

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-468**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	September 24, 2009
<b>From</b>	Robert L. Justice, M.D., M.S.
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	22-468
<b>Supplement #</b>	
<b>Applicant Name</b>	Allos Therapeutics, Inc.
<b>Date of Submission</b>	March 23, 2009
<b>PDUFA Goal Date</b>	September 24, 2009
<b>Proprietary Name / Established (USAN) Name</b>	FOLOTYN/ Pralatrexate injection
<b>Dosage Forms / Strength</b>	Sterile, single-use vials containing pralatrexate 20 mg/mL; 20 mg/1 mL and 40 mg/2 mL
<b>Proposed Indication(s)</b>	FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression free survival or overall survival has not been demonstrated.
<b>Action/Recommended Action for NME:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Shakun Malik
Statistical Review	Qiang Xu, Shenghui Tang
Pharmacology Toxicology Review	W. David McGuinn, S. Leigh Verbois, John Leighton
CMC Review/OBP Review	Sue-Ching Lin, Sarah Pope Miksinski, Rik Lostritto
Microbiology Review	Steven E. Fong
Clinical Pharmacology Review	Gene Williams
DDMAC	Karen Rulli
DSI	Robert Young
CDTL Review	Ke Liu
OSE/ DMEPA	Zachary Oleszczuk
OSE/DDRE	N/A
OSE/ DRISK	N/A
Other	N/A

OND=Office of New Drugs  
DDMAC=Division of Drug Marketing, Advertising and Communication  
OSE= Office of Surveillance and Epidemiology  
DMEPA=Division of Medication Error Prevention and Analysis  
DSI=Division of Scientific Investigations  
DDRE= Division of Drug Risk Evaluation  
DRISK=Division of Risk Management  
CDTL=Cross-Discipline Team Leader

## Division Director Summary Review

### 1. Introduction

This new drug application seeks approval of FOLOTYN (pralatrexate injection) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). The NDA was received on March 24, 2009 and was granted a priority review. This review will briefly summarize the study design, the efficacy and safety results, the recommendations of each review discipline, and the PMR's and PMC's.

### 2. Background

Pralatrexate is a folate analogue metabolic inhibitor that competitively inhibits dihydrofolate reductase. It is also a competitive inhibitor for polyglutamylation by the enzyme foyllypolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other biological molecules the synthesis of which depends on single carbon transfer.

The application is based on a single study which was conducted under a special protocol assessment agreement. Because of the rarity of PTCL and the absence of effective therapies for patients with relapsed or refractory PCTCL it was agreed that depending on the magnitude of the response rate, the duration of response, and the risk benefit ratio, a single study in at least 100 patients may be sufficient to support approval.

### 3. CMC/Device

The Chemistry Review made the following recommendation and conclusion on approvability.

**From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending "acceptable" overall recommendations from both the Office of Compliance and the Microbiology reviewer.**

**Based on the provided stability data, a 12-month expiration dating period is granted for the drug product when stored in the original carton under the proposed refrigerated condition.**

The ONDQA Division Director's Memo stated the following:

**There are no outstanding CMC deficiencies from ONDQA. However, the Microbiology review and overall EES recommendation are pending as of this writing. Thus, ONDQA's recommendation for APPROVAL is pending a satisfactory outcome from the Product Quality Microbiology review and EES.**

The final CMC recommendation concluded the following:

**All CMC deficiencies have been resolved, and there are no outstanding issues with this NDA. Therefore, approval of NDA 22-468 is recommended from a CMC perspective.**

The Product Quality Microbiology Review recommended approval from a microbiology quality standpoint.

*I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 12 months. There are no outstanding CMC issues.*

#### **4. Nonclinical Pharmacology/Toxicology**

The Pharmacology/Toxicology Review and Evaluation stated that “There are no toxicology issues that would prevent approval of pralatrexate for use in the proposed indication.”

The Supervisory Pharmacologist’s memo concurred with the reviewer’s recommendation and stated that “There are no outstanding nonclinical issues related to the approval of FOLOTYN for the proposed indication.”

The Associate Director for Pharmacology concurred with the conclusions that Folutyn may be approved.

*I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval.*

#### **5. Clinical Pharmacology/Biopharmaceutics**

The Clinical Pharmacology and Biopharmaceutics NDA Review stated that “This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.” The review recommended two post-marketing requirements.

1. a clinical study in patients with renal impairment to include patients with severe renal impairment, and
2. completion of the planned mass balance study, and contingent on FDA judgment of the mass balance results, a study in patients with hepatic impairment.

The review also recommended one post-marketing commitment.

**We recommend a post-marketing commitment to perform *in vitro* experiments to learn if transporters are involved in the elimination of pralatrexate.**

The IRT QT Study Review provided the following overall summary of findings:

This was a Phase 1, non-randomized, open-label, two-center study designed to determine the maximal tolerated dose (MTD) of pralatrexate. Triplicate ECGs at pre-specified time points were collected in 14 patients who received pralatrexate at doses of 190 or 230 mg/m<sup>2</sup> administered every 2 weeks over 3-5 minutes or over 1 hour in three treatment cohorts. When data from all cohorts were combined, the upper bound of the two-sided 90% CI for QTcF change from Pre-injection was <10 ms. No patient exhibited a QTcF interval >500 msec. No major changes in HR, PR interval, or QRS interval duration were noted.

The review made the following comments:

- Because the doses studied in this trial are at-least 6-fold greater than the proposed therapeutic dose for PTCL (30 mg/m<sup>2</sup>), 14 subjects (pooled dose analysis) are adequate to rule out large direct effects (>20 ms) on the QT interval.

- [REDACTED] (b) (4)

*I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. I also concur with the clinical pharmacology postmarketing study requirements and commitment.*

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical-Efficacy**

The design and results of the single clinical trial submitted in support of the indication is summarized in the following excerpt from the Clinical Studies section of the agreed-upon package insert:

The safety and efficacy of FOLOTYN was evaluated in an open-label, single-arm, multicenter, international trial that enrolled 115 patients with relapsed or refractory

PTCL. One hundred and eleven patients were treated with FOLOTYN at 30 mg/m<sup>2</sup> once weekly by IV push over 3-5 minutes for 6 weeks in 7-week cycles until disease progression or unacceptable toxicity. Of the 111 patients treated, 109 patients were evaluable for efficacy. Evaluable patients had histologically confirmed PTCL by independent central review using the Revised European American Lymphoma (REAL) World Health Organization (WHO) disease classification, and relapsed or refractory disease after at least one prior treatment.

The primary efficacy endpoint was overall response rate (complete response, complete response unconfirmed and partial response) as assessed by International Workshop Criteria (IWC). The key secondary efficacy endpoint was duration of response. Response assessments were scheduled at the end of cycle 1 and then every other cycle (every 14 weeks). Duration of response was measured from the first day of documented response to disease progression or death. Response and disease progression were evaluated by independent central review using the IWC.

The median age of treated patients was 59.0 years (range 21-85); 68% were male and 32% were female. Most patients were White (72%) and other racial origins included: Black (13%), Hispanic (8%), Asian (5%), other and unknown (<1% each). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status at study entry of 0 (39%), 1 (44%), or 2 (17%). The median time from initial diagnosis to study entry was 15.6 months (range 0.8 – 322.3).

The median number of prior systemic therapies was 3 (range 1-12). Approximately one-fourth of patients (24%, n = 27) did not have evidence of response to any previous therapy. Approximately two-thirds of patients (63%, n = 70) did not have evidence of response to their most recent prior therapy before entering the study.

In all evaluable patients (n = 109) treated with FOLOTYN, the response rate, as determined by independent central review by IWC, was 27% (n = 29) (Table 5).

**Table 5 Response Analysis per Independent Central Review (IWC)**

	Evaluable Patients (N=109)		Median Duration of Response	Range of Duration of Response
	N (%)	95% CI		
<b>Overall Response</b>				
CR+CRu+PR	29 (27)	19, 36	287 days (9.4 months)	1-503 days
CR/CRu	9 (8)			
PR	20 (18)			
<b>Responses ≥ 14 weeks</b>				
CR+CRu+PR	13 (12)	7, 20	Not Reached	98-503 days
CR/CRu	7 (6)			
PR	6 (6)			

Fourteen patients went off treatment in cycle 1; 2 patients were unevaluable for response by IWC due to insufficient materials provided to central review.

CR = Complete Response, CRu = Complete Response unconfirmed,  
PR = Partial Response

The initial response assessment was scheduled at the end of cycle 1. Of the responders, 66% responded within cycle 1. The median time to first response was 45 days (range 37-349 days).

The Clinical Review made the following recommendation on regulatory action:

**I recommend an accelerate approval for pralatrexate as a single agent in the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).**

**My recommendation is based on the following:**

- **There is no therapy approved or standard of care for patients with relapsed or refractory PTCL.**
- **The trial showed a response rate (RR) of 27% in 109 evaluable patients. Twelve percent (12%) of responses lasted  $\geq$  14 weeks with 6% complete responses (CRs).**
- **These patients were previously heavily pretreated with 16% of patients who had received peripheral stem cell transplant prior to the pralatrexate treatment.**
- **This application was discussed in the Oncology Drug Advisory Committee (ODAC) September 2009 meeting. The committee members voted 10 Yes to 4 No to the question "Are the response rate and duration of response results were "reasonably likely" to predict for clinical benefit?"**

The review provided the following risk benefit assessment:

**Although the trial supporting this application was a single arm, non-randomized trial, the magnitude of pralatrexate treatment, i.e., 27% response rate with 12% of responses lasting 14 weeks or more, most likely predicts clinical benefit in patients with PTCL.**

**The most common grade 3 and 4 toxicities were thrombocytopenia, mucositis and neutropenia. The toxicity profile of pralatrexate treatment was found to be acceptable, not different from that of methotrexate, a similar drug of the class of folate analogue metabolic inhibitor.**

**Taken together, the data submitted in this application demonstrated a favorable benefit:risk profile for pralatrexate treatment in patients with relapsed or refractory PTCL.**

The Clinical Review also made the following recommendations for postmarketing study requirements:

To confirm the clinical benefits of pralatrexate treatment and to fulfill the requirement for the recommended accelerated approval, the following postmarket requirements are recommended:

Submit clinical protocols for at least two trials to confirm the clinical benefit of pralatrexate treatment in patients with peripheral T-cell lymphoma (PTCL) with trial end dates and projected dates for the submission of final study reports.

1. One trial can be the proposed randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.
2. Another trial could be a randomized controlled trial of single agent pralatrexate vs. an appropriate control in patients with relapsed or refractory PTCL.

The Statistical Review and Evaluation made the following conclusions and recommendations:

There are no approved agents for treatment of relapsed or refractory PTCL, thus there is an unmet medical need for new agents. The response rate reported by the sponsor was 27% (95% CI: 19-36%). However, due to the major concerns elaborated in Section 3.1.5, the duration of response cannot be accurately estimated by Kaplan-Meier method. Instead, the FDA proposed a response rate for those responses being confirmed to last at least 14 weeks, and such durable response rate was 12% (95% CI: 17-20%). An ODAC meeting was held on Sep 2, 2009 to discuss whether or not the results of this single arm trial demonstrate a favorable benefit-risk profile for pralatrexate in the treatment of patients with refractory or relapsed PTCL. The ODAC voted in favor of the approval of pralatrexate (10 vs 4) as there is an unmet need in this population, and believed that pralatrexate may produce durable response in a small subpopulation of PTCL patients.

The Statistical Team Leader's review stated the following:

This Team Leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Qiang Xu) of this application. The inference regarding favorable benefit-risk profile for pralatrexate in the treatment of patients with refractory or relapsed PTCL based on one single arm trial is deferred to the clinical review team.

The Cross-Discipline Team Leader Review made the following recommendations and risk benefit assessment.

- **Recommended Regulatory Action**

I recommend an accelerated approval for pralatrexate as single agent in the treatment of patients with relapsed or refractory PTCL

- **Risk Benefit Assessment**

My recommendation is based on the following:

- There is no therapy approved or standard of care for patients with relapsed or refractory PTCL.
- The trial showed a response rate (RR) of 27% in 109 evaluable patients. Twelve percent (12%) of responses lasted  $\geq 14$  weeks with 6% complete responses (CRs).
- These patients were previously heavily pretreated with 16% of patients who had received peripheral stem cell transplant prior the pralatrexate treatment.
- This application was discussed in the Oncology Drug Advisory Committee (ODAC) September 2009 meeting. The committee members voted 10 yes to 4 no on the question "Are the response rate and duration of response results were "reasonably likely" to predict for clinical benefit?"

Although the trial supporting this application was a single arm non-randomized trial, the magnitude of pralatrexate treatment, i.e., 27% response rate with 12% of responses lasting 14 weeks or more, was considered to most likely predict clinical benefit in patients with PTCL, a rare disease without currently available therapies.

The most common grade 3 and 4 toxicities were thrombocytopenia, mucositis and neutropenia. The toxicity profile of pralatrexate treatment was found to be acceptable, not different from that of methotrexate, a similar drug of anti-metabolite class.

Taken together, the data submitted in this application demonstrated a favorable benefit:risk profile for pralatrexate treatment in patients with relapsed or refractory PTCL.

The CDTL review recommended the following studies to confirm the clinical benefit of pralatrexate.

- A) One trial can be the proposed randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.
- B) Another trial could be a randomized controlled trial of single agent pralatrexate vs. an appropriate control in patients with relapsed or refractory PTCL.

## 8. Safety

The following summary of safety is excerpted from the adverse reactions section of the agreed-upon package insert. The most common adverse reactions in PTCL were mucositis, thrombocytopenia, nausea, and fatigue.

The safety of FOLOTYN was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m<sup>2</sup> once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range 1-540 days).

### *Most Frequent Adverse Reactions*

Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

**Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥ 10% of patients)**

Preferred Term	N=111					
	Total		Grade 3		Grade 4	
	N	%	N	%	N	%
Any Adverse Event	111	100	48	43	34	31
Mucositis <sup>a</sup>	78	70	19	17	4	4
Thrombocytopenia <sup>b</sup>	45	41	15	14	21	19 <sup>b</sup>
Nausea	44	40	4	4	0	0
Fatigue	40	36	5	5	2	2
Anemia	38	34	17	15	2	2
Constipation	37	33	0	0	0	0
Pyrexia	36	32	1	1	1	1
Edema	33	30	1	1	0	0
Cough	31	28	1	1	0	0
Epistaxis	29	26	0	0	0	0
Vomiting	28	25	2	2	0	0
Neutropenia	27	24	14	13	8	7
Diarrhea	23	21	2	2	0	0
Dyspnea	21	19	8	7	0	0
Anorexia	17	15	3	3	0	0
Hypokalemia	17	15	4	4	1	1
Rash	17	15	0	0	0	0
Pruritus	16	14	2	2	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal <sup>c</sup>	14	13	6	5	0	0
Abdominal pain	13	12	4	4	0	0
Pain in extremity	13	12	0	0	0	0
Back pain	12	11	3	3	0	0
Leukopenia	12	11	3	3	4	4
Night sweats	12	11	0	0	0	0
Asthenia	11	10	1	1	0	0
Tachycardia	11	10	0	0	0	0
Upper respiratory tract infection	11	10	1	1	0	0

<sup>a</sup> Stomatitis or Mucosal Inflammation of the gastrointestinal and genitourinary tracts.

<sup>b</sup> Five patients with platelets < 10,000/μL

<sup>c</sup> Alanine Aminotransferase, Aspartate Aminotransferase, and Transaminases Increased

### ***Serious Adverse Events***

Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (> 3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m<sup>2</sup>.

### ***Discontinuations***

Twenty-three percent of patients (n = 25) discontinued treatment with FOLOTYN due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6%, n = 7) and thrombocytopenia (5%, n = 5).

### ***Dose Modifications***

The target dose of FOLOTYN was 30 mg/m<sup>2</sup> once weekly for 6 weeks in 7-week cycles. The majority of patients (69%, n = 77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

The Warnings and Precautions section of the label includes sections on bone marrow suppression, mucositis, the need for folic acid and B<sub>12</sub> supplementation, the potential for fetal harm, and the need for caution in patients with renal impairment or persistent liver function abnormalities.

## **9. Advisory Committee Meeting**

The outcome of the advisory committee meeting is summarized in the following excerpt from the CDTL review.

An oncologic drug advisory committee meeting (ODAC) was held on September 2, 2009 to discuss the clinical significance of the overall response rate and duration of response as well as the benefit:risk ratio for pralatrexate treatment in patients with relapsed or refractory PTCL. The committee was asked the following question: "Are the response rate and duration of response results "reasonably likely" to predict for clinical benefit? Clinical benefit in lymphomas would be defined as an improvement in overall survival or a robust effect on progression-free survival." The committee voted 10 Yes to 4 No.

## **10. Pediatrics**

Pralatrexate has orphan drug designation and is exempt from PREA.

## 11. Other Relevant Regulatory Issues

- The DSI Clinical Inspection Summary concluded the following.

The clinical investigators, Drs. Horowitz and Pro, and the sponsor, Allos Therapeutics, were inspected in support of this application. Although regulatory deviations were noted during Dr. Pro and Allos Therapeutics' inspections, the noted deficiencies are unlikely to impact data integrity. Data from these sources may be used in support of the pending application.

- Financial disclosure was discussed in the Clinical Review.
- DDMAC recommendations were discussed during the labeling meetings.

*There are no other unresolved relevant regulatory issues.*

## 12. Labeling

Includes:

- Proprietary name

The proprietary name was found to be acceptable.

- Physician labeling

Agreement was reached on the physician labeling. There were no major issues of disagreement.

- Carton and immediate container labels

DMEPA had recommendations regarding the carton and container labels. These were incorporated into the final labels.

- Patient labeling/Medication guide

Not required.

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

I concur with the reviewers' recommendation for accelerated approval and the conclusions that the benefits of pralatrexate outweigh the risks in patients with relapsed or refractory PTCL. ODAC felt that the results of the study were reasonably likely to predict for clinical benefit, such as an improvement in overall survival or a robust improvement in progression-free survival. There is currently no therapy approved for this orphan indication. Although the proportion of responses lasting at least 14 weeks was only 12% (6% CR/CRu), the durations of these responses in a very heavily pretreated population ranged from 98-503 days. The toxicities associated with pralatrexate therapy were no worse than those of other cytotoxic agents which would be used in these patients.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None recommended.

- Recommendation for other Postmarketing Requirements and Commitments

The trials to confirm the clinical benefit of pralatrexate under subpart H were discussed in a telecon with the applicant. It was agreed that at least one confirmatory trial would be conducted in PTCL and that another trial could be conducted in another lymphoma population such as CTCL. The following are the subpart H PMR's.

**1 A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.**

Description of trial: This will be a Phase 3 multi-center, randomized clinical trial of sequential FOLOTYN versus observation in patients with newly diagnosed aggressive peripheral T-cell lymphoma who have responded following initial treatment with CHOP-based chemotherapy. The primary endpoint will be progression-free survival (PFS). The trial will also be sized to detect a realistic difference in survival. Patients will be enrolled prior to initiation of the CHOP-based regimen. Patients responding (CR or PR) after CHOP-based treatment will then be randomized 2:1 to FOLOTYN versus observation.

- 2 A randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with cutaneous T-cell lymphoma (CTCL) who are refractory to at least one prior systemic therapy.

Description of trial: This will be a Phase 3 multi-center, randomized clinical trial in patients with CTCL. The primary endpoint will be progression-free survival (PFS). Response rate will be a secondary endpoint. Prior to initiation of the Phase 3 trial, a Phase 1 trial will be conducted to determine the maximum tolerated dose (MTD) of the combination.

The following are PMR's under section 505(o). The trials are required to determine the effects of renal and hepatic impairment.

- 3 A clinical pharmacokinetic trial in patients with renal impairment to include patients with severe renal impairment.

Description of trial: This will be a Phase 1 clinical trial to evaluate the pharmacokinetics of pralatrexate in relapsed/refractory lymphoma patients (B-cell, T-cell, and Hodgkin's Lymphoma) with mild to severe renal impairment. Three cohorts (N=6 per cohort) will be enrolled in this study for a total of 18 patients. Cohorts will be based on the severity of renal impairment, i.e., cohort A = severely impaired (Creatinine clearance Cockcroft-Gault (CrCl C-G) < 30 mL/min), cohort B = moderately impaired (CrCl C-G = 30-50 mL/min), and cohort C = mildly impaired patients (CrCl C-G = 50-80 mL/min). The pralatrexate dose for cohorts A and B will be determined based on the pharmacokinetics experience from the PROPEL study. Cohort C will be dosed at the recommended dose (30 mg/m<sup>2</sup>) since patients with mild renal impairment were included in the PROPEL trial. Patients will undergo extensive plasma and urine collections following the first dose of FOLOTYN.

- 4 Completion of the planned mass balance trial. Contingent on FDA review of the mass balance results, a clinical pharmacokinetic trial in patients with hepatic impairment may be required.

Description of trial: This is an ongoing Phase 1 mass balance clinical trial to evaluate the excretion and metabolic profile of pralatrexate. Patients will receive a fixed dose of 225 mg radio-labeled pralatrexate. Patients will undergo intense sampling of blood, urine, feces, expired air, and other incidental excreta as needed for up to 7 days. Analysis of the samples will be done by liquid scintillation counting for mass balance determination and HPLC for metabolite profiling. Pralatrexate diastereomer concentrations in plasma and urine will be determined in parallel using a validated LC-MS/MS method.

In addition, the applicant agreed to the following PMC:

5. Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

Description of study: This will be an *in vitro* study to determine whether pralatrexate is a substrate for the organic anion transporter (OAT) family, including but not limited to OAT1 and OAT3, and whether drugs that interfere with or compete for these transporters (e.g., acyclovir, probenecid, NSAIDS) have an effect on pralatrexate transport

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/s/  
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ROBERT L JUSTICE  
09/24/2009