

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Clinical Information Request for NDA 22-468, Folutyn
Date: Friday, August 07, 2009 8:31:17 AM

Linnea,

You reported drugs for treatment of (b) (4). Please clarify what that meant was it
(b) (4)?

Thank You,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov

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/s/

MILINDA F VIALPANDO

08/07/2009

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Clinical request for information for NDA 22-468, Folotyn
Date: Wednesday, July 22, 2009 11:39:45 AM

Linnea,

See the clinical request for information regarding NDA 22-468, Folotyn, and respond.

Pt # 29 with pharyngeal mass had XRT to the site. His only other site of inv was mediastinal LN that was not radiated. (liver and other areas were noted as NA by ADJ review) Pt is continued CR as per scans/PET and physical exam. He went off study August 8th 2008 noted to be PD in CRF. Please explain.

Thank You,

Milinda F. Vialpando

Regulatory Health Project Manager

Division of Drug Oncology Products

Office of Oncology Drug Products, FDA

10903 New Hampshire Avenue

Building 22, Room 2133

Silver Spring, MD 20993

Tel: 301-796-1444

Fax: 301-796-9845

Milinda.Vialpando@fda.hhs.gov

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/s/

Milinda Vialpando
7/22/2009 11:44:18 AM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Clinical request for information for NDA 22-468, Folutyn
Date: Thursday, July 23, 2009 8:07:40 AM

Linnea,

See the clinical request for information below and respond.

Pt # 49 Received CHOP for nodal PTCL and was enrolled for PD. He received 1 dose of cycle 1 and was taken off study ((b) (6)) when he was admitted to the hospital ICU for sepsis.

CRF notes that the reason for off study is another therapy. Please explain.

Regards,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
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Milinda.Vialpando@fda.hhs.gov

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/s/

Milinda Vialpando
7/23/2009 08:11:51 AM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Clarification to Clinical request for information for NDA 22-468, Folutyn
Date: Tuesday, July 21, 2009 4:48:09 PM

Linnea,

See the clinical clarification response below.

#4: Please clarify whether you have any Phase 3 controlled clinical trials either ongoing or planned for clinical development of Pralatrexate in any indication. We note that the Table entitled "**5.2 TABULAR LISTING OF ALL CLINICAL STUDIES**" in your NDA submission, did not list any controlled phase 3 clinical trials. If you have any ongoing phase 3 trials either in US or outside of US, please send trial synopses and trial status updates. If they have any phase 3 trials planned, please send trial synopses.

Regards,
Milinda

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, July 21, 2009 12:58 PM
To: Vialpando, Milinda
Subject: Allos Response to Clinical request for information for NDA 22-468, Folutyn; Request for Teleconference
Importance: High

Milinda,

My team can prepare written responses to Questions 1-3 below within the next 2 days.

However, we request a ½ hour teleconference as soon as possible to clarify Question #4 with the following FDA representatives:

- Robert Justice, M.D., Division Director, DDOP
- Ke Liu, M.D., Clinical Team Leader, DDOP
- Shakun Malik, M.D., Medical Officer, DDOP
- Milinda Vialpando, Project Manager, DDOP

The Allos participants in this meeting would include:

- Pablo J. Cagnoni, M.D., Senior Vice President, Chief Medical Officer
- Jennifer Carver, Director, Project Management
- Linnea Tanner, Senior Director, Regulatory Affairs

Would you confirm whether we can schedule a teleconference with the above FDA representatives in the next couple days to further discuss Question #4?

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

From: Vialpando, Milinda [mailto:Milinda.Vialpando@fda.hhs.gov]
Sent: Tuesday, July 21, 2009 7:10 AM
To: Tanner, Linnea
Subject: Clinical request for information below for NDA 22-468, Folotyn

Linnea,

See the clinical request for information below for NDA 22-468, Folotyn, and respond right away.

Please clarify the following.

1. In "reasons for discontinuation", what were the reasons for "Investigator Decision" to take 6% of the patients off study?
2. Protocol and CRF's did not describe confirmatory scans for responders within 30 days of response designation date. Please confirm.
3. Pt # 43: Response date as per Rad Pharm and CRF was Nov 27th 07 (after 3 cycles) and PD date as per CRF was March 11th 2008.

However, "Listing 16.2.6.8 Duration of Response Status Per RadPharm: IWC " states that pt had response on March 4th and went off therapy on March 4th for other treatment. Please clarify.

4. Please clarify whether you have any Phase III controlled clinical trials either ongoing or planned for clinical development of Pralatrexate.

Thank You,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
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/s/

Milinda Vialpando
7/21/2009 05:13:30 PM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Clinical request for information below for NDA 22-468, Folutyn
Date: Tuesday, July 21, 2009 9:10:25 AM

Linnea,

See the clinical request for information below for NDA 22-468, Folutyn, and respond right away.

Please clarify the following.

1. In "reasons for discontinuation", what were the reasons for "Investigator Decision" to take 6% of the patients off study?
2. Protocol and CRF's did not describe confirmatory scans for responders within 30 days of response designation date. Please confirm.
3. Pt # 43: Response date as per [REDACTED] (b) (4) and CRF was Nov 27th 07 (after 3 cycles) and PD date as per CRF was March 11th 2008.

However, "Listing 16.2.6.8 Duration of Response Status Per [REDACTED] (b) (4) IWC " states that pt had response on March 4th and went off therapy on March 4th for other treatment. Please clarify.

4. Please clarify whether you have any Phase III controlled clinical trials either ongoing or planned for clinical development of Pralatrexate.

Thank You,

Milinda F. Vialpando

Regulatory Health Project Manager

Division of Drug Oncology Products

Office of Oncology Drug Products, FDA

10903 New Hampshire Avenue

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Silver Spring, MD 20993

Tel: 301-796-1444

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/s/

Milinda Vialpando
7/21/2009 05:12:37 PM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Clinical request for information for NDA 22-468, Folutyn
Date: Wednesday, July 22, 2009 11:39:45 AM

Linnea,

See the clinical request for information regarding NDA 22-468, Folutyn, and respond.

Pt # 29 with pharyngeal mass had XRT to the site. His only other site of inv was mediastinal LN that was not radiated. (liver and other areas were noted as NA by ADJ review) Pt is continued CR as per scans/PET and physical exam. He went off study August 8th 2008 noted to be PD in CRF. Please explain.

Thank You,

Milinda F. Vialpando

Regulatory Health Project Manager

Division of Drug Oncology Products

Office of Oncology Drug Products, FDA

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/s/

Milinda Vialpando
7/22/2009 11:44:18 AM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Statistical Information Request for NDA 22-468, Folotyn
Date: Thursday, July 16, 2009 1:05:25 PM

Linnea,

FDA is requesting the following information for NDA 22-468, Folotyn:

Please submit the following datasets: FSUBT, PT and TREATMEN.
The first two datasets were used to generate dataset "RESP".
The last dataset was used to check reasons of transplant.

Thank You,

Milinda F. Vialpando
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/s/

Milinda Vialpando
7/16/2009 01:10:12 PM
CSO

Milinda Vialpando
7/16/2009 01:10:30 PM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Clinical Information Request for NDA 22-468, Folotyn
Date: Monday, June 29, 2009 3:10:55 PM

Linnea,

See the clinical information request below for NDA 22-468, Folotyn, and respond.

Please confirm that for AE (Adverse Event) analysis Table adverse .xpt has been used.

If so what criteria was used for used to generate table 12.3 page 88/373 of the study report?

Also please send SAS codes for this analysis.

Thank You,

Milinda F. Vialpando
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/s/

Milinda Vialpando
6/29/2009 03:20:08 PM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea"; "Marshall, Todd";
Subject: RE: Clinical Information Request for NDA 22-468, Folotyn
Date: Wednesday, June 03, 2009 4:09:17 PM

Linnea,

An additional item is Pt # 36 CRF pg's 36-47 are missing.

Milinda

From: Vialpando, Milinda
Sent: Wednesday, June 03, 2009 4:07 PM
To: 'Tanner, Linnea'; 'Marshall, Todd'
Subject: Clinical Information Request for NDA 22-468, Folotyn

Linnea,

FDA is requesting corrected CRF's of all the responding patients. CRF's they submitted have missing pages and the pages are not in order.

Following are the examples

Pt #10 Missing data in Form for Unscheduled scan for April 13th 2007

Pt # 26 CRF is missing Pg 41-47

Pt # 29 Pg 47 survival status is missing.

Pt # 35 best response CR Nov 1st 2007 (NO RECORDS IN CRF OF NOV 1st scan)

Pg 38-41 are missing,

Pg 47 is missing.

Thank You,

Milinda F. Vialpando

*Regulatory Health Project Manager
Division of Drug Oncology Products
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Milinda.Vialpando@fda.hhs.gov*

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/s/

Milinda Vialpando
6/3/2009 04:16:00 PM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: FW: NDA 22-468; Folutyn (pralatrexate injection); IRB Approvals and Minutes for Memorial Sloan Kettering and Columbia Hospital
Date: Wednesday, May 27, 2009 4:09:29 PM

Linnea,

In order to complete a timely review FDA is requesting IRB minutes only pertinent to this PDX-008 protocol when first approved and at the time of any amendments from both institutions. Submit all responses officially to the NDA to include the information provided regarding the following correspondence:

- 1) Copies of the IRB approvals of the PDX-008 protocol and any amendments, and informed consent for both Memorial Sloan Kettering and Columbia. You can request IRB minutes from the sites.
- 2) Patient consent for the trial from Memorial Sloan Kettering.
- 3) Patient consent for the trial from Columbia Hospital.

(b) (4)

Regards,
Milinda F. Vialpando
*Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
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Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov*

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Wednesday, May 27, 2009 10:06 AM
To: Vialpando, Milinda
Cc: Pazdur, Richard
Subject: NDA 22-468; Folutyn (pralatrexate injection); IRB Approvals and Minutes for Memorial Sloan Kettering and Columbia Hospital

Milinda,

Reference is made to the e-mail below dated May 20, 2009 in which FDA requested documentation regarding the clinical sites of Memorial Sloan Kettering and Columbia Hospital. In response to the FDA request below, attached are copies of the IRB approvals of the PDX-008 protocol, amendments and informed consents for both Memorial Sloan Kettering and Columbia. In addition, attached are IRB minutes from these sites. All documents that have been submitted for Memorial Sloan Kettering and Columbia via e-mail will also be formally submitted as an amendment to the NDA.

If you have any questions regarding this submission or have any difficulty opening this document, please do not hesitate to contact me.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs

Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

From: Vialpando, Milinda [<mailto:Milinda.Vialpando@fda.hhs.gov>]
Sent: Wednesday, May 20, 2009 2:22 PM
To: Tanner, Linnea
Cc: Pazdur, Richard
Subject: RE: Information Request for NDA 22-468, Folutyn

Linnea,

FDA is requesting copies of the IRB approvals of the PDX-008 protocol and any amendments, and informed consent for both Memorial Sloan Kettering and Columbia. You can request IRB minutes from the sites.

We still need the following information that was sent to you in an e-mail dated May 19, 2009:

- 1) Patient consent for the trial from Memorial Sloan Kettering.
- 2) Patient consent for the trial from Columbia Hospital.

(b) (4)

Provide all of the requested information by Friday, May 29, 2009 at 3pm.

Thank You,
Milinda F. Vialpando
*Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov*

From: Tanner, Linnea [<mailto:ltanner@ALLOS.com>]
Sent: Wednesday, May 20, 2009 4:00 PM
To: Vialpando, Milinda
Subject: RE: Information Request for NDA 22-468, Folutyn

Milinda,

Would you clarify that FDA would like copies of the IRB approvals of the PDX-008 protocol and any amendments, and informed consent for these sites. Allos does not have access to IRB minutes.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.

11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

From: Vialpando, Milinda [mailto:Milinda.Vialpando@fda.hhs.gov]
Sent: Wednesday, May 20, 2009 1:43 PM
To: Tanner, Linnea
Subject: Information Request for NDA 22-468, Folotyn

Linnea,

FDA is requesting IRB minutes for the trial from Sloan as well as Columbia right away.

Thank You,
Milinda F. Vialpando
*Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
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Tel: 301-796-1444
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/s/

Milinda Vialpando
5/27/2009 04:40:45 PM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
cc: Pazdur, Richard;
Subject: RE: Information Request for NDA 22-468, Folutyn
Date: Wednesday, May 20, 2009 4:21:54 PM

Linnea,

FDA is requesting copies of the IRB approvals of the PDX-008 protocol and any amendments, and informed consent for both Memorial Sloan Kettering and Columbia. You can request IRB minutes from the sites.

We still need the following information that was sent to you in an e-mail dated May 19, 2009:

- 1) Patient consent for the trial from Memorial Sloan Kettering.
- 2) Patient consent for the trial from Columbia Hospital.

(b) (4)



Provide all of the requested information by Friday, May 29, 2009 at 3pm.

Thank You,
Milinda F. Vialpando
*Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov*

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Wednesday, May 20, 2009 4:00 PM
To: Vialpando, Milinda
Subject: RE: Information Request for NDA 22-468, Folutyn

Milinda,

Would you clarify that FDA would like copies of the IRB approvals of the PDX-008 protocol and any amendments, and informed consent for these sites. Allos does not have access to IRB minutes.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

From: Vialpando, Milinda [mailto:Milinda.Vialpando@fda.hhs.gov]
Sent: Wednesday, May 20, 2009 1:43 PM
To: Tanner, Linnea
Subject: Information Request for NDA 22-468, Folutyn

Linnea,

FDA is requesting IRB minutes for the trial from Sloan as well as Columbia right away.

Thank You,
Milinda F. Vialpando
*Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
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Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845
Milinda.Vialpando@fda.hhs.gov*

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/s/

Milinda Vialpando
5/20/2009 04:26:32 PM

From: Vialpando, Milinda
To: Vesely, Nicole;
Subject: FW: NDA 22-468, Folotyn to ODAC in September
Date: Wednesday, May 06, 2009 4:31:57 PM

Nicole,

The sponsor has been notified they are going to ODAC in September and their contact information is below. Please contact me if you have any questions.

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.
11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
Fax: 303.412.9160
e-mail: ltanner@ALLOS.com

Thanks,
Milinda

From: Vialpando, Milinda
Sent: Wednesday, May 06, 2009 4:30 PM
To: 'Tanner, Linnea'
Subject: NDA 22-468, Folotyn to ODAC in September

Linnea,

FDA is planning to bring NDA 22-468, Folotyn to ODAC in September. This information is **NOT** public and should not be disclosed until the Federal Register publishes.

You will receive a letter informing you of upcoming deadlines.

I would also like to confirm that you have submitted a separate document for your trademark submission.

Regards,

Milinda F. Vialpando

Regulatory Health Project Manager

Division of Drug Oncology Products

Office of Oncology Drug Products, FDA

10903 New Hampshire Avenue

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Fax: 301-796-9845

Milinda.Vialpando@fda.hhs.gov

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/s/

Milinda Vialpando
5/6/2009 04:50:36 PM
CSO

Milinda Vialpando
5/6/2009 04:51:12 PM
CSO

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: Information request for NDA 22-468, Folotyn
Date: Tuesday, May 19, 2009 11:21:16 AM

Linnea,

FDA is requesting the following information for NDA 22-468, Folotyn, right away.

- 1) Patient consent for the trial from Memorial Sloan Kettering.
- 2) Patient consent for the trial from Columbia Hospital.

(b) (4)



Regards,

Milinda F. Vialpando

Regulatory Health Project Manager

Division of Drug Oncology Products

Office of Oncology Drug Products, FDA

10903 New Hampshire Avenue

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Milinda.Vialpando@fda.hhs.gov

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/s/

Milinda Vialpando
5/20/2009 04:29:11 PM

From: Vialpando, Milinda
To: "Tanner, Linnea";
Subject: RE: NDA 22-468 (Pralatrexate; PTCL) Confirm Official Receipt Date
Date: Tuesday, March 24, 2009 5:31:58 PM

Linnea,

This is the list of reviewers that I have so far and will let you know if/when they change.

Clinical Qin Ryan
Non-Clinical William McGuinn
CMC not assigned
Statistics Qiang (Casey) Xu
Clin Pharm Gene Williams

Milinda

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, March 24, 2009 5:26 PM
To: Vialpando, Milinda
Subject: RE: NDA 22-468 (Pralatrexate; PTCL) Confirm Official Receipt Date

Milinda,

Thank you for your feedback. Can you confirm who will be the primary reviewers for NDA 22-468?

Regards,
Linnea

From: Vialpando, Milinda [mailto:Milinda.Vialpando@fda.hhs.gov]
Sent: Tuesday, March 24, 2009 3:14 PM
To: Tanner, Linnea
Subject: RE: NDA 22-468 (Pralatrexate; PTCL) Confirm Official Receipt Date

Linnea,

I received notification that your submission for NDA 22-468 has been received.

Regards,
Milinda

From: Tanner, Linnea [mailto:ltanner@ALLOS.com]
Sent: Tuesday, March 24, 2009 10:39 AM
To: Vialpando, Milinda
Subject: NDA 22-468 (Pralatrexate; PTCL) Confirm Official Receipt Date

Milinda,

Would you confirm what will be considered the official receipt date of NDA 22-468 for pralatrexate in the treatment of relapsed or refractory PTCL? We received the acknowledgement receipt as Mar 23, 2009 08:24:49 PM EDT.

I appreciate your feedback.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
Allos Therapeutics, Inc.

11080 CirclePoint Road
Westminster, CO 80020
Telephone: 720-540-5340
New Fax: 720-540-5476
e-mail: ltanner@ALLOS.com

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From: Tanner, Linnea
Sent: Monday, March 23, 2009 6:30 PM
To: Vialpando, Milinda
Subject: NDA 22-468 (Pralatrexate; PTCL) Submitted Through Gateway on 23 Mar 2009

Milinda,

This is to inform you that NDA 22-468 for pralatrexate in the treatment of relapsed or refractory peripheral T-cell lymphoma was submitted through the EDS Gateway tonight (23 Mar 2009) and we anticipate a formal receipt acknowledgement tomorrow (24 Mar 2009). In follow-up to your e-mail regarding the proprietary names, we submitted the proprietary name of FOLOTYN which we would like the Agency to review immediately. We are not planning to move forward with (b) (4), which had been previously reviewed by DMETS and, thus, an amendment to the NDA will not be necessary to initiate the review.

Would you e-mail the list of reviewers who have been assigned to this NDA? If you have any questions regarding NDA 22-468, please do not hesitate to contact me.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Senior Director, Regulatory Affairs
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Westminster, CO 80020
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New Fax: 720-540-5476
e-mail: ltanner@ALLOS.com

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

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INC

FOLOTYN

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/s/

MILINDA F VIALPANDO
09/09/2009

TELECON MINUTES

TELECON DATE: September 9, 2009

TIME: 1:00 – 1:30 PM

NDA: 22-468

LOCATION: 1313

DRUG: Folutyn (pralatrexate)

SPONSOR/APPLICANT: Allos Therapeutics, Inc

FDA PARTICIPANTS:

Ke Liu, M.D., Ph.D., Clinical Team Leader, DDOP
Shakun Malik, M.D., Medical Officer, DDOP
Amna Ibrahim, M.D., Acting Deputy Director for Safety, DDOP
Julie Bullock, Pharm.D., Clin. PharmTeam Leader, OCP
Gene Williams, Ph.D., Clinical Pharmacology Reviewer, OCP
Michael Pacanowski, Pharm.D., M.P.H., Genomics, OCP
Susan Jenney, M.S., Project Manager for Safety, DDOP
Milinda Vialpando, Project Manager, DDOP

INDUSTRY PARTICIPANTS:

Pablo J. Cagnoni, M.D., Senior Vice President, Chief Medical Officer
Bert Pronk, Ph.D., Senior Director, Pre-Clinical
Linnea Tanner, Senior Director, Regulatory Affairs

BACKGROUND: The applicant requested this telecon additional clarification regarding *in vitro* studies to evaluate the impact of transporter systems in the clearance of pralatrexate.

Summary of the telecom for the following items:

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

FDA: The sponsor's proposed approach to study pralatrexate transport via organic anion transporters, alone and in the presence of pharmacologic inhibitors, appears reasonable. The Agency referred the sponsor to a study published by Takeda, et al. (JPET 2002;302:666-71), for further guidance.

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

FDA: The agency agreed with the sponsor's plans to use the relationship between creatinine clearance and exposure to simulate reduced Folutyn doses for use in the severely impaired and possibly the moderately impaired groups. Interpretation of the resulting data should include a summary of what is known regarding the linearity of clearance with dose in non-

renally impaired patients. The agency stated that the study should also include patients with mild impairment.

Action Items: None.

Milinda F. Vialpando
Project Manager

Concurrence Chair:

Julie Bullock, Ph.D.
Clinical Pharmacology
Team Leader

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

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/s/

JULIE M BULLOCK

09/10/2009

TELECON MINUTES

TELECON DATE: September 3, 2009

TIME: 11:00 – 11:30 AM

NDA: 22-468

LOCATION: 3376

DRUG: Folutyn (pralatrexate)

SPONSOR/APPLICANT: Allos Therapeutics, Inc

FDA PARTICIPANTS:

Robert Justice, M.D., M.S., Division Director, DDOP
Tony Murgo, M.D., M.S., FACP, Associate Director, OODP
Ke Liu, M.D., Ph.D., Clinical Team Leader, DDOP
Shakun Malik, M.D., Medical Officer, DDOP
Shenghui Tang, Ph.D., Statistics, Team Leader, OB
Casey Xu, Ph.D., Statistics Reviewer, OB
Corrine Kulick, Ph.D., Team Leader, OSE
Gene Williams, Ph.D., Clinical Pharmacology Reviewer, OCP
Milinda Vialpando, Project Manager, DDOP

INDUSTRY PARTICIPANTS:

Pablo J. Cagnoni, M.D., Senior Vice President, Chief Medical Officer
Todd Marshall, Director, Regulatory Affairs (CMC)
Adam Boyd, Ph.D., Associate Director, Biostatistics
Linnea Tanner, Senior Director, Regulatory Affairs

BACKGROUND: FDA requested this telecon to discuss the Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs) and CMC changes to the carton and container labels, and the information request from the Microbiology reviewer.

Summary of the telecon.

Postmarketing Requirements:

1. A clinical trial to determine the clinical benefit of maintenance therapy with pralatrexate in patients with PTCL who have a complete or partial response to first line therapies with CHOP or CHOP-like regimens.
2. A clinical trial in patients with renal impairment to include patients with severe renal impairment, and
3. Completion of the planned mass balance trial, and contingent on FDA review of the mass balance results, a trial in patients with hepatic impairment.

Postmarketing Commitment:

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

CMC carton and container label changes:

1. The graphic in its current location and size detracts from the proprietary and established name. Decrease the size and relocate the graphic away from the proprietary name on the principal display panel. The proprietary and established name should be the most prominent information on the label and labeling (see CFR 201.15(a)(6)).
2. Further increase the prominence of the nonproprietary name relative to the proprietary name.
3. As requested by FDA on August 27, 2009, revise the "Contents" on carton labeling to the following:

(For the 40 mg/2 mL size): "Each vial contains 40 mg of pralatrexate in 2 mL of sterile solution. Also contains....."

(For the 20 mg/1 mL size): "Each vial contains 20 mg of pralatrexate in 1 mL of sterile solution. Also contains....."
4. The NDC Product Code (the area next to the Product Type) in SPL Drug Listing Data Element (DLDE) should contain the first two segments of the NDC and thus both the 20 mg/1 mL and 40 mg/2 mL configurations should have the same NDC Product Code. It is noted that you have included the complete NDC (i.e., three segments) in this section of the DLDE. Please revise.

Information Request for Microbiology:

The sponsor has received the request and will submit their response by noon, September 4, 2009.

Additional comment for future trials:

(b) (4)

Action Items:

1. The sponsor will provide a brief description for each of the PMRs, PMCs and required information in the format below.

PMR/PMC #. Title and a brief description of the trial/study.

Final Protocol Submission: Date

Trial/Study Start: Date

Final Report Submission: Date

2. The sponsor to submit Introductory Advertising Materials to DDMAC for review prior to the action date.

Note to Sponsor (post-meeting):

All Subpart H post-marketing investigations previously called Postmarketing Commitments are Post-Marketing Requirements under FDAAA. In addition, the “Trail/Study Completion” date should replace the “Trail/Study Start” date as the goal dates in the Action Items section.

Milinda F. Vialpando
Project Manager

Concurrence Chair: _____
Ke Liu , M.D., Ph.D.
Clinical Team Leader

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

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KE LIU
09/10/2009

MEMORANDUM OF TELECON

DATE: 6/5/09

APPLICATION NUMBER: NDA 22-468, Folotyn (pralatrexate)

BETWEEN:

Name: Pablo J. Cagnoni, M.D., Senior Vice President, Chief Medical Officer
Tony Koutsoukos, Ph.D., Vice President, Biometrics
Beth Crump, Director, Clinical Operations
Jennifer Carver, Director, Project Management
Linnea Tanner, Senior Director, Regulatory Affairs

Phone: 1-888-447-7153

Passcode: 9525464

Representing: Allos Therapeutics

AND

Name: Division of Drug Oncology Products
Ke Liu, M.D., Clinical Team Leader, DDOP
Shakun Malik, M.D., Medical Officer, DDOP
Milinda F. Vialpando, Regulatory Health Project Manager, DDOP

SUBJECT: To clarify questions regarding the case report forms and if additional updated data and documentation is needed.

Ke Liu, M.D.
Clinical Team Leader
Division of Drug Oncology Products

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

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KE LIU

09/09/2009

TELECON MINUTES

TELECON DATE: May 11, 2009

TIME: 9:30 – 10:00 AM

NDA: 22-468

LOCATION: 3376

DRUG: Folutyn (pralatrexate)

SPONSOR/APPLICANT: Allos Therapeutics

FDA PARTICIPANTS:

Robert Justice, M.D., M.S., Division Director, DDOP
Ke Liu, M.D., Ph.D., Clinical Team Leader, DDOP
Shakun Malik, M.D., Medical Officer, DDOP
Milinda Vialpando, Project Manager, DDOP

INDUSTRY PARTICIPANTS:

Pablo J. Cagnoni, M.D., Senior Vice President, Chief Medical Officer
Jennifer Carver, Director, Project Management
Adam Boyd, Ph.D., Associate Director, Biostatistics
Shannon Roark, Ph.D., Associate Director, Medical Writing
Linnea Tanner, Senior Director, Regulatory Affairs

BACKGROUND: The sponsor requested this telecon to discuss their proposal to change the FDA ODAC briefing document.

The summary of telecon.

1) FDA and the sponsor agreed to the following changes:



(b) (4)

2) FDA inquired about the sponsor's plan for confirmatory studies in the pralatrexate clinical development program. The sponsor stated that they were contemplating the following options: 1) Using pralatrexate (PDX), as an add-on to gemcitabine. 2) Using pralatrexate (PDX) as a single agent maintenance versus observation after CHOP first line treatment. FDA stated that the sponsor should describe about plans if questions arise from ODAC.

3) The sponsor asked the FDA whether they should present the updated PDX-008 data (duration of responses) reported at ASCO 2009. The FDA stated if questions arise from ODAC regarding this issue the sponsor may discuss these updated data with the caveat that the FDA has not reviewed that data.

Milinda F. Vialpando
Project Manager

Concurrence Chair:

Ke Liu , M.D., Ph.D.
Clinical Team Leader

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/s/

KE LIU
08/17/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 52,604

Allos Therapeutics, Inc.
Attention: Linnea Tanner, M.S., RAC
11080 CirclePoint Road
Westminster, CO 80020

Dear Ms. Tanner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pralatrexate.

We also refer to the meeting between representatives of your firm and the FDA on July 16, 2008. The purpose of the meeting was as a Pre-NDA meeting.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN. MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 16, 2008 **TIME:** 3-4 PM **LOCATION:** Building 22

IND 52,604, Pralatrexate

Meeting Request Submission Date: April 11, 2008

FDA Response Date: May 29, 2008

Briefing Document Submission Date: June 11, 2008

SPONSOR: Allos Therapeutics, Inc. **TYPE OF MEETING:** Pre-NDA

FDA ATTENDEES:

Ramzi Dagher, M.D., Deputy Division Director, DDOP
Amna Ibrahim, M.D., Medical Team Leader, DDOP
Qin Ryan, M.D., Medical Officer, DDOP
Rajeshwari Sridhara, Ph.D., Deputy Director, TL, DDOP (invited)
Xiaoping, Jiang, Ph.D., Math Statistician, DDOP (invited)
Alice Kacuba, Chief, Project Management Staff, DDOP
Hari Sarker, Ph.D., CMC Reviewer

SPONSOR ATTENDEES:

Pablo J. Cagnoni, M.D., Senior Vice President, Chief Medical Officer
Bert Pronk, Ph.D., Sr. Director, Pre-clinical
Tony Koutsoukos, Ph.D., Vice President, Biometrics
Beth Crump, Director, Clinical Operations
Jennifer Carver, Associate Director, Project Management
Shannon Roark, Ph.D., Associate Director, Medical Writing
Linnea Tanner, Senior Director, Regulatory Affairs
Lisa Lange, Manager, Regulatory Operations

BACKGROUND: Pralatrexate is being investigated for intravenous (IV) administration used as a single-agent treatment for patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Due to computer difficulties, the FDA draft meeting minutes were lost, therefore resulting in these meeting minutes being finalized late. These meeting minutes are based on the Sponsor's meeting minutes that were submitted to the Agency.

QUESTIONS FOR DISCUSSION WITH FDA RESPONSE AND DECISIONS REACHED:

Based on the FDA preliminary responses, the Sponsor chose to focus the meeting on Questions 10-12. The Sponsor confirmed that all other FDA responses were acceptable without further discussion.

NDA CLINICAL AND NONCLINICAL QUESTIONS FOR FDA FEEDBACK

Administrative

1. Pralatrexate was granted a Fast Track Designation on 28 Sep 2006 and has the potential to treat the rare and life-threatening disease of relapsed or refractory PTCL. There are no approved drugs for this indication and current treatment strategies are often ineffective. Does the Agency concur that the NDA may be eligible for priority review?

FDA Response: This is a review issue and will be determined at the time of filing.

2. Pralatrexate has been granted Orphan Drug Designation and is therefore exempt from providing pediatric use information (21 CFR 314.55) in the NDA. Allos does not plan to submit data to support the use of pralatrexate in pediatric patients in the NDA submission and will not submit a waiver. Does the Agency agree with this proposal?

FDA Response: Yes.

3. Allos plans to provide a tabulated summary of FDA interactions and agreements (provided in Appendix 5) as an appendix to the cover letter for the NDA submission. These agreements will be hyperlinked to the associated NDA section that addresses the agreement. Does the Agency agree with this proposed plan?

FDA Response: Yes.

4. 21 CFR Part 314.2 indicates that financial disclosure needs to be provided for a "covered clinical study" defined as a study that is submitted in a marketing application that the applicant or FDA relies on to establish that the product is safe and effective. The following are considered covered clinical studies that will provide the primary data for efficacy and/or safety in the NDA and thus require financial disclosure of investigators: PDX-008 [pivotal study], PDX-007, PDX-009, PDX-010, PDX-011, PDX-012, and PDX-02-078. IND Application 52,604 was transferred from Memorial Sloan Kettering Cancer Center (MSKCC) to Allos on 03 Feb 2003 (Serial No. 063). Clinical studies commenced prior to the IND transfer were conducted under the direction and management of MSKCC. Thus, the following completed clinical studies conducted under the direction of MSKCC will provide secondary safety data and are not considered covered clinical studies requiring financial disclosure of investigators: PDX-97-006, PDX-99-053, PDX-99-083, PDX-01-014, and PDX-01-076. Does the Agency agree that financial disclosure is not required for investigators who conducted MSKCC studies that provide secondary safety data?

FDA Response: Yes, if the information from the MKSCC study is not used to make a claim in the label. The information that will be included in the label will be a review issue.

Labeling

5. Allos intends to provide the proposed content of labeling in Structured Product Labeling (SPL) format in accordance with the "Guidance to Industry: Providing Regulatory Submissions in Electronic Format -Content of Labeling April 2005." In addition, the

annotated labeling will be provided in PDF format and will be hyperlinked to referenced sections to support inclusion of content. Finally, the labeling will also be provided in WORD format that can be used to track changes to the labeling during the review. Does the Agency concur with the proposed plan for the formatting of labeling that will be provided in the NDA?

FDA Response: Yes. The labeling in WORD format should include line numbering.

Clinical Development

6. Allos intends to submit a clinical data package consisting of 1) PDX-008, which will provide the primary basis of efficacy and safety for pralatrexate as a single-agent treatment for relapsed or refractory PTCL, 2) 11 additional Phase 1-2 studies in lymphoma and solid tumors, 3) bioanalytical and analytical methods for human studies, and 4) in vitro studies pertinent to PK using human biomaterials. The complete list of studies for inclusion in Module 5 is provided in this briefing document (Appendix 6). Does the Agency agree that the clinical study reports (CSRs), including abbreviated CSRs for completed studies other than PDX-008, and synopses for ongoing studies, that will be provided in Module 5 fulfill the requirements for submitting the NDA and supporting full approval?

FDA Response: The proposed format appears to be acceptable. It is expected that you will have summaries in Module 2 of the submission. Whether it is sufficient to support a NDA and possible approval will be a review issue.

7. Allos proposes providing CRF patient data listings in Appendix 16.2 of the PDX-008 CSR, and not providing individual patient profiles in Appendix 16.4 of the CSR. Patient data listings that were provided to (b) (4) for their review of patients to assess response will be provided in Appendix 16.4 of the CSR. Does the Agency agree with the proposed plan?

FDA Response: Individual patient profiles are not required but may be helpful to the review process.

8. Per the recommendation of the FDA in the Type A meeting held on 28 Jan 2008 (minutes provided in Appendix 3), Allos intends to provide pathology reports as well as relevant ancillary reports for all patients in PDX-008 as single PDF files bookmarked by patient ID in Appendix 16.4 of the PDX-008 CSR. Does the Agency agree with this proposal?

FDA Response: Yes. It would be helpful to have the pathology report conclusions for each patient to be included in the SAS datasets.

9. As stated in the ICH eCTD Specifications V 3.2, 04 Feb 2004, Allos intends to provide Section 2.7.6 Synopses of Individual Studies as a tabular listing of studies that will link to the synopses of these studies in Module 5. Does the Agency agree with this proposal?

FDA Response: Yes.

10. In the Type C meeting held on 21 Mar 2008 (minutes provided in Appendix 10), the FDA agreed with the proposed statistical analysis plan (SAP) for the Clinical Summary of Safety and Integrated Summary of Safety (CSS/ISS) that would be used to analyze all clinical safety data in support of the NDA. The initial data cut-off date for ongoing studies, except PDX-008, will be 30 Jun 2008 for the original NDA. Allos proposes a data cut-off date at approximately the same time as the NDA submission for the 4-month safety update report. Does the Agency agree that this plan is acceptable?

FDA Response: This appears acceptable. Please specify the cut-off date for the 4-month safety data.

Meeting Discussion: FDA explained that they are unable to approve the 120-day cut-off date without knowing the anticipated date for submitting the NDA. The Sponsor could not provide a specific date without a mutual agreement with the Agency on the timing of the submission of the NDA which will be discussed in a Type A meeting scheduled on September 11, 2008. The FDA indicated that the proposed cut-off dates appear acceptable although this cannot be confirmed without knowing more information.

11. Will the FDA require the radiographic and photographic images from the Independent Review to be submitted in support of the NDA?

FDA Response: No, we will not require scans to be submitted. However, pdf images of the scans may be helpful during the review process.

Meeting Discussion: The Agency does not have the capacity to archive radiographic and photographic images and if they are used in the review, a copy must be archived. If images are submitted, they should be submitted as pdf files. Images should be available on request with a reasonably short turn around time. FDA recommended that images be hyperlinked by patient ID. For this study, photos are important to the endpoint. Sponsor will provide the Agency with information on the size and number of photographic images that will be submitted. The Agency will confer with the e-sub group and will get back to the sponsor and communicate the acceptability of submission of these photographic images.

12. If the answer to question 11 is yes, what are the expectations as to when the images should be submitted and which patients' images should be submitted?

FDA Response: The pdf images will not be required. However, we ask that the images be available upon request during the review period and be provided with a short turn-around such as within 48 hours.

Meeting Discussion: See discussion in Question 11 above.

13. If the answer to question 11 is yes, is the format as described in the (b) (4) Image Submission Module that is provided in Appendix 7 acceptable?

FDA Response: No, scans provided on hard drives will not be acceptable.

Statistical Documentation/Data Analysis Plan

14. The FDA agreed with the pre-specified statistical analysis plan and shell tables for the CSSIIS in the Type C meeting held on 21 Mar 2008. The SAP for PDX-008 was originally sent to the FDA on 20 Sep 2007 in IND Serial No. 0166 and subsequently has been amended to incorporate the relevant discussion points from the Type A meeting held on 28 Jan 2008. Amendment #1 to the SAP for PDX-008 was submitted on 16 Apr 2008 (IND Serial No. 0211). In addition, only the efficacy data of PDX-008 will be included in the clinical summary of efficacy/integrated summary of efficacy/ [CSE/ISE]. The analyses to be presented in the CSE/ISE will be identical to those efficacy analyses proposed in the PDX-008 SAP and hence, no separate SAP for the CSE/ISE will be provided in the briefing document. Does the Agency agree that the PDX-008 statistical analysis plan is adequate to analyze the efficacy and safety data of PDX-008?

Does the Agency agree with the content of the CSE/ISE?

FDA Response: Please include a variable to report the reasons (e.g. subsequent therapy including transplant) for censoring in the dataset for the analysis of duration of response for Study PDX-008. Please include all versions of the SAP and protocols as appendices in the NDA. Please clarify what you mean by "briefing document".

The ISE should be based on all data/studies relevant to reaching an efficacy conclusion.

15. Does the Agency agree with the provided table shells of the CSR for PDX-008 and the synopses for all on-going studies (PDX-007, PDX-009, PDX-010, PDX-011, PDX-012, and PDX-02-078) provided in Appendix 8?

FDA Response: This appears to be acceptable. However, additional information and analyses may be requested during the review process. Please see the response to question 14. Please provide a new table with information on response duration and include information on reasons for censoring (similar to Table 14.2.3).

16. For the response data from the independent central review of scans, the raw data by lesion and by response assessment will be provided as SAS transport datasets, in addition to the dataset with the derived endpoints. The programs for creating the derived endpoints and the programs for their analysis will also be provided. Other SAS programs will be provided upon request. In general, the transport datasets will have both the raw and derived data in the same datasets. The data definitions will indicate which variables are raw and which are derived. Does the Agency agree with this proposed plan?

FDA Response: Yes. Please also include the algorithms that are used for the derived variables in the define.pdf.

17. Allos does not intend to provide patient profiles (individual patient's complete patient profile in a single PDF file) as described in the document "Study Data Specifications" referenced in FDA's guidance Providing Regulatory Submissions in Electronic Format -Human Pharmaceutical Product Applications and Related Submissions Using the eCTD

Specification. The information for each patient will be included in the other data provided.
Does the Agency agree?

FDA Response: Individual patient profiles are not required but may be helpful to the review process.

18. Laboratory assessments are entered directly into the Allos database from copies of laboratory reports received from each investigational site. Copies of these laboratory reports will not be provided with the case report forms (CRFs). Laboratory data will be provided as patient data listings in Appendix 16.2. Per the agreement with the FDA in the Type C meeting held on 21 Mar 2008 regarding the SAP for the CSS/ISS, SAS transport datasets for laboratory assessments will be provided for all studies. Does the Agency agree with this proposed plan?

FDA Response: Yes.

Case Report Forms

19. Based on the agreement in the Type C meeting held on 21 Mar 2008, CRFs will only be provided for those patients in PDX-008 who died, had a serious adverse event (SAE) other than those reported as progressive disease (PD), or withdrew due to an adverse event (AE) other than PD in the initial NDA and 4-month safety update report. For the 4-month safety update report, CRFs will only be provided for those patients who died, had a SAE or withdrew due to an AE between the data cut-off date for the initial NDA and the data cut-off data for the 4-month safety update report. Does the Agency agree with this proposed plan?

FDA Response: Yes. Please have other CRFs available for submission upon request.

20. Allos intends to provide 2 sets of CRF bookmarks per patient; 1 by Visit/Domain and the other by Domain/Visit, with reverse hypertext links from CRF and corresponding query pages. Does the Agency agree with the proposed method of bookmark and linking?

FDA Response: Yes.

Nonclinical Documentation

21. The complete list of nonclinical studies is provided in the Table of Contents for Module 4 in Appendix 6. Does the Agency agree that the nonclinical study reports that will be provided in Module 4 fulfill the requirements for submitting the NDA?

FDA Response: The non-clinical studies listed appear to support the NDA submission for the proposed indication. However, the acceptability of the data is dependent on the review of these study reports.

Format and Media

22. Allos plans to submit an archivable NDA using the eCTD format with all specifications that are stated on the Center for Drug Evaluation and Research (CDER) eCTD specifications website. The NDA will be comprised of the eCTD modules that constitute a reviewable

NDA. Does the Agency concur with the proposed plan for electronic submission of the NDA?

FDA Response: Yes.

23. Allos intends to use the Electronic Submissions Gateway (ESG) for means of submitting the proposed NDA. Does the Agency concur with the proposed plan for electronic submission of the NDA?

FDA Response: Yes.

Literature References

24. Allos proposes to only submit those publications referenced in Module 2. All other publications referenced in Module 3, Module 4, and Module 5 will be available upon request. Does the Agency agree with this proposed plan?

FDA Response: Yes. It will be expected that the publications will be provided within 48 hours of the request.

25. Allos proposes to use a modified Vancouver style for references, eg, Sirotnak FM, Schmid FA, Samuels LL, et al. 10-Ethyl-10-deaza-aminopterin: structural design and biochemical, pharmacologic, and antitumor properties. NCI Monogr 1987; 5: 127-31. Is this modified style for displaying references acceptable?

FDA Response: Yes.

Additional Comments at Meeting:

The Sponsor indicated that the timing for submitting the NDA will be determined at the Type A meeting scheduled on September 11, 2008. However, the Sponsor is now targeting the submission of the NDA by the end of December 2008.

Additional CMC Comments:

1. **Provide a concise pharmaceutical development report in the NDA highlighting the product development and process understanding in the delineation of critical quality attributes and critical process parameters. Also, you are encouraged to take the quality-by-design (QbD) approach to pharmaceutical development as outlined in ICH Q8 Guidance on *Pharmaceutical Development*. If appropriate, please include QbD-related information and questions in a CMC-specific meeting or request a CMC guidance meeting to discuss your QbD approach during your Phase 3 clinical studies.**
2. **We recommend that for the NDA, the stability data be submitted in SAS transport format along with statistical analyses of all stability indicating attributes.**

Linked Applications

Sponsor Name

Drug Name / Subject

IND 52604

ALLOS THERAPEUTICS PDX
INC

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/s/

ALICE KACUBA
01/29/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 52,604

Allos Therapeutics, Inc.
11080 CirclePoint Road, Suite 200
Westminster, CO 80020

Attention: Markus F. Herzig
Vice President, Regulatory Affairs

Dear Mr. Herzig:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PDX (pralatrexate).

We also refer to your June 23, 2006, request, serial number 119, for a special clinical protocol assessment, received June 26, 2006. The protocol is entitled "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".

We have completed our review of your submission and agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission.

If you wish to discuss this letter, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Ann Farrell
7/28/2006 10:25:58 AM
Farrell for Justice

MEETING/TELECON MINUTES

MEETING DATE: February 6, 2006 **TIME:** 2:30pm **LOCATION:** room 1421

IND/NDA: 52,604 Meeting Request Submission Date: November 30, 2006 (N104)

Briefing Document Submission Date: December 22, 2005 (N105)

DRUG: PDX

SPONSOR/APPLICANT: Allos

TYPE of MEETING/TELECON:

1. EOP1-2
2. Proposed Indication: (b) (4) T-cell lymphoma

FDA PARTICIPANTS:

Robert Justice, M.D., Acting Division Director

Ramzi Dagher, MD, Acting Deputy Division Director (internal meeting only)

Amna Ibrahim, M.D., Acting Medical Team Leader, Chair

Qin Ryan, M.D., Ph.D., Medical Reviewer

Mark Rothmann, PhD, Acting Statistical Team Leader

Janet Jiang, PhD, Statistical Reviewer

Shuw-Luan Lee, PhD, Pharmacology/Toxicology Reviewer

Gene Williams, PhD, Clinical Pharmacology Reviewer (internal meeting only)

Ann Staten, RD, Project Manager, Facilitator

INDUSTRY PARTICIPANTS:

Markus F. Herzig, Vice President Regulatory Affairs

Michael Saunders, MD, Vice President Clinical Development

John Hackman, Vice President Biometrics and Statistics

Robert Steffen, Senior Director Pharmacology and Toxicology

(b) (4) Clinical Development Contract Consultant

Owen O'Connor, MD, Principal Investigator, Memorial Sloan-Kettering Cancer Center

Steven Horwitz, MD, Co-investigator, Memorial Sloan-Kettering Cancer Center

Amanda Cannon, Regulatory Affairs Assistant

BACKGROUND:

Pralatrexate is a folic acid analog which is structurally related to methotrexate, and has the ability to polyglutamate to some subsets of lymphoblasts. The proposed indication is treatment (b) (4) T cell lymphoma. The sponsor has conducted several phase 1 solid tumor studies and has an ongoing phase 1-2 lymphoma study. The aim of this meeting is to discuss the design of a phase 2 study of pralatrexate with vitamin B12 and folic acid supplementation in patients with peripheral T-cell lymphoma. Patients with T-ALL, lymphoblastic lymphoma, T-CLL, PLL, T-cell granular lymphocytic leukemia, and CTCL will be excluded. The proposed sample size is 55 patients and response rate will be the primary endpoint.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Clinical

1. Does the FDA concur that the positive signal identified in a subset of lymphoma patients (peripheral T-cell lymphoma [PTCL]) in the ongoing clinical study 02-078 conducted at Memorial Sloan-Kettering Cancer Center is in a patient population which could be pursued for marketing approval? Clinical Study 02-078 is a dose escalation Phase 1 study to determine a maximum tolerated dose (MTD).

FDA Response:

Please clarify your question. The patients that were studied in 02-078 represent a variety of different diseases. In addition, it is not clear whether you propose that the phase 2 part of 02-078 is intended to be a registration trial. It appears that additional studies are warranted and that PTCL is a potential population.

A phase 1 study cannot be the major trial for approval. The phase 2 part of the study could potentially be acceptable, if the population for which the approval will be sought is prespecified. The population of interest should be homogenous and well-defined, with an adequate sample size. We suggest that you include diseases with similar natural history. Please provide a rationale for the patient population proposed for inclusion in the phase 2 portion of the study. Please submit a special protocol assessment if you intend to proceed with this protocol as your registration study.

Discussion Point: The sponsor clarified that study 02-078 was not intended to be a registration trial. FDA recommends that the patient population be as homogenous as possible e.g., similar prior therapy and prognosis.

2. Does the FDA agree that the efficacy endpoints outlined in the Phase 2 protocol would be acceptable to support a New Drug Application (NDA) of pralatrexate administered as a single agent to patients with PTCL?

FDA Response: Yes, if the efficacy endpoints are objective. Clinical evaluations will not be acceptable as part of response evaluation. All lymph nodes, spleen and liver can be

imaged and skin lesions should be photographed with a ruler. There should be a centralized radiologic assessment. The magnitude and duration of responses should be convincing and will be a review issue.

In a single arm study, results for time to event endpoints such as progression-free survival and overall survival are not interpretable.

Discussion Point: Allos plans to submit an SPA for study 008. FDA recommends that Allos includes a plan for a standardized objective response evaluation in the SPA submission. FDA suggested considering a randomized superiority trial design with physician's choice as the comparator (limited number of choices should be defined). Alternatively, an add on trial design can be considered (e.g., Gemcitabine + PDX vs. Gemcitabine alone). In a randomized trial time to event endpoints such as PFS and OS could be evaluated.

Allos intends to utilize PET scans as part of the response evaluation. FDA stated that the primary response evaluation should be based on objective criteria such as CT scans but would be interested in seeing PET results. The proposed role of the PET scans will be evaluated during the review of an SPA submission.

Please include a complete statistical analysis plan with the SPA submission.

3. If the answer to Question 2 is positive, does the FDA agree that a 20% response rate (complete response and partial response) and a 3-6 months' duration of response is a sufficiently long duration to establish a clinical benefit (efficacy) in this heavily pre-treated patient population?

FDA Response: The magnitude and duration of response that will suffice for an approval will be a review issue. This application will likely be discussed in an ODAC meeting.

4. There are many subcategories of T-cell lymphoma within PTCL, each having various incidence/frequency rates. Would the FDA consider a positive study in these patients to be representative of expected effectiveness across all subcategories of T-cell lymphoma included in the protocol?

FDA Response: No. You should attempt to enroll a more homogenous population to your phase 2 study.

Discussion: Discussed under question #1 above.

5. Should the proposed Phase 2 be submitted under the Special Protocol Assessment (SPA) procedure? (This protocol will be included in the briefing package to be submitted 1 month prior to the meeting date.)

FDA Response: Yes, please submit the protocol and a sample of CRF for a special protocol assessment.

Please also consider having an independent central response review for the study and submit a charter for review.

Nonclinical

The dose cycle of pralatrexate in the clinical setting has changed from a cycle of 4 weeks (once a week for 3 weeks followed by 1 week dose free) to a cycle of 7 weeks (once a week for 6 weeks followed by 1 week dose free). Because of the change in dose cycle, Allos proposes to conduct Good Laboratory Practice (GLP) repeat-dose toxicity studies in rats and dogs for 4 cycles (6.5 months) using the 7-week schedule to support registration of pralatrexate.

6. Does the FDA concur that 4 cycles of the 7-week dose schedule in rats and dogs is adequate chronic dosing to support clinical indications for pralatrexate, using dose intensities of 6 of 7 weeks, employing up to or greater than 6 months of dosing?

FDA Response: Yes, we concur.

Comment from the Clinical Pharmacology and Biopharmaceutics Reviewer:

Consistent with our recommendation at the meeting of October 2, 2001, we recommend that you schedule a meeting (a teleconference is often sufficient) to discuss the adequacy of the clinical pharmacology information you've acquired to date and your plans to acquire additional clinical pharmacology data prior to NDA submission. We recommend that this submission occur as soon as reasonably possible, as this timing might allow for needed data to be collected as part of trials which will initiate in the near future.

ACTION ITEMS:

Ann Staten, RD
Project Manager

Concurrence Chair: _____
Amna Ibrahim, MD
Chair, Acting Medical Team Leader

Attachment: EOP2 Regulatory Bullets

FINAL PROTOCOLS

Please refer to the December 1999 DRAFT "*Guidance for Industry - Special Protocol Assessment*" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF) should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we would like to use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs till 45 days after we receive the consultant's written comments.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fml.htm>

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system by will be made available to the public on the Internet at <http://clinicaltrials.gov>.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

FINANCIAL DISCLOSURE FINAL RULE

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 “*Guidance for Industry: Financial Disclosure By Clinical Investigators*” (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data “by gender, age, and racial subgroups” in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATE GORY		NUMBER EXPOSED To STUDY DRUG	NUMBER EXPOSED To STUDY DRUG	NUMBER EXPOSED To STUDY DRUG
Gen- der	Males	All Females	Females >50	
Age:	0-≤1 Mo. 12-16	>1 Mo.-≤ 2Year 17-64	>2-<12 ≥65	
Race:	White Other	Black	Asian	

CHEMISTRY

Prior to initiating pivotal clinical studies, we request a complete, updated submission of chemistry, manufacturing and controls (CMC). Please refer to the appropriate CDER guidelines for assistance in preparing this submission. At the time of this submission, we strongly urge you to request a meeting to discuss CMC issues, e.g., impurity profile, stability protocols, approaches to specifications, and attributes, packages, etc.

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/s/

Amna Ibrahim
2/27/2006 09:25:40 AM

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See the Advisory Committee Meeting Information located on the FDA Website Below.

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/default.htm>

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☒ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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..

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
 To confirm clinical benefits
 - ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
 - ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for NDAs)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Not applicable

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☒ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

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- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
To confirm the clinical benefits
 - ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
 - ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Checklist

NDA: 22-468

Drug: Folutyn™ (pralatrexate) injection

Sponsor: Allos Therapeutics, Inc.

Reviewing Division: Division of Drugs Oncology Products

PMR 3

Description:

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

PMR/PMC Schedule Milestones: Final protocol Submission Date: 01/31/2010
Study/Clinical trial Completion Date: 06/30/2012
Final Report Submission Date: 01/31/2013
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

There was no dedicated PK trial conducted in renally impaired patients. The population pharmacokinetics data revealed that clearance correlates with renal function..

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Due to findings that clearance correlates with renal function a dedicated PK trial in patients with mild, moderate and severe renal impairment is needed in order to identify a safe dose for these patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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, ie, cohort A = severely impaired (CreaCLCG < 30 mL/min), cohort B = moderately impaired (CreaCL CG = 30-50 mL/min), and cohort C = mildly impaired patients (CreaCLCG = 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/m²) since patients with mild renal impairment were included in the PROPEL study. Patients will undergo extensive plasma and urine collections following the first dose of FOLOTYN.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☒ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
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- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for NDAs)

PMR/PMC Development Checklist

NDA: 22-468

Drug: Folutyn™ (pralatrexate) injection

Sponsor: Allos Therapeutics, Inc.

Reviewing Division: Division of Drugs Oncology Products.

PMR 4 Description: 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.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 10/29/2008
Study/Clinical trial Completion Date: 06/30/2010
Final Report Submission Date: 12/31/2010
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

The mass balance trial is ongoing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Review of this study is needed to identify the elimination pathways of pralatrexate and the need for additional end organ impairment studies

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Phase 1 mass balance clinical study 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.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☒ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for NDAs)

PMR/PMC Development Checklist

NDA: 22-468

Drug: Folutyn™ (pralatrexate) injection

Sponsor: Allos Therapeutics, Inc.

Reviewing Division: Division of Drugs Oncology Products

PMR/PMC Description: Perform in vitro studies to determine if transporters are involved in the elimination of pralatrexate.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>NA</u>
Study/Clinical trial Completion Date:	<u>1/31/2011</u>
Final Report Submission Date:	<u>7/31/2011</u>
Other: <u>Study Start Date:</u>	<u>12/1/2009</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 [Takeda M et al. Characterization of methotrexate transport and its drug interactions with human organic anion transporters. Journal of Pharmacological and Experimental Therapeutics (2002)]

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
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 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

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-

PMR/PMC Development Coordinator:

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(signature line for NDAs)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MILINDA F VIALPANDO
09/24/2009

AMNA IBRAHIM
09/24/2009

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 26, 2009

TO: Milinda Vialpando, Regulatory Project Manager
Shakun Malik, Medical Officer
Division of Oncology Drug Products

FROM: Robert Young
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22 468

APPLICANT: Allos Therapeutics, Inc.

DRUG: Folutyn (pralatrexate)

NME: Yes

THERAPEUTIC CLASSIFICATION: Review

INDICATIONS: Treatment of relapsed or refractory peripheral T cell lymphoma

CONSULTATION REQUEST DATE: 4 June 2009

DIVISION ACTION GOAL DATE: 12 August 2009

PDUFA DATE: 23 September 2009

I. BACKGROUND:

Allos Therapeutics, Inc. submitted this New Drug Application for the approval of pralatrexate as an antineoplastic folate analog indicated for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL). One pivotal study, PDX-008, was submitted as the sole adequate and well controlled study in support of the indication. PDX-008 was 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. The assigned inspections were routine surveillance inspections.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	# of Subjects:	Inspection Date	Classification
Steven M Horwitz, MD Memorial Sloan- Cancer Center 1275 York Ave, New York, NY 10021	11	10 Aug 2009	Pending Interim classification: NAI
Barbara Pro, MD The University of Texas M.D. Anderson Cancer Center 1515 Holcombe Blvd Houston, TX 77030-4009	11	22 June 2009	Pending Interim classification: VAI
Allos Therapeutics, Inc. 11 080 Circle Point Road Westminster, CO 80020		27 July 2009	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. Steven M Horwitz, MD

Note: this summary is based on written communications with the FDA investigator. An inspection summary addendum will be generated after the EIR has been received and reviewed if there is a significant change in findings resulting in a change in classification.

- a. **What was inspected:** The records for six of eleven enrolled subjects were reviewed. The case reports were complete and well organized. There were no

limitations to the inspection.

- b. **General observations/commentary:** There were no significant protocol violations and no 483 was issued.
- c. **Assessment of data integrity:** The data is acceptable in support of the pending application.

2. **Barbara Pro, MD**

- a. **What was inspected:** All eleven subject's case reports were reviewed. The clinical investigator was on vacation and study personnel assisted with the inspection.
- b. **General observations/commentary:** The study records were in order except for five deviations described in the issued Form FDA 483:
 - i. Two subjects were dosed with prior sponsor approval even though their platelet counts fell short of the protocol minimum of greater than 50,000, i.e. 48,000 and 49,000.
 - ii. Two subjects did not receive vitamin supplementation as required by the protocol, i.e. folic acid ten days short, and B-12 six weeks short.
 - iii. One subject did not have a screening EKG, because a recent EKG was within normal limits.
- c. **Assessment of data integrity:** Although regulatory violations noted, it is unlikely that they would impact data integrity. The data submitted is acceptable in support of the pending application.

3. **Allos Therapeutics, Inc.**

Note: this summary is based on verbal communications and a Form FDA 483 issued by the field investigator. An inspection summary addendum will be generated after the EIR has been received and reviewed if there is a significant change in findings resulting in a change in classification.

- a. **What was inspected:** Sponsor records including contracts, operating procedures and study records.
- b. **General observations/commentary:** Several deviations were observed and described in the issued Form FDA 483:

- i. Failure to obtain and submit lab certifications for three local New York clinical labs used by Dr. Horwitz (New York)
 - ii. Failure to properly monitor and maintain adequate drug accountability records for Drs. Horwitz and Pro.
 - iii. Failure to report to FDA transfer of obligations to a CRO.
 - iv. Failure to submit a timely 1572, i.e. the failure to list a fellow as a sub-investigator (for seven months).
- c. **Assessment of data integrity:** The noted deficiencies are unlikely to impact data integrity. The data submitted is acceptable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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.

Note: This summary is based on preliminary communications of inspectional findings with the field investigator for the inspections of Dr. Horwitz and Allos Therapeutics. An inspection summary addendum will be generated after the EIR has been received and reviewed if there is a significant change in findings resulting in a change in classification.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT S K YOUNG

08/26/2009

TEJASHRI S PUROHIT-SHETH

08/26/2009