.

*Cardiology*

A clinical QTc assessment was completed in a subgroup of 14 evaluable patients who received pralatrexate doses of 190 or 230 mg/m$^2$ every 2 weeks over 3-5 minutes or over 1 hour in the completed Phase 1 clinical trial of patients with previously treated NSCLC (PDX-007). The information provided did not raise any major cardiac safety concerns.

## Safety in special populations

Safety of pralatrexate has not been evaluated in patients with hepatic impairment or moderate and severe renal impairment.

In relation to age, patients over 65 years experienced more mucosal inflammation (85% vs. 62%) and epistaxis (38% vs. 20%) than patients below 65 years.

Female patients experienced more thrombocytopenia (57% vs. 33%) and anaemia (46% vs. 29%) than male patients.

No study data of pralatrexate are available in pregnant women or in subjects under 18 years old.

## Safety related to drug-drug interactions and other interactions

No formal clinical assessments of pharmacokinetic drug-drug interactions between pralatrexate and other medicinal products have been conducted.

In a phase 1 study with pralatrexate, co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure.

Due to the substantial contribution of renal excretion (approximately 34%; PDX-008) to the overall clearance of pralatrexate, concomitant administration of medicinal products that are subject to substantial renal clearance (e.g. NSAIDs, trimethoprim/sulfamethoxazole) could potentially result in delayed clearance of pralatrexate.

## Discontinuation due to adverse events

Twenty-six patients (23%) withdrew from pralatrexate treatment due to an AE as listed in PDX-008, Table 30. The timing of the patients' withdrawals due to AEs varied. Four patients withdrew after 1 dose of pralatrexate. However, 12 patients did not withdraw due to AEs until after cycle 1, including 4 patients who remained on treatment for > 6 months prior to withdrawal. Most reasons for discontinuation correspond to the most common severe toxicities seen in the safety population.

**Table 31 PDX-008: AEs responsible for treatment withdrawal**

| Adverse Event Term Listed | Total Number of Patients | Relationship to Pralatrexate |
|---|---|---|
| Mucosal inflammation | 7 | Related (all) |
| Thrombocytopenia | 4 | Related (all) |
| Neutropenia | 2 | Related (both) |
| CMV colitis | 1 | Related |
| Renal failure | 1 | Not related |
| Pyrexia | 1 | Related |
| Liver function test abnormal | 1 | Related |
| Bile duct cancer | 1 | Not related |
| Cardiopulmonary arrest | 1 | Related |
| Nausea | 1 | Related |
| Pain | 1 | Related |
| Pulmonary embolism | 1 | Related |
| Pneumonia | 1 | Not related |
| Pneumonitis | 1 | Related |
| Urticaria | 1 | Related |
| Thrombosis | 1 | Not related |

## Post marketing experience

Pralatrexate has been commercially available in the US since accelerated approval was granted on 24 September 2009 for the treatment of relapsed or refractory PTCL. Based on product distribution data, the potential exposure in the post-marketing setting is estimated to be 1,157 to 2,025 patients. Review of Post-Marketed Safety Surveillance data from the last 2 years demonstrated that spontaneously reported AEs in the post-marketing setting were consistent with or related to events reported in clinical studies.

## 2.6.1. Discussion on clinical safety

The safety database presented in this application included data on 689 patients who were treated with pralatrexate across all clinical studies, of which 141 patients with relapsed/refractory PTCL who received single-agent pralatrexate (PDX-008 = 111 patients; PDX-02-078 = 30 patients). In addition, post-marketing experience in the USA is estimated include 1,157 to 2,025 patients. Overall, the total exposure of pralatrexate is approximately 1,298 to 2,166 patients in the requested indication. Although the presented safety discussion lack the solidity of randomised data it is considered that that the safety database, including the experience from performed studies as well as the postmarketing setting, is reasonably sufficient to allow to determine the toxicity profile..

The overall frequency of adverse events was high. Most reported side effects of pralatrexate, including bone marrow suppression and mucositis, are class-specific and thereby expected. Although generally manageable, erious events and also deaths related to these terms occurred. In this setting of possible long-term treatment, the prevalence of mucosal inflammation, even at low grades, should be noted.

Across all studies covered, treatment-related SAEs occurred in 20% of patients. The most commonly reported terms were, in decreasing order, mucosal inflammation, febrile neutropenia, pyrexia, and thrombocytopenia. These terms were also the most commonly reported in the PDX-008 study, where treatment-related SAEs occurred in 25% of patients; treatment-related SAEs of grade 4 consisted of thrombocytopenia, mucosal inflammation and sepsis.

Pralatrexate treatment is associated with the risk of development of tumour lysis syndrome. Routine prophylaxis should be applied.

As of 31 January 2011, 17 cases with serious dermatological reactions in a total of 689 patients across all studies were reported, corresponding to an incidence of approximately 2.5%; within the total experience 6 deaths have been reported. Interpretation of the incidence figures is difficult without controlled data for comparison. These dermatological events included skin exfoliation, ulceration, and toxic epidermal necrolysis. Twenty seven patients (4%) reported a grade 3-5 AE in the skin and subcutaneous tissue disorders SOC; grade 3-5 treatment-related dermatological AEs occurred in 23 patients overall (3%). Clinical findings suggest exaggerated cutaneous responses to minor trauma and impaired cutaneous wound healing, and epithelial tropism with pralatrexate is possible. Notably, a toxic skin effect was also observed in patients with non-small cell lung cancer and transitional cell carcinoma, presumably without any skin involvement of the disease. An epithelial tropism with pralatrexate is possible.

Extensive skin disease and heavy pre-treatment with chemotherapy and/or radiation were identified as risk factors for development of severe dermatological reactions, The fact that severe dermatological reactions occur early in treatment, generally after the first dose (as for 5 of the 6 reported deaths), is problematic as no prodrome can be used for treatment decisions. Further vigilance is mandated and in the event of a future approval educational material for healthcare workers concerning prevention of serious dermatological reactions should be considered. Treatment with pralatrexate is associated with a risk of serious and fatal dermatological reactions that currently cannot be fully predicted or avoided. Interpretation of the incidence figures is difficult without controlled data for comparison.

Five thromboembolic SAEs were reported in PDX-008. Four of the cases were grade 3 and not considered related to study drug. The last case, a SAE of pulmonary embolus grade 4, was assessed by the investigator as possibly related to pralatrexate. It is acknowledged the pathogenesis of thromboembolic events in cancer patients are complex. In consequence the interpretation of the reason for its occurrence in the individual patient is difficult. No definitely association of an increased likelihood of thromboembolism following administration of pralatrexate has been observed.

The observed hepatotoxicity was generally manageable. However, as development of more severe hepatotoxicity from pralatrexate would limit also other treatment options for the patient, it is considered important to evaluate the possibility to prospectively identify patients that might be of increased risk for hepatotoxicity. It is acknowledged that due to the limited safety data from patients with pre-existing hepatic impairment it cannot presently be evaluated whether such patients have a greater risk to develop hepatotoxicity, or more severe hepatotoxicity, upon pralatrexate treatment than patients with pre-treatment normal hepatic function.

Elimination of the related compound methotrexate is known to be prolonged in patients with ascites or pleural effusion and it is recommended to drain ascites and pleural effusion in advance of treatment. The effect of third space compartment fluid accumulation of pralatrexate (e.g., pleural effusions, ascites, significant peripheral oedema) is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to initiation of treatment with pralatrexate.

Further key information on renal clearance of pralatrexate and the impact of renal impairment on the pharmacokinetic and safety profiles of pralatrexate will be forthcoming from 2 ongoing clinical pharmacology studies (Study PDX-016 and Study PDX-019).

### 2.6.2. Conclusions on the clinical safety

The overall frequency of pralatrexate-related AEs was high. Most reported side effects were class-specific, expected, and manageable. A high prevalence of mucositis was noted. Deaths related to treatment with pralatrexate were reported.

Treatment with pralatrexate is associated with a risk of serious and fatal dermatological reactions that currently cannot be fully predicted or avoided.

Although the presented safety discussion lack the solidity of randomised data the CHMP considered that the present safety data base, including the experience from performed studies as well as the postmarketing setting, is reasonably sufficient to allow to characterise the toxicity profile.

## *2.7. Pharmacovigilance*

### Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements provided that a deficiency was rectified.

### Risk Management Plan

The Applicant submitted a risk management plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on risk minimisation activities at this time.

## *2.8. User consultation*

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

# 3. Benefit-Risk Balance

## *Benefits*

### Beneficial effects

The single arm pivotal PDX-008 study is considered to have been well-conducted, with enrolled patients reflecting the heterogeneity of PTCL entities encountered in clinical practise, and with the individual diagnoses and response assessments centrally reviewed.

In this study, treatment of patients with relapsed or refractory PTCL with single pralatrexate induced a response (CR, CRu, or PR) in 32 of 109 (29%) evaluable study subjects. Response to pralatrexate was of relatively rapid onset, with 63% of responders observed to respond within 1 cycle of treatment as assessed by central review.

Responses were noted also in patients resistant to any previous therapy and in patients previously treated with methotrexate.

Median PFS was 106 days (95% CI, 51-146) according to central review, while 121 days (95% CI, 77-148) based on response assessed by investigator (43/109, 39%).

OS was 14.5 months (95% CI, 10.6-22.5) with a range of 1.0-24.1 months.

Median duration of response (confirmed and unconfirmed) was 306 days (95% CI, 103-not estimable) or 10.1 months, with a range of 1-673 days. Forty-four percent of the responding (confirmed and unconfirmed) patients had a duration of response in excess of 6 months.

Not predefined analyses are presented that indicate that pralatrexate induces longer PFS and, in certain analyses, higher response rate than the corresponding estimates, including TTP, seen in previous lymphoma treatment/s. These analyses are, however, associated with the weaknesses of all retrospective analyses and historical comparisons.

## Uncertainty in the knowledge about the beneficial effects

The choice of study design (single arm) as well as primary endpoint (response rate) severely hampers the interpretation of the significance of the results obtained in the PDX-008 study. It has to be pointed out, that CHMP, for this reason in the protocol assistance given clearly stated that neither the design nor the primary endpoint was acceptable for a registration study.

The first major problem is the interpretation of the study results in terms of magnitude. In the absence of generally accepted treatment recommendations and published reports of randomised studies in the setting of relapsed/refractory PTCL, there is no reference point to rely upon in the judgement of response. Results in previously published single-arm studies with other agents are also of very limited value, due mainly to small study populations with often non-comparable entities of T/NK-cell lymphoma. Similarly, registry data are for obvious reasons of limited help and cannot be used for direct comparisons. The presented historical control comparison is not acceptable as evidence of relevant efficacy. Therefore, without a comparator arm, the magnitude of response achieved with pralatrexate in the PDX-008 study cannot be critically assessed. The observed response rate cannot be considered as dramatic activity.

The second major problem relates to the interpretation of the clinical benefit of the primary endpoint, the response rate. It is actually not known whether or to what extent a response in this setting of PTCL translates into clinical benefit. Furthermore, accepted markers of clinical benefit as PFS and OS, both secondary endpoints in the pivotal study, are not possible to interpret in a single-arm design.

### *Risks*

## Unfavourable effects

Based on the data cut-offs of the 120-Day Safety Update, the clinical study safety database comprises 141 patients with relapsed/refractory PTCL who received single-agent pralatrexate (PDX-008 = 111 patients; PDX-02-078 = 30 patients). Combined with patients in the postmarketing setting (N = 1157 to 2025), the total exposure of pralatrexate is approximately 1298 to 2166 patients in the requested indication. Although the presented safety discussion lack the solidity of randomised data the CHMP considered that the present safety data base, including the experience from performed studies as well as the postmarketing setting, is reasonably sufficient to allow to characterise the toxicity profile. Mucosal inflammation (68% of patients in PDX-008) and bone marrow suppression are class-related toxicities and were commonly reported. Although severe reactions occurred and in some cases led to treatment discontinuation in the PDX-008 study, these toxicities are considered generally manageable at institutions familiar with lymphoma chemotherapy. The number and severity of neutropenia-related infections do not raise any major concern.

The clinical chemistry abnormality profile suggests a hepatotoxic potential of pralatrexate. However, no grade 4 liver enzyme abnormalities were reported in the PDX-008 study. Elevated creatinine levels were reported in all studies, but at low frequencies.

In the entire safety population, 6 deaths were considered to be at least possibly related to study treatment, whereof 3 in patients with PTCL: Two related to neutropenia and one due to whole body desquamation.

Tumour lysis syndrome was reported in one patient with CTCL and three patients with PTCL, emphasising the importance of preventive measures.

Seventeen serious cases, including cases associated with death, of dermatological reactions in a total of 689 patients across all studies correspond to an incidence of approximately 2.5%. Treatment with pralatrexate is associated with a risk of serious and fatal dermatological reactions that currently cannot be fully predicted or avoided.

## Uncertainty in the knowledge about the unfavourable effects

Safety of pralatrexate has not been evaluated in patients with hepatic or moderate and severe renal impairment.

The incidence of serious dermatological reactions may be high, but interpretation of the figures is difficult without controlled data for comparison.

### *Benefit-risk balance*

## Importance of favourable and unfavourable effects

Tumour response is not a clinical benefit endpoint *per se* and cannot be considered as an established surrogate endpoint for important clinical benefit endpoints such as PFS and OS.

The overall frequency of pralatrexate-related AEs was high. A high prevalence of mucositis was noted. Deaths related to treatment with pralatrexate were reported. Serious dermatological reactions, including cases associated with death, were observed.

## Benefit-risk balance

Tumour response is not a clinical benefit endpoint and cannot be considered as an established surrogate endpoint for important clinical benefit endpoints. Therefore, the benefits have not been established. In the absence of established benefits, a positive benefit-risk balance cannot be considered established.

### *Discussion on the benefit-risk balance*

The overall benefit-risk balance of Folotyn in the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) (nodal, other extranodal and leukaemic/disseminated) is negative.

Due to the uncontrolled design of the pivotal study, evidence of efficacy is lacking in terms of relevant clinical benefit endpoints such as OS and PFS. The baseline-controlled studies presented do not include a concurrently randomized control group. In the absence of dramatic activity, such studies have important methodological limitations due to untestable assumptions. Thus, the evidence of efficacy presented was not considered sufficient to establish a clinical benefit.

# 4. Recommendations

### *Outcome*

Based on the CHMP review of data on quality, safety and efficacy for Folotyn in the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy, the CHMP considers by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the conditional Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- In the absence of established benefits, a positive benefit-risk balance cannot be considered established.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

Divergent position to the majority recommendation is appended to this report.

# 5. Re-examination of the CHMP opinion of 19 April 2012

Following the CHMP conclusion that Folotyn was not approvable for the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy, as in the absence of established benefits a positive benefit-risk balance could not be considered established, the Applicant submitted detailed grounds for the re-examination of the grounds for refusal.

## Detailed grounds for re-examination submitted by the Applicant

Following a request from the Applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the Applicant's response.

The Applicant presented in writing and at an oral explanation the grounds that the adopted CHMP Opinion may not have considered the data fully in the proper clinical context for the purpose of assessing the clinical benefits of pralatrexate in an orphan disease setting where there is hitherto no authorised treatment available. Further analyses were provided by the Applicant to support the clinical efficacy of pralatrexate in the proposed indication.

The Applicant outlined the following detailed grounds to be taken into account during the re-examination.

**Ground 1** – The magnitude of clinical efficacy of pralatrexate in the treatment of patients with PTCL who have progressed after at least one prior therapy (relapsed/refractory PTCL) can be assessed based on the data provided. These data provide sufficient evidence to support the clinical efficacy of pralatrexate on the following basis:

- Features of the unique mechanism of action of pralatrexate have demonstrated preferential activity in T-cell lymphomas.

- Clinical efficacy in relapsed/refractory PTCL has been demonstrated in both the pivotal study, PDX-008 and the supportive Phase 1/2 study PDX-02-078.
- The clinical efficacy of pralatrexate is demonstrated in PDX-008 through the response rate (29% and 39% by central review and investigator, respectively, with a median duration of response of 12.6 months and a median duration of CR/CRu of 44.2 months), durable responses (59% and 47% of responders with > 6 and > 12 months of response duration, respectively), and clinical benefits achieved through those responses, including the improved outcomes for patients in comparison to their most immediate prior therapy, using patients as their own controls.
- The magnitude of the clinical efficacy benefit of pralatrexate is further confirmed by comparisons to historical database and matched-control analyses, in which pralatrexate demonstrated an improved overall survival (OS) outcome (hazard ratio of 0.39 [95% CI: 0.26, 0.60] and median OS of 19.0 months for pralatrexate vs. 5.8 months for matched controls). Given that the natural course of the disease is well-known and characterised, this approach should be considered appropriate to inform the assessment of clinical efficacy.

**Ground 2** – PTCL is an orphan disease with a very aggressive clinical course, and there are no therapies in the EU approved specifically for this indication; thus, pralatrexate addresses a significant unmet medical need.

**Ground 3** – Immediate patient access on the public health grounds outweighs the risk inherent in scientific uncertainties surrounding the benefit assessment.

According to the Applicant, the approach taken to conclude a positive benefit-risk balance for pralatrexate is consistent with the established principles set out in the applicable CHMP guidelines, especially the "Guideline on the Evaluation of Anticancer Medicinal Products in Man", and the "Guideline on Clinical Trials in Small Populations."

## Additional expert consultation

1. **The SAG is asked to describe how impressive they view the efficacy data to be (based on response rate, duration of response, PFS, OS) in light of the methodological limitations of the study, in particular the absence of a randomised control group, but taking into account the novel mechanism of action and observed responses in patients who were non-responders.**

   **The SAG is also asked to comment on whether the observed duration of responses are considered to be exceptional in this disease setting.**

   The SAG considered the additional analyses presented, the mechanism of action, and the observed responses in patients assessed as non responders to prior regimens. The duration of response in selected responders was considered promising. However, the SAG maintained its view that although pralatrexate has shown antitumour activity in patients with relapsed PTCL, the activity in terms of response rate appears to be in the same range of other single-agent or combination regimens which are currently used in this setting, although the efficacy of such treatment options cannot be considered established according to conventional scientific or regulatory standards.

The SAG maintained its view that there are serious concerns from the point of view of external validity in view of the design of the pivotal study, especially the non-randomised design of the study. Such design does not allow establishing the efficacy of pralatrexate in terms of relevant clinical benefit endpoints such as PFS or OS. Overall, the clinical benefit cannot be considered established and therefore the benefit cannot be considered to outweigh the risks.

2. **Do the case matched controls offer an opportunity to place the observed effect of pralatrexate into clinical context and can the magnitude of effect be considered sufficient to conclude that clinically relevant efficacy has been established?**

   The matched case control did not add convincing data to allow placing the observed effect into clinical context in terms of clinically relevant endpoints, mainly due to possible bias in patient selection in this heterogeneous disease. Similarly, the magnitude of effect was not considered sufficient in view of the possible biases. Although the matched controls analyses can be considered useful as hypothesis generating, the data are not sufficient to establish the clinical efficacy of pralatrexate in the target indication.

3. **Do the data from the Phase I study provide significant independent corroboration of an effect?**

   The phase I data showed hints of antitumour activity but the magnitude was not considered exceptional. These data in their own right were not sufficient to provide independent corroboration of an effect of pralatrexate in the target indication.

4. **Does the SAG consider that the proposal to demonstrate a 50% improvement in Overall Survival in the confirmatory study is a realistically achievable goal?**

   **If not, does the SAG consider the results of the ongoing PDX-017 study of value and supportive/confirmatory in terms of efficacy for the current indication applied for, or is there another patient group which is considered relevant for the indication applied for where a controlled study would be considered feasible to conduct?**

   The proposed trial looks for an improvement of median OS of 61% (from 9 to 14.5 months). The expected magnitude of improvement does not seem to be a realistic goal given the available data on antitumour activity.

   The results of the PDX-017 study may be of limited value for the current application, due to important differences in terms of line of therapy, patient selection, and treatment schedule. This study is not expected to be of sufficient support or to confirm the efficacy in the target indication.

   A controlled study in the target indication is considered feasible and best way to establish clinical efficacy. Considering the design and size of the study, different possible approaches (including different primary endpoints to OS) should be considered. A collaborative study and prospectively planned meta-analysis should also be considered. Scientific Advice is recommended.

## Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the Applicant and considered the views of the Scientific Advisory Group.

Regarding Ground 1, the CHMP maintained the view that without a comparator arm, the magnitude of response cannot be critically assessed. The observed activity in terms of response rate cannot be considered dramatic and it is not known whether or to what extent a response might translate into clinical benefit for this patient group.

The Applicant presented an analysis where pralatrexate appears to reverse the trend of decreasing response to successive lines of chemotherapy and decreasing median PFS. However, this type of comparison cannot be considered as convincing to establish efficacy as it relies on strong assumptions, similar to a historical comparison.

The Applicant has provided a matched historical controlled analysis, with comparisons made against OS data. The criteria specified represent key prognostic factors, but there are multiple other potential differences between a clinical trial population, who must satisfy a range of inclusion / exclusion criteria, and those historical databases which will include a broader set of patients. Inclusion criteria for a clinical trial might include a certain life expectancy and performance status; exclusion criteria might include presence of other active concurrent malignancies, cardiac problems or uncontrolled hypertension, concurrent HIV etc. Any bias introduced by these underlying differences would not be addressed in the primary analysis or either sensitivity analysis.

The Applicant has used medical review to determine the comparability of the matched groupings but the potential for bias remains, as important dissimilarity of treatment and control groups cannot be excluded. For example, it is not possible to determine whether the subjects were treated in a similar setting and manner (potential differences in compliance, concomitant and supportive treatments, adequacy of dose and treatment duration, stage or severity of disease) and thus whether the matches were comparable except for the interventions under consideration.

Overall, externally controlled trials tend to overestimate the effect of test therapies and, despite the magnitude of the effect described, the interpretation that pralatrexate improved OS in comparison to matched historical controls can be considered as hypothesis generating only because of the multiple potential biases which cannot be excluded convincingly.

With respect to Ground 2, the CHMP acknowledged that PTCL is an orphan disease with an aggressive clinical course and a poor prognosis. There are currently no approved therapies in the EU specifically for the claimed indication and there is an unmet medical need. Therefore, the committee agreed that there is a need for new therapies with established efficacy in this disease. However, the submitted clinical data for Folotyn are not considered to be sufficient to inform a favourable benefit-risk assessment. Even if there is currently no consensus on standard therapy for PTCL, the data submitted do not allow drawing any conclusion on the efficacy of Folotyn. Therefore, concerning the arguments presented by the Applicant for Ground 3 the CHMP considered that because the benefits have not been demonstrated the need for immediate access is not justified.

In conclusion, following assessment of the analyses provided in response to the grounds for refusal, the submitted data are still considered insufficient to establish the efficacy of Folotyn in patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy. Therefore, the CHMP has maintained its previous position that the efficacy has not been established.

# 6. Recommendations following re-examination

Based on the arguments of the Applicant and all the supporting data on quality, safety and efficacy for Folotyn in the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal

of the granting of the conditional Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- In the absence of established benefits, a positive benefit-risk balance cannot be considered established.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

Divergent position to the majority recommendation is appended to this report.

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**APPENDIX 1**

**DIVERGENT POSITIONS**

## DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

In general, the factual presentation of the efficacy and safety data for Folotyn for the treatment of relapsed or refractory PTCL as reflected in the Day 180 JAR is agreed with. However, another and more positive conclusion on the benefit-risk balance may be reached when looking at the possibility of a conditional approval.

**Unmet medical need and PTCL is a life-threatening disease**

It has long been recognised that the majority of PTCLs have an inferior prognosis compared with their B-cell counterparts. The standard therapy for PTCLs is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or a comparable CHOP-like regimen that incorporates anthracyclines. With the exception of anaplastic lymphoma kinase–positive anaplastic large cell lymphoma (ALK+ ALCL), the cure rate for PTCLs with CHOP is low with a long-term survival of only 10% to 30%. It has been suggested that anthracyclines may not be effective in PTCL due to inherent overexpression of P-glycoprotein (Pgp) which is known to contribute to anthracycline resistance.

As stated in the ASH (American Society of Haematology) Education Book p.514-25, December 2011, several experts question the adequacy of regimens building on a CHOP backbone in the first-line setting since neither the shortening of the treatment interval from CHOP21 to CHOP14 or the addition of etoposide to CHOP have improved OS. The addition of alemtuzumab to CHOP has increased toxicity without improving the prognosis. The inclusion of HD-Chemotherapy + HSCT as consolidation has resulted in conflicting results in terms of cure rate.

First-line combinations that bypass the Pgp efflux pump are now being investigated. Pralatrexate may have an interesting mechanism of action in that respect.

In conclusion first-line therapy for PTCL appears to be inadequate in terms of long-term disease-free survival.

If the first-line therapy is inadequate and exhausts most of the available classical cytostatics in that setting, the treatment results of second-line or later line therapy are so dismal that the US National Comprehensive Cancer Network (NCCN) Guideline for relapsed/refractory PTCL (2009) states that clinical trials are the preferred option in both first and second relapse.

Thus, the high medical need for new medicines for the treatment of patients with PTCL cannot be questioned.

**Positive Risk/Benefit Balance**

In contrast to the CHMP Scientific Advisory Group for Oncology, it is the opinion of the divergent CHMP members that an ORR of about 30% (and 11% in CR/CRu) for a single agent in patients with PTCL is comparable to the activity of other classical approved cytostatics when used as single agents. The 11% CR patients had a median duration of response of 44 months and some of these patients may be candidates for curative high-dose therapy with haematopoietic stem cell support. Moreover, pralatrexate has a new mechanism of action that most probably makes it suitable for use in combination with other anticancer agents. The apparent selective activity in T-cell lymphomas (O.A. O'Connor et al. J Clin Oncol 2009; 27:4357-64) is also of clinical interest.

It is not to be expected that any new single agent therapy will dramatically change the prognosis in advanced aggressive non-Hodgkin's lymphoma where 4-5 drug combinations have been standard of care for more than 30 years.

A median duration of response of 10.5 months and a median overall survival of 14.5 months for the 109 patients included in the phase II trial PDX-008 are strong indicators of clinical benefit even if it is fully acknowledged that additional [comparative] data are still required.

The safety profile of pralatrexate, although not trivial, is sufficiently well described from the submitted clinical trials as well as the post-marketing experience outside the EU to allow a benefit/risk judgment.

Therefore, in the opinion of the divergent CHMP members the benefits to public health of making pralatrexate immediately available on the market outweigh the risk inherent in the fact that additional data are still required.

**Conditional Marketing authorisation**

In accordance with Regulation (EC) No 726/2004, conditional marketing authorisations will be valid for one year on a renewable basis. In the case of the conditional marketing authorisation, authorisation is granted before all data are available. The applicant at the CHMP oral explanation and at the CHMP Scientific Advisory Group for Oncology hearing confirmed that the PDX-3501 randomised, controlled in relapsed/refractory PTCL comparative trial planned for initiation by Q2 2012 would be feasible. The divergent CHMP members are of the opinion that this trial together with other trials in the ongoing clinical development programme for pralatrexate will provide the required additional data within a reasonable period of time taking into consideration the orphan indication.

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| Jens Heisterberg | Catherine Moraiti |
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| Natalja Karpova | Pieter Neels |
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| Romaldas Mačiulaitis | Outi Mäki-Ikola |