CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204824Orig2s000

MEDICAL REVIEW(S)

Addendum to Original Medical Officer's Review of NDA 20-4824

DOC TYPE: NDA 20-4824
Sponsor: Antares Pharma
Drug: Otrexup
Route of Administration: Subcutaneous
Dosage Form: Solution for injection
Active Ingredient(s): Methotrexate
Pharmacologic Category: Folate antagonist
Proposed Indication: Moderate to severe psoriasis

Medical Officer: Snezana Trajkovic, M.D.
Team Leader: Tatiana Oussova, M.D.
Project Manager: Barbara Gould

The applicant submitted the NDA 20-4824 on December 14, 2012. The applicant sought approval under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for Otrexup (methotrexate) injection, a drug-device combination product, for the new route of administration, subcutaneous (SQ), and for an extension of the current psoriasis indication. The applicant requested extension of psoriasis indication from "symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation" to " treatment of moderate to severe psoriasis".

Listed drugs, Methotrexate Sodium Preservative Free Injection EQ 50mg base/2ml, of Hospira (NDA 011719 approved on August 10, 1959), Methotrexate Tablet 2.5mg of Dava (NDA 08085 approved on December 7, 1953) and Methotrexate Sodium Preservative Free Injection from Bedford (ANDA 40-632, approved on August 12, 2005) are approved for the indication of "symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation".
To support a new subcutaneous route of admiration of Otrexup and to provide clinical bridge to previously approved products, the applicant conducted two bioavailability/ bioequivalence (BA/BE) studies. The applicant established that Otrexup, when administered subcutaneously, is bioequivalent to the listed drugs administered subcutaneously or intramuscularly. However, because of the considerable risk associated with treatment with methotrexate, the clinical benefit for patients with moderate to severe psoriasis is different from the one for patients with "severe, recalcitrant, disabling psoriasis unresponsive to other forms of therapy". Therefore, the treatment with methotrexate is not suitable for the population of patients with moderate to severe

psoriasis and no additional safety data could justify the proposed extension of indicating. Therefore, the recommended regulatory action was complete response (August 30, 2013).

During the labeling negotiations, the applicant accepted the labeling that reflects already approved indication "symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation". Because the applicant agreed to the already approved indication and provided the clinical bridge to the listed drugs, this reviewer recommends approval for this NDA.

Snezana Trajkovic, MD
Medical Officer
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

SNEZANA TRAJKOVIC
10/11/2013

TATIANA OUSSOVA
10/11/2013

MEDICAL OFFICER - MEMO TO FILE

Date:	September 26, 2013
Subject:	Labeling issues for NDA 204824, Otrexup (methotrexate) for Injection
From:	Peter Starke, MD, Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Introduction

This memo summarizes the decisions made with respect to major labeling and indication issues for the proposed Otrexup (methotrexate) auto-injector submitted by Antares Pharma, Inc. These issues arose during the review cycle while making edits to the proposed labeling for the product, and were addressed through consultation with the Divisions of Oncology Products 2 (DOP2) and Dermatology and Dental Products (DDDP), the SEALD labeling team, and with the CDER senior management.

Background

This 505(b)(2) new drug application references three applications for methotrexate: NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira, ANDA 40-632 for Methotrexate Preservative-Free Injection from Bedford, and NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals. NDA 11-719 and NDA 08-085 currently reside in the FDA oncology division (DOP2). The proposed Trade Name for the product is Otrexup, and the PDUFA date is October 14, 2013 (action date October 11, 2013). Background regarding the product is below, followed by a summary of the labeling and indication issues.

Methotrexate is a folate analog metabolic inhibitor currently indicated for the treatment of neoplastic diseases, severe psoriasis, rheumatoid arthritis (RA), and polyarticular-course juvenile rheumatoid arthritis (JRA) now called polyarticular juvenile idiopathic arthritis (pJIA).

The proposed product is a drug/device combination consisting of a single-use, prefilled auto-injector intended for subcutaneous (SC) administration. It will be supplied in doses of 10 to 25 mg in 5 mg increments (10, 15, 20 and 25 mg). Because it is intended as a convenience formulation for self or caregiver use in the home setting, the applicant's proposed indications for this product are limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. The applicant also requested a new indication of moderate psoriasis, and this was considered by the Division of Dermatology and Dental Products (DDDP) and rejected (b) (4) .

No clinical trials were performed to support the application. Support for approval is based on:

1. The Agency's previous findings of the safety and effectiveness of methotrexate in patients with RA, polyarticular JRA (pJIA), and psoriasis.
2. Literature reviews that support the safety and efficacy of SC administration of methotrexate as an alternative to oral or IM administration of MTX for these conditions and for the age groups for which they are currently approved. The literature supports SC administration, with higher systemic exposure and improvements in efficacy when administered SC or IM

compared with similar oral doses, particularly at doses above 15 mg. The safety review of the literature and of the studies provided to this application did not reveal any new safety signals that would require additional labeling beyond those already labeled in the reference products.

3. A BA study (and MTX-11-003) in adults that supports efficacy with SC administration in patients with RA and psoriasis because it showed equal or greater bioavailability of the proposed MTX auto-injector product administered SC when compared to systemic exposure with orally administered MTX tablets.
4. A BE study (MTX-10-001) in adults that showed bioequivalence of systemic exposure between this auto-injector product administered SC in either the abdomen or the thigh and the approved injectable product administered with a needle and syringe either by the SC or IM route.
5. The applicant also performed an actual use labeling study (MTX-11-002) and a labeling and human factors study (MTX-11-004) to support the labeling and use of the proposed product, demonstrating that patients and caregivers could be taught to successfully use the product. These studies were requested by our CDRH colleagues.

Labeling Issues

Background

The labeling for methotrexate is very old, the listed originator oral and parenteral products having been approved in the 1950's. There are multiple generic products. None of the labels are in PLR format, although they have been updated at some point with the DESI indications, and the PI for the parenteral formulation is unified in that it contains includes oral dosing information. This will be the first methotrexate product to use PLR formatting. The labeling contains a Boxed Warning for multiple toxic effects as well as multiple Warnings and Precautions. There are no clinical trials listed in the Clinical Trials section, although a scattering of clinical information may be found in multiple sections, including the Clinical Pharmacology, Adverse Events, and Pediatrics sections, as well as in the D&A section.

The applicant wishes to update the labeling with some new clinical and other information and add clinical trials from the literature. However, this is not appropriate for a 505(b)(2) application for which the applicant is not the listed drug.

The doses used in RA, pJIA, and psoriasis range from about 5 mg to 30 mg. For RA, the recommended starting dose is 7.5 mg administered orally as a single weekly dose. For pJIA the recommended starting dose is 10 mg/m^2, and the route is not specified. For Psoriasis, the recommended starting dose is between 10 and 25 mg, administered orally, IM, or IV. For oncologic indications, doses range much higher (high-dose treatments, often with leucovorin rescue) and are administered IV and by other routes (intra-arterial, intrathecal).

Adverse events noted with methotrexate use span the full range of doses and indications, making separation of adverse events, warnings, and warnings contained in the Boxed Warning difficult or impossible based on the indication. Nevertheless, it is clear that some of these warnings and other wording are directed at the oncology indications, creating difficulty in separating out the labeling that is specific for one indication from that for the others.

Major Issues

Because this is the first instance of PLR labeling and the current labeling is not up to date with regard to today's science, two major issues arose during efforts to convert the existing labeling to PLR format and to edit the applicant's proposed additions. The first was whether to include the oncology indications in the labeling, and the second was how to address the scientific inconsistencies and lack of up to date information in the originator labels during the PLR conversion process.

Oncology Indications

The first major issue that the Agency addressed was whether to include the oncology indications in the labeling of this product since the product is bioequivalent to the parenteral product delivered either by the IM or SC routes. Of note, these indications were not requested by the sponsor. The rationale for not including the oncology indications relate to the packaging [as an auto-injector with limited doses available] and route of administration [SC, which is not used for oncology indications] of the proposed product. However, inclusion of the oncology indications would avoid creation of a product and label with indications that differ from those for the currently available products. Furthermore, given that it is not possible to separate the safety information in the current label by indication, doing so would simplify the path to creation of a label for this product. Additionally, a label including all the indications would not differ substantively from that of the originators and of their generics, (b) (4) for Otrexup.

Lack of a neoplastic disease indication was extensively discussed with DOP2 as well as with senior management, and the decision was made to exclude the oncology indications from the Otrexup labeling. This is acceptable for a number of reasons, including that the proposed doses and route of administration do not adequately address the needs for treatment of neoplastic diseases (for neoplastic indications, in addition to oral administration, higher doses are often used intravenously and the parenteral product may also be administered intrathecally and intra-arterially). This raises potential safety concerns with granting oncology indications for a product to be delivered subcutaneously and available only in limited doses.

Updating the Science

The second major issue was that much of the labeling language is not scientifically up to date, including some statements that are no longer scientifically accurate. Because of the problems with the wording in the labels for the listed drugs, updating the labeling for this product was quite difficult, and a decision had to be made whether to correct and update the information to bring it up to date with today's medical practices. However, to do so would mean that this product would have a substantially different label, (b) (4) Further, the sponsor did not perform studies or provide data to support substantial changes to the listed drugs' labels.

Examples of difficulties with updating the labeling with today's science include

1. Liver biopsies: For psoriasis, the current Warnings/Precautions section contains wording stating that a liver biopsy should be obtained pre-therapy or within 2 to 4 months after initiation of therapy, as well as after a total cumulative dose of 1.5 grams and after each

additional 1.0 to 1.5 grams dosed. The recommendations are somewhat modified for RA patients: "Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis)." If the Warnings were updated based on current scientific information, pre-treatment and concurrent treatment biopsies for patients with psoriasis would be modified to more closely match the language for RA patients. (b) (4) Furthermore, leaving the current language might language might constitute a risk to some patients.

2. Reproductive risks: The labeling for MTX contains a Boxed Warning for fetal death and congenital abnormalities, and Warnings for embryotoxicity, abortion, impairment of fertility, oligospermia, and menstrual dysfunction. For RA and psoriasis patients, MTX is Pregnancy Category X. Therefore, MTX is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks, and the labeling contains a Contraindication in pregnant women with psoriasis and RA, with use in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Because of prolonged effects post-treatment, the Contraindication specifically states that: "Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients." However, current recommendations call for avoiding pregnancy for 6 months after stopping MTX, both for females and for males. If the language were updated based on current scientific information, the recommendations would be changed to six months after therapy for male patients, and for at least six ovulatory cycles after therapy for female patients. However, doing so would give this product a competitive disadvantage in the marketplace compared with the labeling for other MTX products. Furthermore, leaving the current language might constitute a risk to some patients.

Although the sponsor of this product submitted the proposed labeling in PLR format, they did not submit sufficient information to fully update the labeling language to current scientific standards.

Other Labeling Issues

Other labeling issues included how to handle the Dosage and Administration section. The applicant wished to express the recommended starting doses based on Otrexup rather than on other formulations of methotrexate. However, as mentioned earlier in this review, the recommended starting doses for RA and pJIA for the listed drugs do not match those proposed for this product, and the recommended route of administration does not include SC dosing for any indication except pJIA. The D&A section also needs to accommodate for the fact that patients may switch back and forth between other formulations (including oral, the most commonly used formulation and route) and switched Otrexup, and that patients may require doses higher, lower, or in between the available Otrexup doses.

Labeling Decisions

In early August, DPARP requested guidance from senior management with regard to the labeling concerns discussed above. DPARP had already met with DOP2, DDDP, and the SEALD team to discuss a path forward for the labeling, and together, we began work on a 'mock' PLR label for this product maintaining all of the language of the listed products, including warnings, precautions, and adverse events for all of the indications. This 'mock' or 'generic' PLR label served as basis for creation of a label for this product that does not differ substantively from those for the listed originator and generic products. We considered but rejected possible inclusion of the oncology indications while severely limiting the Dosage and Administration section, similar to what was done for Fluoxetine 60 mg tablets in 2011 (see accompanying labels). We also considered how we could transpose the labeling to PLR and how to update the out-of-date statements. Because of the complexity of the labeling issues, DPARP, DOP2, DDDP, and SEALD requested input from CDER senior management regarding these issues prior to proceeding further. A meeting was held with representative of all of the divisions, SEALD, and CDER senior management on August 8, 2013, and the following decisions were made:

1. Keep the PDUFA timelines.
2. Do not request the applicant to add the oncology indications (i.e., to leave the proposed indications alone). (b) (4)
3. There was hesitancy about requiring a 505(b)(2) product to take on the task of updating the science for the reference product. Therefore, the decision was made to not update the language to today's scientific standards and transpose the out-of-date label from the originators to PLR keeping the language the same wherever possible rather than converting and updating the labeling. This required deviating from following all of the PLR conversion rules and guidances that are currently part of PLR conversions. (b) (4)
4. (b) (4)

Following this guidance, DPARP worked closely with DOP2, DDDP, and the SEALD team to create a new PI for this product. Using a backbone PI submitted by the applicant in PLR format, the labeling from the listed originator parenteral product was transposed to the document to ensure word-for-word capture of the language from the originator, after which the team set out to move the material into the correct locations and add language as required for PLR labeling. Once this was done, we considered the applicant's requests for labeling language, and added back only that language that was considered specific to and appropriate for this application. We then set about to define the limitations of use for the product, and finally, the Highlights.

Summary

Otrexup is a new subcutaneous auto-injector formulation of methotrexate. Although the reference product labeling (that is in old format) includes indications for neoplastic diseases as

well as RA and Psoriasis, the 505(b)(2) applicant has only proposed labeling Otrexup for the RA and Psoriasis indications. DOP2 agrees with the applicant's proposal for omitting the neoplastic diseases because the subcutaneous auto-injector would not provide appropriate dosing for these indications.

In addition, the applicant did a very poor job of PLR converting the applicable information from the old formatted methotrexate labeling into the new format. The currently approved methotrexate labeling has a significant amount of old information that needs updating and an adequate conversion could take months. (b) (4) The decision was made to adequately PLR convert the reference methotrexate labeling (b) (4)

Labeling 505(b) (2) products can be quite challenging. (b) (4)

DPARP worked directly with SEALD in the development of the Otrexup labeling. The approach was to keep the listed methotrexate product labeling information intact (with some exceptions) and move the information to the appropriate PLR labeling section. We removed efficacy information pertinent to the neoplastic diseases and added specific information pertinent to Otrexup (e.g., Dosage and Administration). We also added limitations of use for the oncology indication and D&A restrictions based on the available doses and route of administration for this product. It was a major challenge to place old information in the new format.

Attached is the draft IR explaining the Agency's reasoning and the version in of the PI that is being sent to the applicant. A teleconference is set with the applicant on

Drs. Jenkins and Woodcock have been notified of the issues related to this labeling because it is anticipated that the applicant may object because the draft labeling differs so much from their proposed labeling.

NDA 204824 - Otrexup (methotrexate) injection

Information Request

Draft 9/12/2013

We are providing the following initial labeling comments for your product. Additional comments, including comments about the Instructions for Use (IFU), trainer Instructions for Use (TIFU), and Patient Package Insert (PPI) will be forthcoming as our reviews progress.

1. We have made significant changes to the proposed Prescribing Information (PI) for your product. We recognize that Otrexup will be the first instance of Physicians Labeling Rule (PLR) labeling for a methotrexate product, and that you have proposed new language to deal with these changes. However, your product relies on listed drug labeling and you have not conducted studies that would justify having a PI with significant differences compared to the listed drug labeling. Thus, we did not accept most of your newly proposed language, choosing to carry over the labeling of the listed drugs to PLR format and keep as much of the language the same as the reference, after which we considered your proposed language and added information specific to and appropriate for your product.

   Note that the PI contains comments that may help you understand our reasoning for the changes that were made. Additionally, the document contains an embedded, highlighted comment in Section 2.4 that you will need to address, after which the comment should be deleted. Other highlighted areas relate to areas that need updating by you, such as dates and phone numbers. Please address these sections as well.

   Several examples of these changes include:

   a) PLR labeling necessitates moving information from one section to another within which the information is appropriately presented. We have moved many sections, paragraphs, and sentences, keeping the language the same as that of the listed drugs as much as possible.

   b) In certain instances, we deleted information that pertains to an indication (i.e., treatment of malignancies), dose (high-dose regimens and leucovorin rescue regimens), or route of administration (i.e., intrathecal administration) for which your product is not appropriate.

   c) The Dosage and Administration section was adjusted to deal with the fact that other formulations may need to be used for alternative doses and routes of administration, that the starting doses of methotrexate for RA and pJIA in the listed products differ from those available with Otrexup, and that patients are likely to be transferred to Otrexup after starting with other formulations.

   d) When a Boxed Warning appears in a labeling, the Warnings and Precautions section must contain the same information. We therefore made substantial changes to this section to include this information.

   e) The Clinical Studies section now contains studies from other parts of the labeling of the listed drugs, and does not include any of the information you proposed from the literature.

2. While we understand that you do not plan to co-package the active and "trainer" devices, we note that the proposed devices look very similar. This is a potential safety issue, in that the active and the trainer devices may be easily be confused with one another. To minimize confusion between the two devices, we recommend that the color gray only be used for demonstration "trainer" devices that contain no active drug, and that the active drug product not contain any visible components with a gray color. Revise the active and trainer products as follows.

   a) Revise the labeling on the trainer device to distinguish the trainer device from the active product:

      i. Replace the word (b) (4) with the word "TRAINER", and add the words "Contains NO needle and NO medicine." This information should be prominently displayed, such that the font for the word "TRAINER" is larger than that of "Otrexup".

      ii. Change the (b) (4) background color to gray.

      iii. Provide an additional instruction showing how to reset the trainer device.

   b) Revise the color scheme for the active product, taking into account the following:

      i. Choose a different color for the plastic twist-off cap (currently gray in color and marked as 1). This may be done as a post-marketing commitment (PMC) if you are unable to make these changes quickly.

      ii. Choose a different color for the safety clip (currently gray in color and marked as 2). This may be done as a PMC if you are unable to make these changes quickly.

      iii. Consider changing the cover on the needle guard (currently white in color and unmarked) that would allow it to be more easily recognized as the end containing the needle. For example, you may wish to consider changing it to orange to match the body color of the arrow pointing to the needle end.

3. Follow labeling requirements outlined in 21 CFR 201.10(g)(2), 21 CFR 201.15(a)(5), and 21 CFR 201.15(a)(6) for all instances of appearance of the proprietary name and established name on the container, carton, Package Insert (PI), and Instructions for Use (IFU) of your drug product. In particular, we refer to the following:

   a) All instances of the established name should be at least half the font size of the proprietary name. The font should be easily readable and not in *italics*.

   b) Remove the (b) (4) from above the proprietary name in the carton and container labeling, as it distracts from the proprietary name.

   c) Increase the font size of "injection xx mg.0.4 mL" on all carton and container labels.

   d) Increase the font size of "for subcutaneous use only" on all carton and container labels.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PETER R STARKE
09/26/2013

JANET W MAYNARD
09/27/2013

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	20-4824 Original 2
Priority or Standard	Standard
Submit Date(s)	December 14, 2012
Received Date(s)	December 14, 2012
PDUFA Goal Date	October 14, 2013
Division / Office	DDDP/OND
Reviewer Name(s)	Snezana Trajkovic
Review Completion Date	August 30, 2013
Established Name	Methotrexate sodium
(Proposed) Trade Name	Otrexup
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Antares Pharma Inc.
Formulation(s)	Solution for subcutaneous Injection
Dosing Regimen	10mg to 25mg SC once a week until adequate response is achieved
Indication(s)	Moderate to severe psoriasis
Intended Population(s)	18 years of age and older

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the data submitted by the applicant, this reviewer recommends the complete response for this NDA. Because of the considerable risk associated with treatment with methotrexate, the clinical benefit for patients with moderate to severe psoriasis is different from the one for patients with "severe, recalcitrant, disabling psoriasis unresponsive to other forms of therapy". Moderate to severe psoriasis is not a life threatening disorder and the vast majority of patients can be treated effectively with agents that do not have the potential toxicities associated with methotrexate. Thus, the treatment with methotrexate is not suitable for this patient population and no additional safety data would be able to justify the proposed extension of indication, to include patients with moderate to severe psoriasis.

The applicant submitted the NDA 20-4824 on 12/14/2012 to the division of Pulmonary, Allergy, and Rheumatology Products (DPARP). This NDA seeks approval under Section 505 (b)(2) of the Federal Food Drug and Cosmetic Act for Otrexup (methotrexate) injection, a drug-device combination product, for the new route of administration, subcutaneous (SQ). In addition, the applicant submitted data to support an extension of the current indication to include treatment of patients with moderate to severe psoriasis. The device used for this combination product is a single-use disposable autoinjector (AI) designed to deliver subcutaneously a fixed volume of 0.4mg yielding a single dose of 10mg; 15mg; 20mg or 25mg of methotrexate.

Because the applicant requested extension of psoriasis indication from "symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation" to " treatment of moderate to severe psoriasis" this submission was administratively split to: "Original 1" to be reviewed by the DPARP and "Original 2" to be reviewed by Division of Dermatology and Dental Products (DDDP). The focus of this review is evaluation of data submitted by the applicant in support of extension of psoriasis indication.

The listed drugs (LD) are: Methotrexate Sodium Preservative Free Injection EQ 50mg base/2ml, of Hospira (NDA 011719 approved on August 10, 1959); Methotrexate Tablet 2.5mg of Dava (NDA 08085 approved on December 7, 1953) and Methotrexate Sodium Preservative Free Injection from Bedford (ANDA 40-632, approved on August 12, 2005).

Currently, Methotrexate Sodium Preservative Free Injection and Methotrexate Tablet are approved for the same indication of "symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only

when the diagnosis has been established, as by biopsy and/or after dermatologic consultation". The recommended dose of Methotrexate Sodium Preservative Free Injection and Methotrexate Tablet is 10mg to 25mg per week administrated as IM or IV injection or oral tablet.

To support a new subcutaneous route of admiration of Otrexup and to provide clinical bridge to previously approved products, the applicant conducted two bioavailability/ bioequivalence (BA/BE) studies. The applicant established that Otrexup, when administered subcutaneously, is bioequivalent to the LD administered subcutaneously or intramuscularly.

To support an extension of the current indication to include treatment of patients with "moderate to severe psoriasis", the applicant submitted literature reports of studies in patients with moderate to severe psoriasis.

Methotrexate labeling contains boxed warning for death and serious adverse events associated with its use. Many of these events, especially hepatotoxicity including fibrosis and cirrhosis, malignant lymphomas, bone marrow suppression, aplastic anemia, interstitial pneumonitis and opportunistic infections, are life threatening and result in death and hospitalizations. Because of this considerable risk, methotrexate's use is limited to patients with most severe disease that is also non-responsive to other forms of therapy.

It is reasonable to conclude that because methotrexate is effective in treating severe psoriasis, it would also be effective in treating patients with milder disease. In addition, it is expected that the safety profile in the population of patients with milder psoriasis would not be different from that with severe disease. However, given considerable risk associated with treatment with methotrexate, the clinical benefit for patients with moderate to severe psoriasis is different from the one for patients with "severe, recalcitrant, disabling psoriasis unresponsive to other forms of therapy". Moderate to severe psoriasis, while a serious disease with substantial impact on quality of life is not a life threatening disorder and the vast majority of patients can be treated effectively with agents that do not have the potential toxicities associated with methotrexate.

Use of a drug that is associated with potentially life threatening adverse events in population of patients with the milder disease and for whom there are available effective therapies without the risks that of methotrexate cannot be justified. Therefore, this reviewer recommends complete response for this NDA.

1.2 Risk Benefit Assessment

The applicant seeks approval under Section 505 (b)(2) of the Federal Food Drug and Cosmetic Act for the new route of administration, subcutaneous (SQ), and expanded indication. In order to be able to rely on the Agency's finding of safety and efficacy for

the listed drugs, the applicant established a clinical bridge that consists of two pharmacokinetic (PK) studies MTX-10-001 and MTX-11-003.
PK study (MTX-10-001) was conducted to evaluate if Otrexup drug/device combination product is bioequivalent to the listed drugs and therefore is safe and effective for the approved indications including that of symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy. The results of this study revealed that Otrexup administered subcutaneously is bioequivalent in terms of Cmax and AUC to the same dose of subcutaneous or intramuscular injection of approved methotrexate injection. The 90% Confidence Intervals (CIs) for the Otrexup administered SC, were within the bioequivalence range of 80% to 125% when compare to the SC and IM of the approved methotrexate injection product. Therefore, Otrexup administered subcutaneously met bioequivalence criteria relative to the marketed methotrexate injection, administered subcutaneously or intramuscularly.

Study MTX-11-003 was conducted to evaluate the relative bioavailability of Otrexup in comparison to Methotrexate Tablet and to compare bioavailability of Otrexup administered subcutaneously into the abdomen or anterior thigh. The study showed that administration of Otrexup subcutaneously into abdomen or anterior thigh leads to similar exposure.
Bioavailability of subcutaneous administration of Otrexup at doses of 10mg, 15mg, 20mg or 25mg, was higher than oral administration of same doses of Methotrexate Tablet, particularly at the higher (20mg to 25mg) dose levels at which time the plateau of systemic exposure is reached. This finding was not unexpected, given the known limitations of methotrexate gastrointestinal absorption. See Clinical Pharmacology review by Sheetal Agarwal, Ph.D.

This NDA also provides for extension of current indication from “symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy” to “moderate to severe psoriasis”. To establish safety and efficacy of Otrexup in the treatment of moderate to severe psoriasis the applicant relied on 6 study reports available in the public domain. None of the studies evaluated safety and efficacy of subcutaneously administered methotrexate. Four out of 6 (Reich et al., Yan et al., Gottlieb et al., Saurat et al.) studies evaluated oral methotrexate and in the remaining 2 (Heydendael et al; Flystrom et al) the methotrexate dosage form was not specified.

- Five out of six randomized, double blind studies compared methotrexate therapy to an active control. Authors of these studies concluded the following:
    - There was no significant difference in efficacy between methotrexate and cyclosporine (Heydendael et al)
    - Cyclosporine was more effective than methotrexate (Flystrom et al)
    - Briakinumab (unapproved product; monoclonal antibody against IL-12 and IL-23) showed to be more effective than methotrexate (Reich et al.),
    - LFA-3IgFP (unapproved product; recombinant human Lymphocyte Associated Antigen 3 –antibody fusion protein) did not differ significantly (Yan et al) from methotrexate.

  - In the study by Gottlieb et al, methotrexate was used in the combination with etanercept; therefore safety and efficacy of methotrexate alone were not evaluated.
- Only one study included a placebo arm (Saurat et al.). The author concluded that the methotrexate was more effective then placebo in the treatment of subjects with moderate to severe psoriasis. Statistical analysis comparing methotrexate to placebo was not prespecified.

For the complete information refer to section **5.3 Discussion of Individual Studies / Clinical Trials.**

Data provided from the above studies are very limited because none of the published studies evaluated subcutaneous route of MTX administration, most of the studies used active control for comparison to MTX, none of the studies provided complete safety results or subject-level data to allow independent efficacy and safety assessment. Therefore this reviewer finds that the design and conduct of these studies were not adequate to provide the evidence that the benefits of methotrexate, in subjects with moderate to severe psoriasis, outweigh its risks. However, it is reasonable to conclude that because methotrexate is effective in treating severe psoriasis, it would also be effective in treating patients with milder disease. In addition, it is expected that the safety profile in the population of patients with milder psoriasis would not be different from that with severe disease. Moderate to severe psoriasis, while a serious disease with substantial impact on quality of life is not a life threatening disorder and the vast majority of patients can be treated effectively with agents that do not have the potential toxicities associated with methotrexate.

Methotrexate labeling contains boxed warning for death and serious adverse events associated with its use. Many of these events, especially hepatotoxicity including fibrosis and cirrhosis, malignant lymphomas, bone marrow suppression, aplastic anemia, interstitial pneumonitis and opportunistic infections, are life threatening and result in death and hospitalizations. In addition, due to potential for acute and chronic liver toxicities, methotrexate labeling contains recommendation for periodic liver biopsies, an invasive procedure that carries a risk of serious hemorrhage and bile peritonitis, complications that can result in hospitalization and death. Because of this considerable risk, methotrexate's use is limited to patients with most severe disease that is also non-responsive to other forms of therapy.

Given the considerable risks associated with methotrexate treatment and availability of other less toxic therapies, the extension of currently approved indication of "severe, recalcitrant, disabling psoriasis unresponsive to other forms of therapy" to include patients with moderate to severe psoriasis cannot be justified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Given the long history of clinical use of methotrexate, which includes 60 years of experience of use for the treatment of cancer, rheumatoid arthritis, juvenile rheumatoid arthritis and psoriasis, the well documented and well known adverse event (AE) profile associated with the use of the drug, and the lack of identification of additional safety signals in this review, no postmarketing risk evaluation and mitigation activities are required at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Given the long history of clinical use methotrexate, the well documented AE profile associated with the use of the drug, and the lack of identification of additional safety signals in this review, no PMRs are required at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Otrexup (methotrexate sodium) is drug/device combination product for which the applicant seeks approval under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for the treatment of moderate to severe psoriasis in patients 18 years of age and older. This application provides for the new route of administration, and extended indication.

The Listed Drugs are: Methotrexate Sodium Preservative Free Injection EQ 50mg base/2ml, of Hospira, the holder of the approved application (NDA 011719 approved on August 10, 1959, EQ 50mg/ml); Methotrexate Tablet (NDA 08085, approved on December 7, 1953; by Dava Pharmaceutical Inc.) and Methotrexate Sodium Preservative Free Injection from Bedford (ANDA 40-632, approved on August 12, 2005).

Listed Drugs (LD) were approved for the “symptomatic control of **severe**, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.” The approved routes of administration for the LDs, in the treatment of psoriasis, are intramuscular (IM) and intravenous (IV) and oral (PO). The reason for use of Bedford’s methotrexate injection was the shortage of Hospira’s methotrexate injection.

The applicant, Antares Pharma Inc., developed a methotrexate drug/device combination product, Otrexup, a single-use prefilled autoinjector for subcutaneous administration. Subcutaneous administration represents a new rout of administration of MTX in the

treatment of psoriasis. The applicant constructed the clinical bridge to support this new route of administration.

This NDA relies on the Agency's findings of safety and effectiveness for the listed drugs, Methotrexate Sodium Preservative Free and Methotrexate Tablet, for the indication of "symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation." The scientific justification for this reliance is provided by data from one bioequivalence and one bioavailability study performed in humans, "the clinical bridge".
Bioequivalence is defined in 21CFR 320.1 as: the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents of pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in appropriately designed study." If bioequivalence is established, then the active moiety of Otrexup and Methotrexate Sodium Preservative Free will be available at the site of drug action without a significant difference in rate or extent. One can infer then that there would not be a significant difference between Otrexup and Methotrexate Sodium Preservative Free, in safety and efficacy when used to treat severe, recalcitrant psoriasis.

The applicant is requesting change of indication to include "treatment of **moderate to severe** psoriasis" for which LDs are not approved. For the indication of treatment of "moderate to severe psoriasis", this NDA relies on published literature. The applicant has not conducted clinical studies to evaluate safety and efficacy of Otrexup in the treatment of subjects with moderate to severe psoriasis.

The LDs are also approved for the treatment of:

- Neoplastic diseases (choriocarcinoma, hydatiform mole, chorioadenoma destruens, acute lymphoblastic leukemia, meningeal leukemia, Burkitt's lymphoma, mycosis fungoides, osteosarcoma);
- Rheumatoid arthritis
- Polyarticular juvenile rheumatoid arthritis.

The approved routs of administrations are: intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial, and intra-thecal and oral (PO).

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there are several products approved in the United States for the treatment of moderate to severe or severe psoriasis:

Table 1: Currently Available Treatments for Moderate to Severe Psoriasis

Approved Product	NDA/BLA #/Year of Approval in United States	Class	Indication
Methotrexate Preservative Free (methotrexate sodium)	NDA 11,719 (8/10/59)	Folate inhibitor	Severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy
Soriatane (acitretin)	NDA 9-821 (10/28/96)	Retinoid	Severe psoriasis in adults
Neoral (cyclosporine)	NDA 50-715 (7/14/95)	T-helper cell inhibitor	Severe, recalcitrant, plaque psoriasis who failed to respond to at least one systemic therapy
Amevive (alefacept)	BLA 125,036 (1/30/03)	Inhibits interaction between CD2 and its ligand LFA-3	Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy
Enbrel (etanercept)	BLA 103,795 (11/2/98)	TNF- blocker	Adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Humira (adalimumab)	BLA 125,057 (12/31/02)	TNF- blocker	Adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Remicade (infliximab)	BLA 103,772 (8/24/98)	TNF- blocker	Adult patients with chronic severe plaque psoriasis who are candidates for systemic therapy
Stelara (briakinumab)	BLA 125,261 (9/25/09)	IL-12 and IL-23 antagonist	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Source: reviewer

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate has been marketed in the United States since 1953. Methotrexate is currently available in tablet and injectable solution dosage forms. Injectable methotrexate has been approved for administered by the intramuscular (IM), subcutaneous (SC), intravenous (IV), intrathecal and intra-arterial route. Several generic formulations of both dosage forms are available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Methotrexate has been marketed for 60 years and its safety profile has been well characterized over this period of time. Methotrexate prescribing information includes a boxed warning that describes bone marrow, liver, lung, gastrointestinal, renal and skin toxicities; fatal opportunistic infections; fatal death and congenital anomalies; drug and radiotherapy interactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Pre-IND meeting was held on February 5, 2009
The Agency advised the applicant that bioavailability study, in order to be able to serve as a bridging study, should be designed to demonstrate that methotrexate administered via the device would be similar to methotrexate administered SC without the device, with respect pharmacokinetics and local tolerability. In addition, bridging to IM route of administration would be necessary to link preclinical studies.
The applicant would also need to construct a clinical bridge to the oral route of administration in order to link to the efficacy, safety, and dosing for oral methotrexate.

End-of-Phase 2 meeting was held on September 13, 2011
The Agency advised the applicant that because of the lack of clear dosing information for the parenteral route, they would need to provide information to support the proposed dosing for their product.

Pre NDA meeting was held on November 2, 2012
The content and format of the NDA submission were discussed at this meeting.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No clinical study sites were recommended for inspection.

Given the limitations of a literature-based submission, the overall quality of the submission was acceptable. The applicant used available resources to provide efficacy and safety data to support their application.

3.2 Compliance with Good Clinical Practices

The applicant stated that studies were designed, monitored, and conducted in accordance with Good Clinical Practice (GCP) requirements and the ethical principles. Trial protocols, the subject information and informed consent forms, subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The sponsor obtained an approval from IRB prior to trial initiation.

Part of the submission derived from publicly available sources is not a subject of the review of good clinical practice.

3.3 Financial Disclosures

The applicant certified (Form 3454) that they had not entered into any financial arrangements with any of the clinical investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug component of the Otrexup Injection drug/device combination product is methotrexate injection, a clear, sterile, (b) (4) preservative free aqueous solution. Methotrexate injection is contained within a single-dose syringe with a 27-gauge, ½ -inch needle with a soft needle shield within a pressure-assisted autoinjector, which is equipped with a needle safety guard and safety cap. Otrexup is designed for subcutaneous (SC) administration of a fixed volume of 0.4ml, to yielding final dose of 10mg, 15mg, 20mg or 25mg of methotrexate.

The final drug-device presentation includes:

- Pre-filled syringe and
- Single use autoinjector that delivers the labeled dose contained in pre-filled syringe.

The purpose of the drug delivery device is to aid in ease of self-administration and to protect from accidental needle stick.

The component and composition of Methotrexate Injection are listed in the Table 2 below.

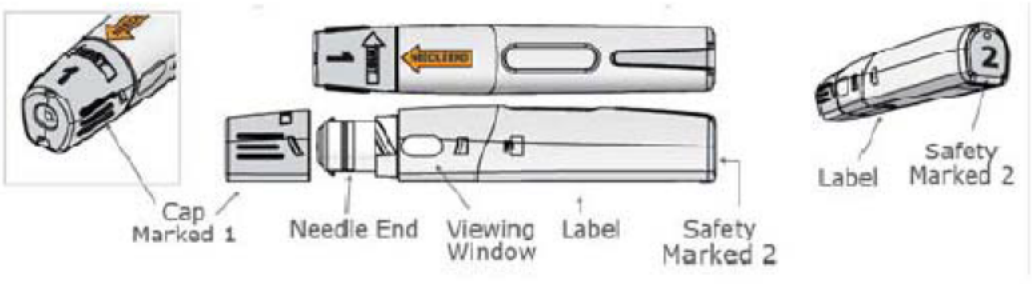
Table 2: Components and Unit Composition of Methotrexate Injection

Dose (mg/0.4 mL)	Methotrexate, USP (mg/mL)	Fill Volume (mL)	Sodium Chloride, USP/Ph. Eur. (mg/mL)	Sodium Hydroxide, NF/Ph. Eur.	Hydrochloric Acid, NF/Ph. Eur.	Water for Injection, USP/Ph. Eur.	(b) (4)
10	(b) (4)	0.4				(b) (4)	
15		0.4					
20		0.4					
25		0.4					
Function	Active Ingredient	N/A	(b) (4)	pH adjuster	pH adjuster	(b) (4)	

[1] qs = quantity sufficient to adjust pH
Source: Applicant's submission, 3.2.P.2.1, Table 1, p1

Device
The device is designed for single use of a fixed dose, and discarded after use. The schematic representation of the autoinjector device is presented in Figure1 below.

Figure 1: Representative Schematic of the Autoinjector



Source: Applicant's submission, 3.2.P. Figure 1, p 5.

For the complete CMC information, reader is referred to the review by Arthur B. Shaw, Ph.D.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The applicant has not conducted any nonclinical studies. The Sponsor submitted controlled extraction studies of the syringe, needle shield, and plunger stopper. In addition, controlled extraction, leachables, and stability studies were performed with aged methotrexate and control drug product. Pharmacology/Toxicology reviewer,

Andrew C. Goodwin, Ph.D., has reviewed applicant's submitted data and made the following conclusion: "Based on the potential patient exposure levels and a review of available information the safety of each of these potential leachables, extractables, impurities, and degradants in OTREXUP is considered qualified from the nonclinical perspective."

For the complete Preclinical Pharmacology/Toxicology information reader is referred to the review by Dr. Andrew C. Goodwin.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Methotrexate (MTX) is a folate antagonist that inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates before they can be utilized as carriers of one-carbon groups in the synthesis of purines nucleotides and thymidylate. Inhibition of dihydrofolic acid reductase leads to depletion of intracellular stores of activated folate and interferes with DNA synthesis, repair, and disrupts cellular replication.
In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This difference in proliferation rates is the basis for the use of methotrexate to control psoriatic process. However, the precise mechanism of action in the treatment of psoriasis is unknown.

4.4.2 Pharmacodynamics

After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. Methotrexate is partially metabolized by intestinal flora after oral administration.

The terminal half-life reported for methotrexate is approximately 3-10 hours for patients receiving less than 30 mg/m^2. For patients receiving high doses of methotrexate, the terminal half-life is 8-15 hours.

The primary route of elimination is by renal excretion. Renal excretion occurs by glomerular filtration and active tubular secretion. There is limited biliary excretion amounting to 10% or less of the administered dose.

4.4.3 Pharmacokinetics

The applicant conducted two pharmacokinetic studies (MTX-10-001 and MTX-11-003) in order to establish clinical bridge to the listed drugs (LDs).

Study MTX-10-001

Title: A Phase 2, Open-Label, Randomized 3-Way Crossover Study to Compare the Exposure, Safety, and Local Tolerance of a Subcutaneous Injection of Methotrexate Using the Vibex MTX Device with the Subcutaneous Injection of Methotrexate without the Device and With the Intramuscular Administration of Methotrexate in Adult Subjects with Rheumatoid Arthritis

Study initiated: 1/17/2011
Study completed: 5/31/11

Study design: This was a randomized, open-label, multicenter, three-way crossover design, conducted in adult subjects with RA undergoing treatment with methotrexate.

Study Objectives:
1. To compare the PK profile of:
   - Otrexup following a SC administration using the device
     to
   - Marketed MTX following a SC administration using a needle and syringe

2. To compare the PK profile of:
   - Otrexup injection following a SC administration using the device
     to
   - Marketed MTX following IM administration using a needle and syringe

3. To assess safety and local tolerance of SC MTX injection.

This study was conducted in adult subjects with rheumatoid arthritis (RA).
The marketed MTX was Methotrexate Sodium Preservative Free from Bedford (ANDA 89-340, approved on September 16, 1986), which is listed in the Orange Book as a RLD.

Study subjects
Adult male and female subjects, ≥18 years of age, with RA who are undergoing treatment with methotrexate for at least 3 months prior to randomization.

Study procedures:
During the screening period, each subject was assigned to one of the four MTX dosing groups (10 mg, 15 mg, 20 mg, or 25 mg). MTX dose was based on the disease status (RA controlled vs. RA uncontrolled).

Each subject received three different MTX treatments, administered separately, one week apart:

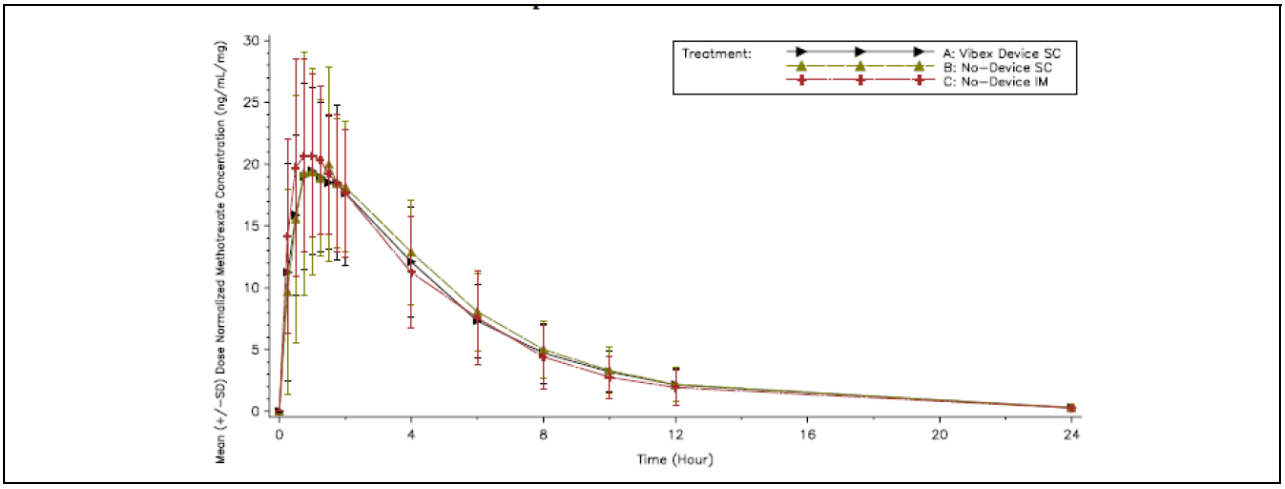
- Otrexup administered SC using Vibex device (previously used name for autoinjector) into anterior abdominal wall (Treatment A)
- Marketed MTX administered SC using a needle and syringe, into anterior abdominal wall (Treatment B);
- Marketed MTX administered IM using a needle and syringe, into outer thigh (Treatment C).

Blood samples for MTX PK analyses were obtained on Day 1 of each treatment period (pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, and 12 hours post-dose) and on Day 2 of each treatment period (24 hours post-dose).

Safety evaluation
Vital signs (BP, pulse rate), physical examinations, injection site reactions, and clinical laboratory evaluations (serum pregnancy test, hematology, biochemistry, HCV Ab, HIV Ab, HbsAg, and urinalysis,) were performed at screening and at the end of the study visits. A 12-lead ECG, and urine drug and alcohol screen, were performed at screening visit. Monitoring for AEs was done throughout the duration of the study.

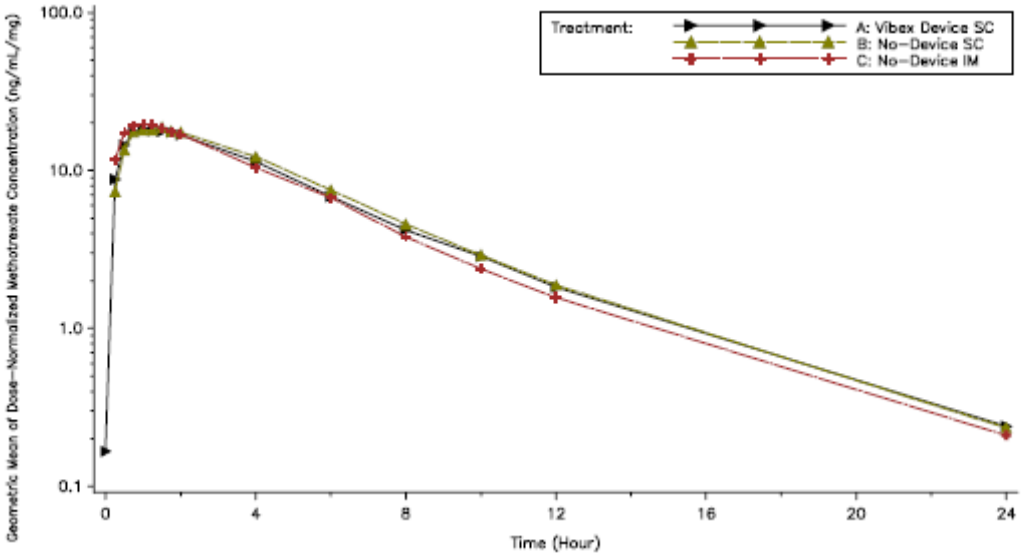
Pharmacokinetic Results
Figure 2 and Figure 3 display the profiles for time vs. the mean dose-normalized plasma concentration of MTX by treatment.

Figure 2: Plot of Mean (±SD) Dose-Normalized Methotrexate Concentration vs. Time by Treatment on Original Scale-Pharmacokinetic Population



Source: Applicant's submission, 5.3.1.2. MTX-001 Study Report Body, Figure 1, p 49.

Figure 3: Plot of Geometric Mean Dose-Normalized MTX Concentration vs. Time by Treatment on Logarithmic Scale- Pharmacokinetic Population



Source: Applicant's submission, 5.3.1.2. MTX-001 Study Report Body, Figure 2, p 50.

Bioequivalence Determination

The relative bioavailability of Otrexup administered SC using Vibex device was compared to SC injection of marketed MTX administered without a device (Treatment A vs. Treatment B).

Bioequivalence ratios of the geometric least-squares (LS) means of the AUC (0-24)/Dose, AUC(0-inf)/Dose, and Cmax/Dose PK parameters for Treatment A and Treatment B are presented in the Table 3 below:

Table 3: Analysis of Dose-Normalized Pharmacokinetic Parameters for Determination of Bioequivalence: Mixed Model – Treatment A vs. Treatment B – Pharmacokinetic Population

Dose-Normalized PK Parameter	Treatment A N = 36 Geometric LS Mean [1]	Treatment B N = 36 Geometric LS Mean [1]	Ratio of Geometric LS Mean (%)	90% CI for Ratio (%) [2]	Intra-Subject CV (%) [3]
AUC(0-24)/Dose (ng□hr/mL/mg)	111.3	115.7	96.22	(92.3, 100.3)	10.5
AUC(0-inf)/Dose (ng□hr/mL/mg)	112.6	117.0	96.24	(92.3, 100.3)	10.6
Cmax/Dose (ng/mL/mg)	20.2	20.9	96.76	(87.9, 106.5)	24.6

Treatment A: SC injection with Vibex device.
Treatment B: SC injection without device.
A mixed model is performed on logarithm-transformed dose-normalized PK parameters. The model contains sequence, period, and treatment effects as fixed effects, and subject within sequence as a random effect.

1. Geometric LS means are the least square means from the mixed model presented after back transformation to the original scale.
2. The 90% CIs are presented after back transformation to the original scale.
3. Intra-subject CV (%) is calculated as 100*SQRT (EXP (SIGMA**2) -1), where SIGMA**2 is the residual variance estimate from PROC MIXED.
AUC(0-24)/Dose = dose-normalized area under the curve from time zero to 24 hours; AUC(0-inf)/Dose = dose normalized area under the curve from time zero to infinity; CI = confidence interval;
Cmax /Dose = dose-normalized maximum observed plasma concentration; CV = coefficient of variation; LS = least-squares; PK = pharmacokinetic; SC = subcutaneous.

Source: Applicant's submission, 5.3.1.2. MTX-001 Study Report Body, Table 9, p 53.

Because the CIs of all ratios were contained within the bioequivalence range of 80% to 125%, Treatment A was considered bioequivalent to Treatment B.

The relative bioavailability of Otrexup administered via SC injection with the Vibex device was compared to marketed MTX administered via IM injection (Treatment A vs. Treatment C).
Bioequivalence ratios of the geometric LS means of the AUC (0-24)/Dose, AUC (0-inf)/Dose, and Cmax/Dose PK parameters for Treatment A and Treatment C are presented in the Table 4 below.

Table 4: Analysis of Dose-Normalized Pharmacokinetic Parameters for Determination of Bioequivalence: Mixed Model – Pharmacokinetic Population – Treatment A vs. Treatment C

Dose-Normalized PK Parameter	Treatment A N = 36 Geometric LS Mean [1]	Treatment C N = 36 Geometric LS Mean [1]	Ratio of Geometric LS Mean (%)	90% CI for Ratio (%) [2]	Intra-Subject CV (%) [3]
AUC(0-24)/Dose (ng□hr/mL/mg)	111.3	110.1	101.14	(97.1, 105.4)	10.5
AUC(0-inf)/Dose (ng□hr/mL/mg)	112.6	111.2	101.28	(97.2, 105.6)	10.6
Cmax/Dose (ng/mL/mg)	20.2	22.5	89.79	(81.6, 98.8)	24.6

Treatment A: SC injection with Vibex device.
Treatment B: SC injection without device.
A mixed model is performed on logarithm-transformed dose-normalized PK parameters. The model contains sequence, period, and treatment effects as fixed effects, and subject within sequence as a random effect.
1. Geometric LS means are the least square means from the mixed model presented after back transformation to the original scale.
2. The 90% CIs are presented after back transformation to the original scale.
3. Intra-subject CV (%) is calculated as 100*SQRT (EXP (SIGMA**2) -1), where SIGMA**2 is the residual variance estimate from PROC MIXED.
AUC(0-24)/Dose = dose-normalized area under the curve from time zero to 24 hours; AUC(0-inf)/Dose = dose normalized area under the curve from time zero to infinity; CI = confidence interval;
Cmax /Dose = dose-normalized maximum observed plasma concentration; CV = coefficient of variation; LS = least-squares; PK = pharmacokinetic; SC = subcutaneous.

Source: Applicant's submission, 5.3.1.2. MTX-001 Study Report Body, Table 9, p 54.

Because the CIs of all ratios were contained within the bioequivalence range of 80% to 125%, Treatment A was considered bioequivalent to Treatment C.

Conclusion
Based on the results presented above, Otrexup administered SC with the Vibex device (Treatment A) was bioequivalent to marketed MTX administered SC without the device (Treatment B) and to marketed MTX administered IM without the device (Treatment C).

Study MTX-11-003
Title: A Phase 2, Open-Label, Randomized, 3-Way Crossover Study to Compare the Relative Bioavailability of Methotrexate and the Vibex MTX Device in Adult Subjects with Rheumatoid Arthritis

Study initiated: 5/2/12
Study completed: 7/16/12

Study design: This was a randomized, open-label, multicenter, three-way crossover design, conducted in adult subjects with RA undergoing treatment with methotrexate.

Study Objectives:

- To compare the relative bioavailability of methotrexate (MTX) tablet following oral administration to that obtained after Otrexup subcutaneous (SC) injection into the abdomen using the Vibex device.
- To compare the relative bioavailability of MTX following oral administration to that obtained after Otrexup SC injection into the thigh using the Vibex device.
- To compare the relative bioavailability of Otrexup following SC injection into the abdomen to that obtained after SC injection into the thigh, using the Vibex device.

Study subjects
Adult male and female subjects, ≥18 years of age, with RA who are undergoing treatment with methotrexate for at least 3 months prior to randomization.

Study procedures
Each eligible subject was assigned to one of 4 MTX dosing groups (10 mg, 15 mg, 20 mg, or 25 mg of MTX). MTX dose was based on the subject's baseline MTX therapy and disease status (RA controlled or RA uncontrolled).
At the assigned dose, each subject received three different MTX treatments, each separated by interval of one week:

- Treatment A: Oral MTX (2.5mg tablet)
- Treatment B: Otrexup SC injection of MTX into the abdomen using the Vibex MTX device,
- Treatment C: Otrexup SC injection of MTX into the thigh using the Vibex MTX device.

The sequence of treatments was randomly determined.

Blood samples for MTX PK analyses were obtained on Day 1 of each treatment period (pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, and 12 hours post-dose) and on Day 2 of each treatment period (24 hours post-dose).

Safety evaluation
The following safety monitoring was performed:

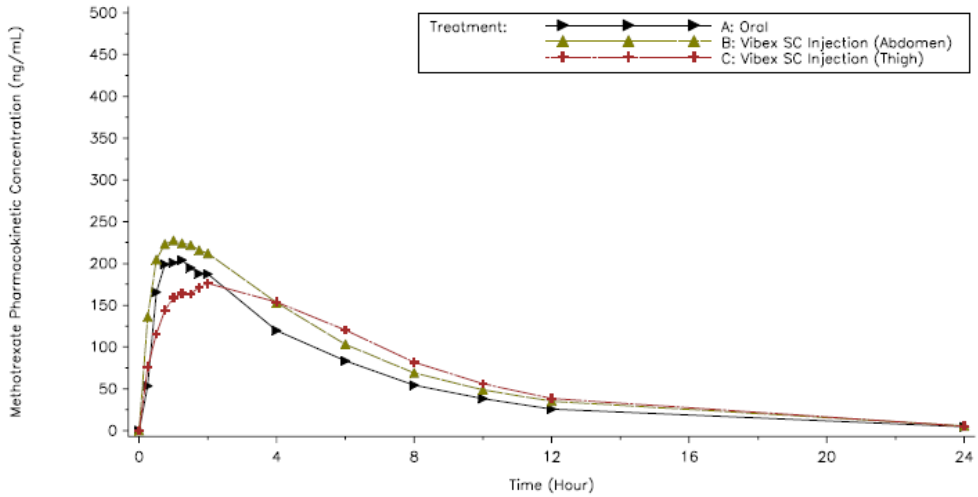
- Vital signs at each visit (BP)
- Physical examination at Screening
- Chest X-ray at Screening
- Laboratory assessments (hematology, biochemistry and urinalysis) at Screening and Visit 8.
- Serum pregnancy test at Screening and urine pregnancy test at Visit 2, 4, and 6
- Urine drug and alcohol screen at Screening.

Adverse events were monitored throughout the study starting at the Screening visit.

Results

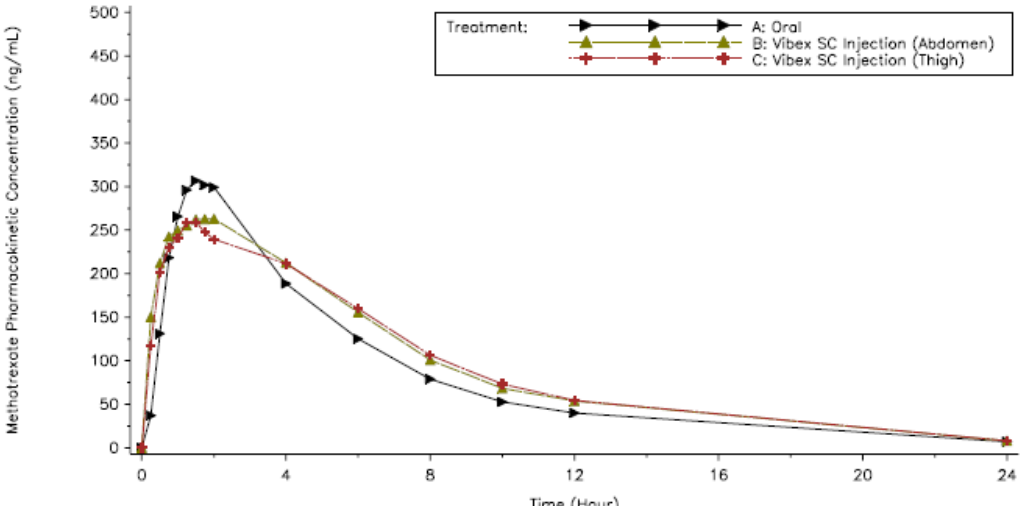
Figures 4 through Figure 7 display the plots of mean MTX concentration versus time on the original scale by treatment for the PK population. After 4 hours post-dose, the mean MTX concentration was consistently higher with the VIBEX SC device as compared to oral MTX. This trend was observed at all dose levels but was most apparent at the 15mg, 20mg, and 25mg dose levels. MTX concentrations peaked by approximately 2 hours post-dose. The peak MTX concentration increased in a dose-proportional manner for the 10mg, 15mg and 20mg dose levels across all treatments. However, at the 25mg dose level, a dose-proportional increase in the peak MTX concentration was seen in the SC injection abdomen group only.

Figure 4: Plot of Mean MTX Concentration vs. Time on Original Scale by Treatment-PK Population (MTX 10mg Dose Group)



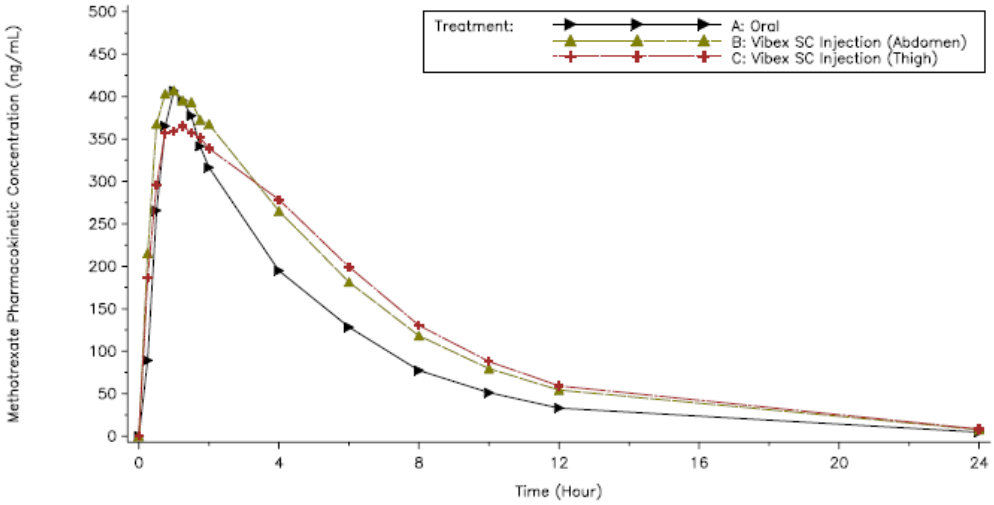
Source: Source: Applicant's submission, 5.3.1.2. MTX-11-003 Study Report Body, Figure 1, p 46.

Figure 5: Plot of Mean MTX Concentration vs. Time on Original Scale by Treatment-PK Population (MTX 15mg Dose Group)



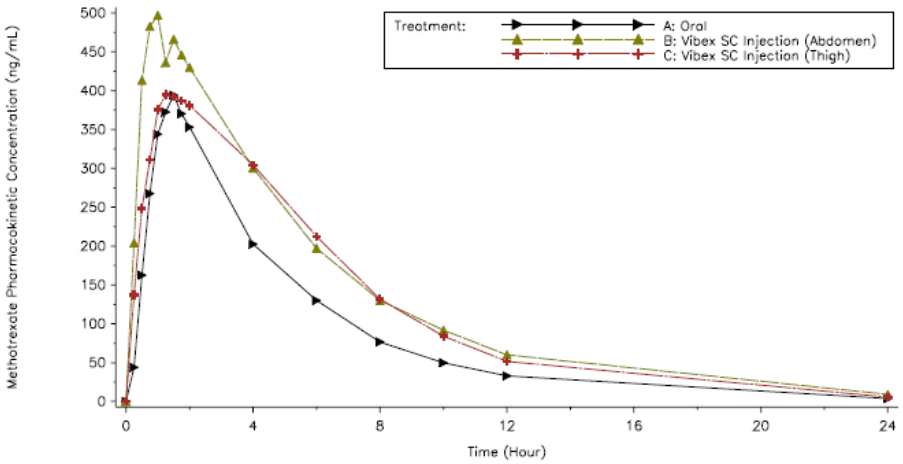
Source: Source: Applicant's submission, 5.3.1.2. MTX-11-003 Study Report Body, Figure 2, p 47.

Figure 6: Plot of Mean MTX Concentration vs. Time on Original Scale by Treatment-PK Population (MTX 20mg Dose Group)



Source: Source: Applicant's submission, 5.3.1.2. MTX-11-003 Study Report Body, Figure 3, p 47.

Figure 7: Plot of Mean MTX Concentration vs. Time on Original Scale by Treatment-PK Population (MTX 25mg Dose Group)



Source: Source: Applicant's submission, 5.3.1.2. MTX-11-003 Study Report Body, Figure 4, p 48.

Bioequivalence Determination

Table 5 represents the relative bioavailability of dose-normalized MTX administered via SC in the abdomen with the VIBEX device versus SC injection in the thigh with VIBEX device (Treatment B versus Treatment C).

Table 5: Analysis of Dose-Normalized Methotrexate Pharmacokinetic Parameters: Mixed Model – Pharmacokinetic Population – Treatment B vs. Treatment C

Dose-Normalized PK Parameter	**Treatment B Geometric LS Mean**	**Treatment C Geometric LS Mean**	**Ratio of Geometric LS Mean (%)**	**90% CI for Ratio (%)**	**Intra-Subject CV (%)**
n	49	47			
AUC(0-24)/Dose (ng□hr/mL/mg)	131.4	129.1	101.82	(99.4, 104.3)	7.0
AUC(0-inf)/Dose (ng□hr/mL/mg)	133.9	131.4	101.85	(99.4, 104.4)	7.0
Cmax/Dose (ng/mL/mg)	20.5	17.8	115.63	(108.8, 122.9)	17.7

Source: Applicant's submission, 5.3.1.2. MTX-11-003 Study Report Body, Table 2, p 61.

Because the CIs of all ratios were contained within the bioequivalence range of 80% to 125%, Treatment B (Otrexup SC injection of MTX into the abdomen) was considered bioequivalent to Treatment C (Otrexup SC injection of MTX into the thigh).

Study MTX-10-003 showed that Otrexup administration (into abdomen or thigh) leads to higher methotrexate exposures as compared with the oral methotrexate administration. This result is not unexpected as Otrexup is not designed to be bioequivalent to the oral methotrexate tablets. For the complete information reader is referred to the review by Sheetal Agarwal, Ph.D.

5 Sources of Clinical Data

The applicant submitted a NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act relying on publicly available information as the primary source of data necessary to demonstrate clinical safety and efficacy of Otrexup for the treatment of moderate to severe psoriasis. The applicant conducted a comprehensive search of scientific literature using the following databases: MEDLINE and EMBASE.

The applicant used the following parameters in the search of scientific literature:

1. Intervention	Subcutaneous methotrexate, intramuscular methotrexate, parenteral methotrexate
2. Comparator	Oral methotrexate
3. Treatment duration	Chronic use
4. Condition of interest	Rheumatoid arthritis, psoriasis, inflammatory bowel disease
5. Population	Human, all ages
6. Endpoints	Safety, efficacy, pharmacokinetics, human pharmacology
7. Study design	Systematic reviews, meta-analyses, randomized controlled trials, and evidence-based guidelines

A total of 632 publications were retrieved and were screened by title and abstract for eligibility. The list of publications that support this application is presented in section **5.1 Tables of Studies/Clinical Trials** below**.**

5.1 Tables of Studies/Clinical Trials

The applicant conducted clinical studies, presented in the Table 6, in support of the current application.

Table 6: Studies Conducted by the Applicant

Trial number	Objective	Study design	Test product	No. of subjects	Study subjects	Duration of treatment
MTSX-10-001 Initiated: 1/17/11 Completed: 5/31/11	PK of: SC Otrexup injection using a device compared to SC injection of marketed MTX using a needle and syringe And SC Otrexup injection using a device compared	Randomized, open-label, 3-way crossover	SC Otrexup injection with device at doses of 10mg, 15mg, 20mg, or 25mg, in the anterior abdominal wall SC marketed MTX injection using a needle and syringe at doses of 10mg, 15mg, 20mg, or 25mg, administered in the anterior	36	Adult subjects with RA	Single MTX dose, 3 treatment periods, one week in duration, separated by one week

	to IM injection of marketed MTX using needle and syringe		abdominal wall IM injection of marketed MTX using needle and syringe, at doses of 10mg, 15mg, 20mg, or 25mg, administered in the outer thigh			
MTX-11-003	To compare relative bioavailability of: Oral MTX compared to SC Otrexup injection with device into abdomen Oral MTX compared to SC Otrexup injection with device into thigh SC Otrexup with device into thigh compared to SC Otrexup injection with device into abdomen	Randomized, open-label, 3-way crossover study	Oral MTX (2.5mg tablet) administered at doses of 10mg, 15mg, 20mg, or 25mg SC Otrexup injection with device at doses of 10mg, 15mg, 20mg, or 25mg, administered in the anterior abdominal wall SC Otrexup injection with device at doses of 10mg, 15mg, 20mg, or 25mg, administered into thigh	49	Adult subjects with RA	Single MTX dose, 3 treatment periods one week in duration
MTX-11-002	To assess the safe usability of Otrexup device for SC self-injection	Open label, single dose, single arm	SC Otrexup at doses of 10mg, 15mg, 20mg, or 25mg, administered in the anterior abdominal wall	101	Adult subjects with RA	Single SC MTX dose of 10mg, 15mg, 20mg, or 25mg using a device
MTX-11-004	Summative round of usability testing	2 one-on-one sessions, one week apart. Session one: subjects and lay caregivers were trained to use the Vibes device. Session two: Subjects and caregivers simulated the use of the	SC Otrexup device	50	Adult subjects with RA Lay caregivers Healthcare professionals	Subjects with RA and lay caregivers participated on two days separated by one week. Professional caregivers completed simulation injection on one day.

		device. The professional caregivers were not given any training and participated in one session in which they simulated using the device on a patient.				

MTX: methotrexate; SC: subcutaneous; IM: intramuscular; RA: rheumatoid arthritis
Source: Applicant's submission.

To establish safety and effectiveness of Otrexup for the indication of moderate to severe psoriasis, in addition to clinical studies described in Table above, the applicant relies on published literature. The applicant identified six scientific publications as "adequate and well-controlled clinical trials" in support of the safety and efficacy of their product for the treatment of moderate-to-severe psoriasis. The applicant has identified an additional six scientific publications as "supportive evidence for the efficacy of MTX in moderate-to-severe" psoriasis. The list of publications supporting this NDA application is presented in Table 7 below.

Table 7: List of Published Study Reports Supporting this NDA

Scientific publications: "efficacy and safety of methotrexate in treatment of moderate to severe psoriasis" ("adequate and well controlled clinical trials")
Methotrexate versus Cyclosporine in Moderate-to-Severe Chronic Plaque Psoriasis. Vera M.R. Heydendael et al. N Engl. J Med 2003; 349:658-65.
Methotrexate vs. cyclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. B. Flystrom et al., BJD, 2008; 158, pp116-121.
A 52-Week Trial Comparing Briakinumab with Methotrexate in Patients with Psoriasis. Kristian Reich et al. N Engl. J Med 2011; 365:1586-96.
Treatment of psoriasis with recombinant human LFA3-antibody fusion protein: a multi-enter, randomized, double-blind trial in a Chinese population. Heng Yan et al. Eur. J Dermatol. 2011; 21(5): 737-43
A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. A.B. Gottlieb et al. BJD 2012; 167, p 649-657.
Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). J.H. Saurat et al. BJD 2008; 158, pp558-566.

Scientific publications : "Supportive evidence for the efficacy of MTX in moderate-to-severe" psoriasis
Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. M. Akhyani et al. JEADV 2010, 24, 1447-1451.
Methotrexate-betamethasone weekly oral pulse in psoriasis. Ramji Gupta, Srthak Gupta. Journal of Dermatological Treatment, 2007; 18: 291-294.
The Combination of Etanercept and Methotrexate Increases the Effectiveness of Treatment in Active Psoriasis Despite Inadequate Effect of Methotrexate Therapy**.** Claus Zachariae et al. Acta Derm Venereol. 2008; 88: 495-501.
Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis; a multicenter prospective randomized controlled clinical trial. S. Fallah Arani. BJD 2011. 164, p 855-861.
Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial. J. Barker et al. BJD 2011; 165, p 1109-1117.
Methotrexate/narrowband UVB phototherapy combination vs. narrowband UVB phototherapy in the treatment of chronic plaque-type psoriasis- a randomized single-blinded placebo-controlled study. R. Mahajan et al. JEADV 2010, 24, p 595-600.
Benefits and adverse drug experiences during long-term methotrexate treatment of 248 psoriatics. A. Nyfors. Danish Medical Bulletin. October 1978, Vol. 25 No.5, p 208-211.

Source: Applicant's submission, White paper, Table 1, p 5 and Table 7, p17.

5.2 Review Strategy

Discussion of pharmacokinetic clinical studies conducted by the applicant is presented in the section **4.4.3 Pharmacokinetics.** In this section, discussion of device usability study MTX-11-002 will be presented.

For the information regarding study MTX-11-004, a training device-only study, in which there was no administration of MTX, reader is referred to the review by clinical reviewer Dr. Peter R. Starke, of DPARP dated 8/20/2013.

Discussion of published study reports will be presented in this section. Because clinical studies contained in published articles are of different design, conduct and statistical analysis, each study will be discussed separately. Discussion of each study includes analysis of trial elements: trial design, conduct, efficacy and safety results, and statistical analysis.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Discussion of Individual Studies/Clinical Trials Conducted by the Applicant

In this section, device usability study MTX-11-002, will be discussed. During the conduct of this study, subjects were dosed with a single dose of MTX and safety data were collected. The safety information from this study is discussed in the section 7.3 Major Safety Results.

Study Title: A Phase 2, Multi-Center, Open-Label, Single-Dose, Single-Arm, In-Clinic Study to Evaluate the Actual Human Use of Methotrexate Subcutaneously Administered Via the VIBEX MTX Auto-Injector Device in Adult Patients With Rheumatoid Arthritis.

Study Period: From May 7, 2012 to July 3, 2012.

Study Objective: The primary objective was to assess the safe usability of the VIBEX MTX device for subcutaneous (SC) self-injection with methotrexate (MTX) in adult patients with rheumatoid arthritis (RA) after standardized training by site personnel and review of written instructions.

Study Design: This was multicenter, open-label, single dose, single arm study.

Study Population: The population for this study was male and female subjects ≥18 years of age with RA who had been undergoing treatment with MTX for ≥3 months prior to enrollment.

Study Visits and Procedures: Each study subject was assigned to one of four doses (10mg; 15; 20mg; or 25mg of MTX), based on the subject's baseline MTX therapy and disease status (RA controlled of RA uncontrolled).
There were 3 visits: Screening (Visit 1), Treatment (Visit 2) and Follow-up (Visit 3).

Study Drug Administration: At Treatment visit, subjects received standardized SC self-injection training. After standardized training, subjects administered an SC self-injection with predetermined dose of MTX using Vibex device.

Safety Monitoring: The following safety monitoring was performed:

- Vital signs at Screening and Treatment visit.
- Physical examinations at Screening.
- Urine pregnancy test at Screening.
- Injection site reactions: pre-dose and post-dose, at Treatment visit.

Efficacy and Endpoint Measures: The primary endpoint for determination of safe usability was successful SC self-injection using the VIBEX MTX device.

Discussion of safety is presented in section 7.3 Major Safety Results.

For Discussion of efficacy, reader is referred to review by clinical reviewer Dr. Peter R. Starke of DPARP.

5.3.2 Discussion of Individual Studies/Clinical Trials from the Published Literature Submitted by the Applicant

5.3.2.1 Methotrexate versus Cyclosporine in Moderate-to-Severe Chronic Plaque Psoriasis. Vera M.R. Heydendael et al. N Engl. J Med 2003; 349:658-65.

Trial objective: To compare efficacy and safety of methotrexate and cyclosporine in treatment of subjects with moderate-to-severe psoriasis.

Trial design: This was randomized, evaluator blind, active control trial. The design of this study did not include placebo arm.

Study population
Number of subjects: 88 subjects were included.

Inclusion criteria:
1. 18 years of age or older
2. Subjects with moderate-to-severe chronic plaque psoriasis. Moderate-to-severe psoriasis was defined by score of at least 8 on Psoriasis Area-and–Severity Index (PASI). Score of 0 indicates the absence of psoriasis and a score of 72 the most severe disease possible. Subjects also had insufficient response to topical or UVB therapy (or both).
3. Subjects had not been previously treated with either methotrexate or cyclosporine.

Exclusion criteria
1. Liver or renal impairment
2. Insulin-dependent diabetes mellitus
3. High risk of liver-function abnormalities
4. Positive serologic test for hepatitis B virus
5. Uncontrolled hypertension
6. History of cancer, including skin cancer
7. Severe cardiovascular, pulmonary, cerebra, neurologic, or hematologic disease
8. Acute infection requiring antimicrobial therapy or associated with human immunodeficiency virus infection.
9. Pregnant, breast-feeding or noncompliant with an effective regimen of contraception.
10. Subjects with moderate to severe steatohepatitis (as established by ultrasonography).

Study visits and procedures
During the screening period no therapy was permitted. Screening lasted 2 weeks for subjects who were previously on topical therapy and 4 weeks for subjects who were previously treated with UVB, PUVA or systemic therapy.
Eighty eight subjects were randomized in a 1:1 ratio to receive treatment with methotrexate or cyclosporine for 16 weeks.
After completing 16 weeks of study drug dosing, subjects were followed up for another 36 weeks, every two weeks during the first month and monthly thereafter. During the follow up period, active treatment for psoriasis was permitted if needed.

Study drug administration
Methotrexate dosing was initiated at 15mg per week (given in three divided doses with a 12-hour interval between doses, according to the schedule of Weinstein and Frost[1]).
Cyclosporine was initiated at 3mg/kg of body weight per day (given in two divided doses).
After 4 weeks of dosing, in subjects who had less than 25% of reduction of PASI score from baseline, the doses of MTX were increased up to 22.5mg /week and the doses of cyclosporine were increase to 5mg/kg per day. During the last 4 weeks of dosing, cyclosporine dose was tapered down to zero at Week 16. The dose of the study drug could be decreased in the event of adverse event.

Dosage forms, route of administration or source of methotrexate and cyclosporine were not specified. For methotrexate dosing, authors cited publication by Weinstein and Frost that discusses oral dosing. Starting dose of MTX was higher than recommended starting dose in the approved MTX labeling. Dose of MTX (10mg/week) that may be effective in subjects with moderate psoriasis was not evaluated.

Safety monitoring
Ultrasonography of the liver was performed in all eligible subjects.
Subjects treated with methotrexate underwent the following laboratory evaluations: CBC, hepatitis B screening, electrolytes, serum creatinine, blood urea nitrogen (BUN), AST, ALT, and bilirubin.
Subjects treated with cyclosporine, in addition to above laboratory evaluations, also underwent urinalysis and magnesium measurement.
Laboratory evaluations were performed every two weeks during the first month of dosing and once a month thereafter until week 20.

Efficacy and Endpoint Measures
1. Primary Efficacy Endpoints

The primary efficacy endpoint was PASI score measured monthly up to the end week 16. PASI combines assessments of erythema, scaling, and skin thickness, each weighted according to the size of the affected area.

2. At each visit, investigator performed a global assessment using a IGA scale of 0 to 10, with a score of 0 indicating the worst imaginable disease and a score of 10 the absence of disease activity. The content of IGA scale was not provided.

Timepoint for efficacy evaluation was not specified. Statistical analysis was not prespecified.

Results

Demographics

Of 88 randomized subjects, three subjects were excluded from the trial due to low creatinine clearance (2 subjects) and one subject withdrew consent.

Forty three subjects were included in methotrexate group and 42 in cyclosporine group. Baseline characteristics of all subjects are presented in the Table 8 below.

Table 8: Baseline Characteristics of Subjects

Subject characteristics	Methotrexate Group (N=43)	Cyclosporine Group (N=42)
Sex (no. of subjects)		
Male	28	29
Female	15	13
Age (yr)	41.6±13.0	38.3±12.4
Psoriasis PASI	13.4±3.6	14.0±6.6
Previous therapy (no. of subjects)		
Ultraviolet B	28	25
Methoxsalan with ultraviolet A	10	8
Acitretin	5	5
Fumaric acid	3	0
Topical only	8	14
Age oat onset of disease (yr)	25±14.5	24±13.3
Psoriatic arthritis (no. of subjects)	3	1

Source: Original publication

The majority of subjects were male. Information on the number of subjects with moderate or severe psoriasis included in this trial, and specifically in the MTX group, was not provided.

Thirteen subjects were discontinued from the trial due to adverse events (12 in the methotrexate group and 1 in cyclosporine group). All subjects were included into the analysis.

Efficacy

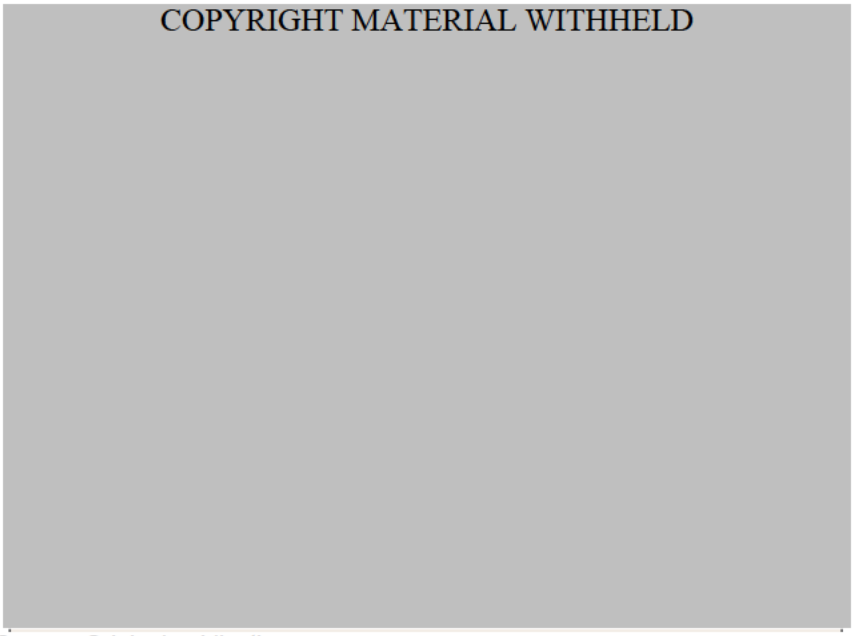
At week 16, the mean PASI score in the methotrexate group was 5.0±0.7 (baseline was 13.4±3.6) and in the cyclosporine group was 3.8±0.5 (baseline was 14.0±6.6). The relative reduction of the PASI score was 64% in methotrexate group and 72% in

cyclosporine group. The mean scores for the PASI during the dosing and follow-up is presented in **Figure** below.

Sixty percent of subjects in the methotrexate group and 71% of subjects in the cyclosporine group had reduction of more than 75% in the PASI score.

Forty percent of in the methotrexate group and 33% in the cyclosporine group had reduction of more than 90% of the PASI score (defined as almost complete remission) at Week 16. The mean scores for the PASI during the treatment and follow-up are presented in Figure 8 below.

Figure 8: Mean (±SE) Scores for the PASI During Treatment and Follow-up



Source: Original publication

The authors concluded that there were no significant differences in efficacy between methotrexate and cyclosporine groups.

This trial did not have placebo arm, therefore it is difficult to assess the effect of MTX. The efficacy in population of subjects with moderate psoriasis was not evaluated. Statistical analysis plan was not prespecified.

Safety

Discontinuations

One subject in the cyclosporine group discontinued due to AE (elevation of bilirubin). In the methotrexate group, 12 subjects discontinued due to AEs (elevation of liver enzymes). All these AEs were mild and resolved within 8 weeks upon discontinuation of study drug treatment. No additional information regarding AEs requiring discontinuation of subjects was provided.

Adverse Events
A total of 113 adverse events (AE) were reported by 29 subjects in methotrexate group and 116 AEs reported by 35 subjects in cyclosporine group. Number of subjects with AEs in two treatments is presented in Table 9 below.

Table 9: Adverse Events

Source: Original publication

In addition to adverse events presented in the Table 9 above, abdominal discomfort, oral ulcers and cytopenias were reported in the MTX group; however authors did not provide any information regarding these AEs.

Authors of this study presented partial safety information. Out of 229 AEs, only 91 AEs were presented (Table above). No information was provided regarding relationship between study drug, dose, duration of dosing, and subjects' disease severity on the frequency and severity of adverse events.

Laboratory evaluations
Thirteen subjects had elevation of liver enzymes, 12 in methotrexate group and 1 in cyclosporine group. Study drug treatment was discontinued in all subjects with elevation of liver enzymes. Upon discontinuation of study drug treatment, elevation of liver enzymes resolved in all subjects within 8 weeks.
Although cytopenias were mentioned in the discussion section of this publication, no further information regarding these AEs was provided.

This study has the following limitations:

1. This was randomized active controlled study. Without the placebo arm, the efficacy of the study drug cannot be accurately determined.
2. Statistical analysis was not prespecified.
3. The efficacy data in the subpopulation of subjects with moderate psoriasis was not presented.
4. No subject-level efficacy data was included to allow independent assessments of the results.
5. Methotrexate dosage form and the source were not specified.
6. Complete safety database was not provided.
   Authors commented on the resolution of laboratory abnormalities (elevation of liver function tests), however no information regarding resolution of other AEs was provided. Authors did not provide any information regarding reported AEs of

cytopenias. Relationship of AEs to the study drug administration was not provided.

7. No information was provided regarding the effects of study drug dose, duration of dosing, or subjects' disease severity on the frequency and severity of AEs. No assessment of relationship between study drug administration and AEs was provided.

In Conclusion: The design and conduct of this study were not adequate to provide the evidence that the benefits of methotrexate in subjects with moderate to severe psoriasis outweigh its risks.

5.3.2.2 Methotrexate vs. Cyclosporin in Psoriasis: Effectiveness, Quality of Life and Safety. A Randomized Controlled Trial. B.Flystrom et al. BJD 2008; 158, p116-121.

Trial objective
The objective was to compare the effectiveness, quality of life and adverse events of methotrexate and cyclosporine treatment, in a context reflecting normal clinical practice.

Trial design
This was randomized, investigator blind, active control trial. No placebo arm was included into the trial design.

Study population
Inclusion criteria

1. Adult subjects 18 years of age and older
2. Subjects with chronic plaque psoriasis with inadequate response to topical and/or UV treatment
3. Psoriasis classified by physician and subject as moderate to severe. No lower limit of the PASI score was used.

Exclusion criteria
Subjects who met any of the following criteria were excluded:

1. Liver impairment
2. Renal impairment
3. Uncontrolled hypertension
4. Hematological disease
5. History of cancer
6. Immunosuppression
7. Medication contraindicated for use with methotrexate or cyclosporine
8. Substance abuse
9. Planned or ongoing pregnancy or breastfeeding
10. Noncompliance

11. UV treatment was not permitted within 2 weeks of randomization and treatment with methotrexate, cyclosporine or acitretin was not permitted with 4 weeks of randomization.

Inclusion criteria did not adequately define study population. Subjects with moderate to severe psoriasis were included into the trial. Basis for determination of psoriasis severity was not described. Baseline PASI score was not specified (no lower limit of the PASI score was used) allowing subjects with mild psoriasis to be included into the trial.

Study visits and procedures

Subjects were randomized in a 1:1 basis to receive either methotrexate of cyclosporine for 12 weeks.

Study drug administration

Methotrexate was administered at 7.5mg weekly given according to the schedule by Weinstein and Frost[1]. If the subject did not have reduction of PASI score >50% and no considerable adverse events were reported, the dose was increased gradually to a maximal dose of 15mg weekly. Folic acid 5mg was given daily except on days of dosing with methotrexate.

The initial dose of cyclosporine was 3mg/kg daily, divided into two doses and could be increased to maximum of 5mg/kg daily using the same criteria for methotrexate.

Topical treatment was allowed during the treatment period, however no details were provided.

Dosage form and source of MTX were not specified. Maximal MTX dose was relatively low. Dosing recommendation of the approved MTX labeling in the treatment of severe recalcitrant psoriasis is up to 25mg/week. Therefore, the effects of administration of higher doses (20mg/week to 25mg/week) of MTX were not be evaluated.

Safety monitoring

Subjects randomized to methotrexate, underwent the following laboratory evaluations, at baseline and at Week 12: CBC, albumen, ALT, AST, alkaline phosphatase, bilirubin, urine analysis, and procolagen III peptide. In addition, CBC, ALT and AST were measured at Week 2, 4, and 8.

Subjects randomized to cyclosporine underwent the following laboratory evaluations at baseline and at Week 12: CBC, electrolytes, serum creatinine, BUN, ALT, AST, alkaline phosphatase, bilirubin, urine analysis, cholesterol, triglycerides and magnesium. Blood pressure (BP) was measured tree times before initiation of study drug treatment. BP and serum creatinine were measured every other week during dosing period. Cyclosporine concentration was measured after 4 weeks of dosing.

Efficacy and Endpoint Measures

The primary outcome measure was the PASI. PASI was performed at baseline and monthly thereafter up to Week 12.

Timepoint for efficacy evaluation was not prespecified. Statistical analysis plan was not prespecified.

Results
Eighty four subjects were randomized and 68 subjects were included into the trial. Thirty seven subjects were included into methotrexate group and 31 subjects in cyclosporine group. Four subjects assigned to methotrexate group were withdrawn before the first dose due to elevation of liver enzymes (1), thrombocytopenia (1), and withdrawn consent (2). Twelve subjects assigned to cyclosporine group were withdrawn before the first dose due to thrombocytopenia (1), elevated creatinine (2), hyperlipidemia (1), ineligible (2) and withdrew consent (5).

Of randomized subjects 4 subjects in cyclosporine group discontinued treatment due to adverse events and none of subjects from methotrexate group discontinued the treatment. Demographic characteristics of study subjects are presented in Table 10 below.

Table 10: Demographic Characteristics of Study Subjects at Baseline

Source: Original publication

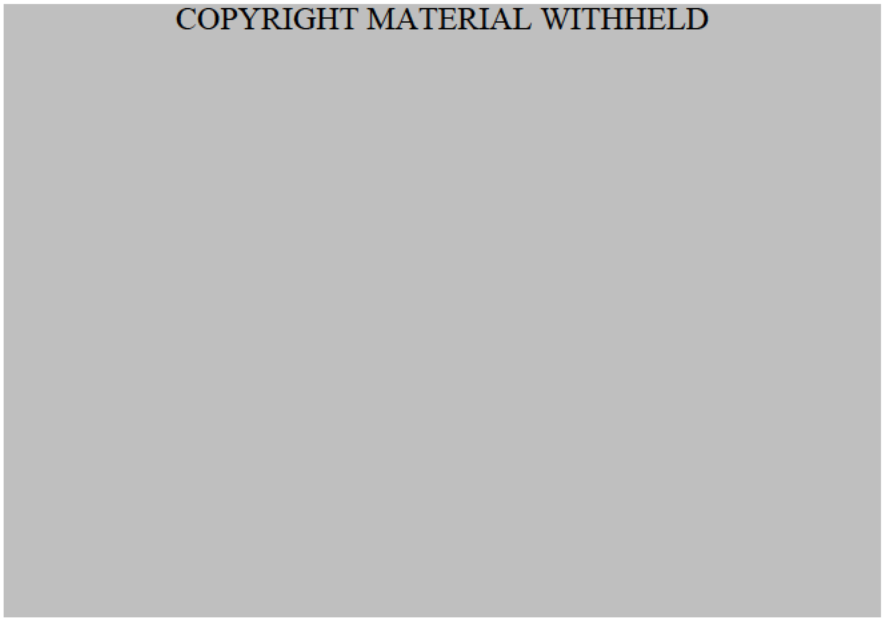
Subjects with mild psoriasis (PASI score as low as 3.8) were included into the trial. The authors did not provide information on how many subjects with mild and moderate

psoriasis were included into the trial. Inclusion of subjects with mild disease may have influenced the magnitude of treatment effects of methotrexate.

Efficacy results
The mean PASI score was 5.6 ±3.8 (baseline PASI was 14.1 ±7.0) in methotrexate group and 3.6 ± 3 (baseline PASI was 15.5± 6.3) in cyclosporine group after 12 weeks of treatment. The mean change in PASI score from the baseline was 58% in the methotrexate group and 72% in cyclosporine group.

Reduction of >75% from the baseline PASI score was achieved by 24% of subjects on methotrexate and in 58% of subjects on cyclosporine.
The mean PASI scores during 12 weeks of treatment are presented in Figure 9 below.

Figure 9: Mean Scores (± SD) of the PASI Scores During 12 Weeks of Treatment



Source: Original publication:

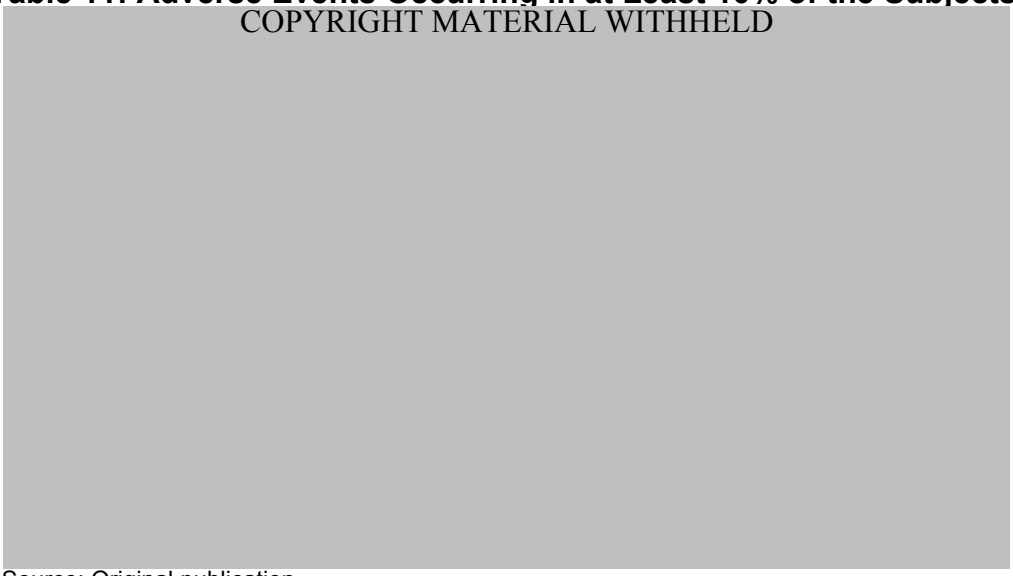
The authors of this study concluded that cyclosporine was more effective than methotrexate in this short term study. Because the study population included subjects with mild psoriasis, the results reflect MTX treatment in the population with mild to severe psoriasis and not moderate to severe psoriasis.

Safety
Four subjects in the cyclosporine group discontinued treatment due to adverse events (fatigue and gastrointestinal symptoms). None of subjects from the methotrexate group discontinued treatment.

No serious adverse events were reported during the conduct of the trial. Approximately the third of subjects in both treatment groups required lowering of study drug dose due

to adverse events. The reasons in the methotrexate group were gastrointestinal symptoms and elevation of liver enzymes. In the cyclosporine group the reasons were: elevation of creatinine, high cyclosporine concentration, headache and paresthesia. Four subjects in methotrexate group and one in the cyclosporine group had to temporarily discontinue treatment due to upper respiratory infection. No further information regarding these adverse events was provided.
Adverse events occurring in at least 10% of subjects are presented in Table 11 below.

Table 11: Adverse Events Occurring in at Least 10% of the Subjects



Source: Original publication

Complete safety database was not presented. Only AEs occurring in at least 10% of subjects were reported. Therefore, AE occurring in less than 10% of subjects were not reported or discussed.

This study has the following limitations:

1. This was randomized active controlled study. Without the placebo arm, the efficacy of the study drug cannot be accurately determined.
2. Study population was not well defined. Subjects with mild disease were included into the study and therefore the efficacy results may have been affected by this population.
3. The contribution of allowed topical treatment to the efficacy of the study drug cannot be determined.
4. Efficacy in subjects with moderate psoriasis was not evaluated.
5. Timepoints of endpoint evaluation were not prespecified
6. Statistical analysis plan was not prespecified.
7. Methotrexate dosage form and the source were not specified.
8. Relatively low doses of MTX were used in this trial. Because the higher doses of MTX (20mg to 25mg/week) were not evaluated during this study, safety and

efficacy of MTX at doses recommended by approved MTX labeling could not be established.
8. Complete safety information was not provided. Relationship of AEs to the study drug administration was not provided.
9. Information regarding the effects of study drug dose, duration of dosing, or subjects' disease severity on the frequency and severity of AEs was not provided.

Conclusion: The design and conduct of this study were not adequate to provide the evidence that the benefits of methotrexate in subjects with moderate to severe psoriasis outweigh its risks.

5.3.2.3 Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION) J.H. Saurat et al. BJD, 2008 **158**, pp558-566.

Trial objective
Objective was to compare a biologic agent with methotrexate and define the role of biologic in psoriasis.

Trial design
This is randomized, double-blind, placebo controlled trial.

Study population
Inclusion criteria
1. Subjects ≥18 years of age and older
2. Moderate to severe psoriasis defined as ≥10% of body surface area (BSA) and Psoriasis and Severity Index (PASI) of ≥10.
3. Plaque psoriasis lasting for at least one year and stable plaque psoriasis for at least 2 months
4. Subjects who were candidates for systemic therapy and have had psoriasis despite topical agents.
5. Naïve to treatment with TNF-antagonists and methotrexate.
6. Women of childbearing potential and all men willing to use contraception
7. Subjects willing to self-administer subcutaneous injects or have qualified person administer the.
8. Subjects with evidence of latent tuberculosis were permitted to enroll in they received prophylactic treatment prior to administration of study drug. Prophylaxis did not need to be completed prior to initiation of study drug.

Exclusion criteria
1. Subjects with history of clinically significant hematologic, renal or liver disease/abnormal laboratory values.

2. History of demyelinating disease.
3. Lymphoproliferative disease (other than successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma *in situ* of the cervix.
4. Immunocompromised subjects.

Study visits and procedures
Eligible subjects were randomized in a 2:2:1 ratio to receive adalimumab, methotrexate or placebo, for 16 weeks.
Oral methotrexate tablets were supplied by Wyeth Pharma. Both the methotrexate and placebo were administered as capsules (encapsulated tablets) as a single weekly dose. Methotrexate treatment was initiated with a dose of 7.5mg per week and then slowly titrated, as needed and as tolerated, to a maximal dose of 25 mg per week. The following schedule of methotrexate dose titration was followed:

Week	Methotrexate (mg)
0 to 2	7.5
2 to 3	10
4 to 7	15
8 to 11	20
12 to 15	25

All subjects received supplementation with oral folate (approximately 5mg weekly) throughout the study. Folate was administered on any day beginning 48h after ingestion of oral study medication. Dose could be withheld or reduced for safety reasons.
Adalimumab was administered subcutaneously at initial dose of 80mg, and then at a 40mg every other week, as a maintenance dose.

Safety monitoring
Laboratory evaluation, vital signs were assessed throughout the study and 70 days after last treatment.

Efficacy and endpoint measures
The primary efficacy assessment was the proportion of subjects achieving at least 75% reduction in PASI (PASI 75) at week 16 relative to baseline. Statistical analysis was not prespecified to compare methotrexate to placebo.

Results
Two hundred seventy one subjects were randomized, of whom 110 were assigned to treatment with the methotrexate, 108 to adalimumab and 53 to placebo.

Fifteen subjects (5.5%) discontinued the study, of whom 4 (3.7%) were in the adalimumab group (one due to adverse event, 2 due to withdrawal of consent, one for other reasons), 6 in the methotrexate group (all due to adverse events) and 5 in the

placebo group. Baseline demographic characteristics of study subjects are presented in Table 12 below.

Table 12: Baseline Demographic and Clinical Characteristics of Randomized Subjects

Source: Original publication

Efficacy

At the end of 16 week of treatment, 79.6% of subjects in adalimumab group, 35.5% in the methotrexate and 18.9% in the placebo group achieved PASI 75.

Sixteen subjects did not have week 16 assessment for PASI. To confirm the results of the primary efficacy analysis, a sensitivity analysis was performed to evaluate PASI 75 responses rates with missing data imputed as Last Observation Carried Forward (LOCF). The PASI 75 LOCF results were: 79.6% for the adalimumab group, 36.4% for the methotrexate group and 18.9% for placebo group.

Results of PASI response rates over 16 weeks are presented in Figure 10 below.

Figure 10: PASI 75 response rates over 16 weeks

Source: Original publication

The placebo response was 19% which the authors acknowledge to be higher than previously reported in published literature. Authors explained this difference as a possible effect of folate supplementation, by the effect of ethnic characteristics of the study population (subjects were primarily European) and by subjects being naïve to MTX therapy. The results of this study were discussed in the review by Menter et al.[15] The following concerns regarding interpretation of the methotrexate versus placebo comparison: "…. the placebo response rate of 19% is dramatically higher than is seen in a clinical trial of this type, raising doubt about the validity of the study".

Safety
Seventy nine subjects (73.8%) reported adverse events in the adalimumab group, 89 (80.9%) in the methotrexate group and 42 (79.2%) in the placebo group.
There were no deaths. There were 4 SAEs reported, two in the adalimumab group (pancreatitis and enlargement of an ovarian cyst), one in methotrexate group (hepatitis) and one in the placebo group (calculus of the right uretero-pelvic junction). No additional information regarding these SAEs was provided. No serious infections were reported in this study.

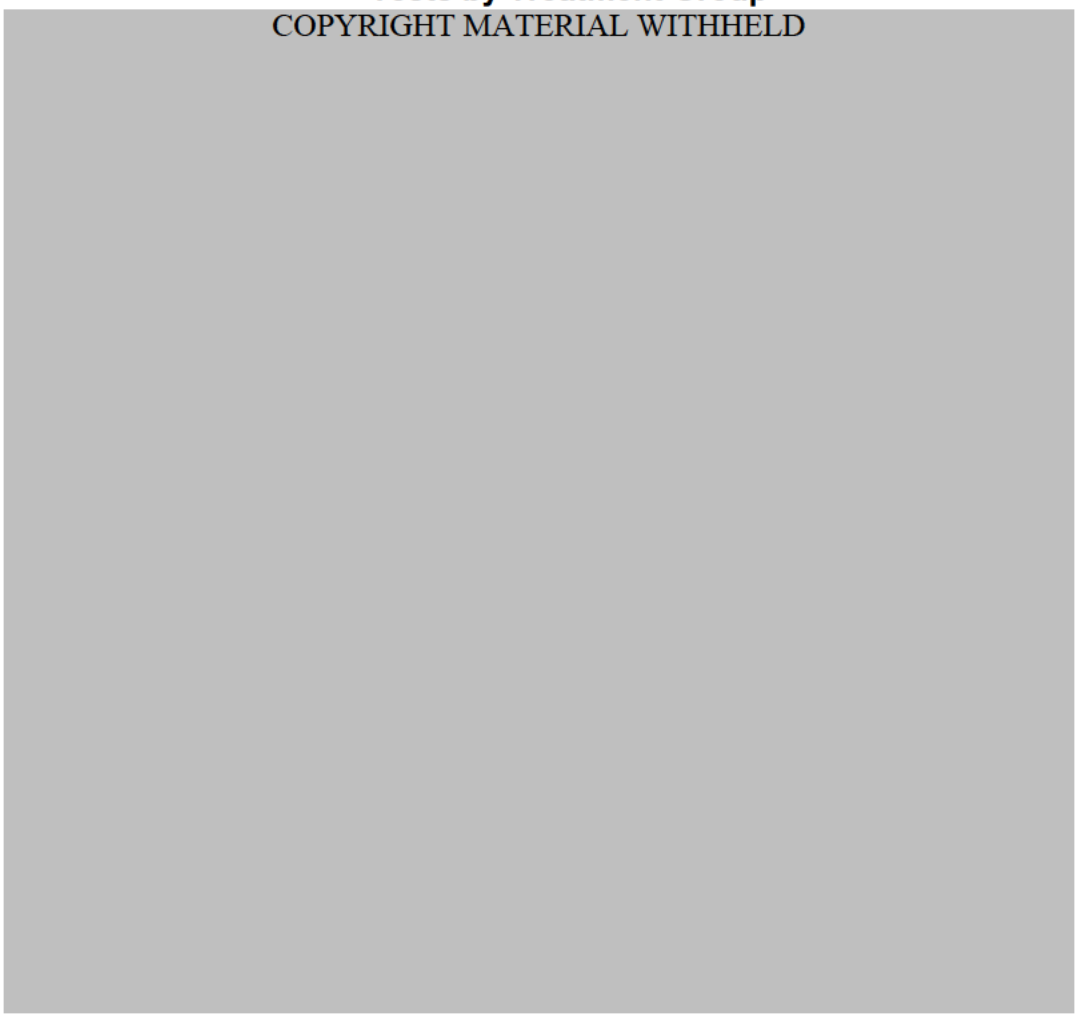
Eight subjects discontinued treatment because of an adverse event:

- One subject in the adalimumab group (elevated aminotransferase concentration)
- Six subjects in the methotrexate group (one with upper abdominal pain, one with retrobulbar optic neuritis, one with hepatitis and three with abnormal liver function tests).
- One subject in the placebo group (increased liver enzymes).

Detailed information regarding AEs requiring subject discontinuation was not provided by the authors of this study.

More subjects in the methotrexate group (9.1%) had elevated liver enzymes than in adalimumab (1.9%) or placebo group (7.5%). Adverse events reported in ≥5% of subjects are presented in Table 13 below.

Table 13: Adverse by Treatment Group; Adverse Events that Occurred in ≥5% of Subjects in Any Treatment Group, and Elevation of Liver Function Tests by Treatment Group



Source: Original publication

Complete safety database was not provided by the authors of this study. Only AEs occurring in ≥5% of subjects were presented. No information regarding relationship to the study drug administration was provided. No information on effects of study drug, dose, duration of dosing, or subjects' disease severity on the frequency and severity of AEs, were provided.

This study has the following limitations:

1. Complete safety and database was not provided. Relationship of AEs to the study drug administration was not provided.
2. Oral MTX was used in this study. Because subcutaneous MTX administration showed higher bioavailability, safety in subjects with moderated psoriasis cannot be inferred from data collected during oral MTX administration.

3. Information regarding the effects of study drug dose, duration of dosing, or subjects' disease severity on the frequency and severity of AEs, was not provided.
4. Statistical analysis plan was not prespecified.
5. No subject-level efficacy data was included to allow independent assessments of the results.

Conclusion: In this study, methotrexate was superior to placebo, however insufficient evidence was provided to determine if benefits of Otrexup treatment, in subjects with moderate to severe psoriasis, outweigh its risks.

5.3.2.4 A 52-Week Trial Comparing Briakinumab with Methotrexate in Patients with Psoriasis. Kristian Reich et al. N Engl. J Med 2011; 365:1586-96.

Trial objective
To assess the efficacy and safety of briakinumab as compared to methotrexate in subjects with psoriasis.

Trial design
This was multicenter, randomized, double-blind, active controlled trial.

Study population
Inclusion criteria
1. 18 years of age and older
2. Diagnosed with psoriasis for at least 6 months and stable plaque psoriasis for at least 2 years and candidates for systemic therapy or phototherapy.
3. Had at least involved of 10% BSA, had a score on PGA of 3 or higher and PASI score of 12 or higher at baseline. Score on PGA range from 0 to 5, with scores of 2, 3, 4 and 5 indicating mild, moderate, severe and very severe disease respectively.

Exclusion criteria
Exclusion criteria were not specified. Therefore, the appropriateness of selected subject population cannot be determined.

Study visits and procedures
At baseline, subjects were randomly assigned in a 1:1 ratio, to receive briakinumab or methotrexate. Study drug was administered for 52 weeks. Subjects who completed this study were enrolled in the open-label continuation study. Data from the continuation study were not presented in this publication.

Study drug administration
Briakinumab was administered subcutaneously at a dose of 200mg (weeks 0 and 4), and 100mg every 4 weeks from week 8 through week 48.

Methotrexate was administered orally at a dose of 5mg to 25 mg per week, plus folate administered at dose of 5mg per week, from week 0 through week 51. Dosing of methotrexate was done as per following schedule:

Week	Methotrexate
0	5mg
1	10mg
2 through 9	15mg

Subjects who did not have response of at least PASI 75 had further increase of dose as follows:

Week	Methotrexate
10	20mg
16	25mg

To maintain the blind, placebo capsules matching methotrexate and folate or placebo injection to match briakinumab injections were administered. Source of MTX was not specified.

Safety monitoring
Adverse events, laboratory monitoring and vital signs were assessed throughout the study. A follow-up call was made 45 days after the last dose of the study drug.

Efficacy and endpoint measures
The primary efficacy endpoints were:

- PASI 75 at week 24
- The PGA score of 0 or 1 at week 24
- PASI 75 score at week 52
- The PGA score of 0 or 1 at week 52.

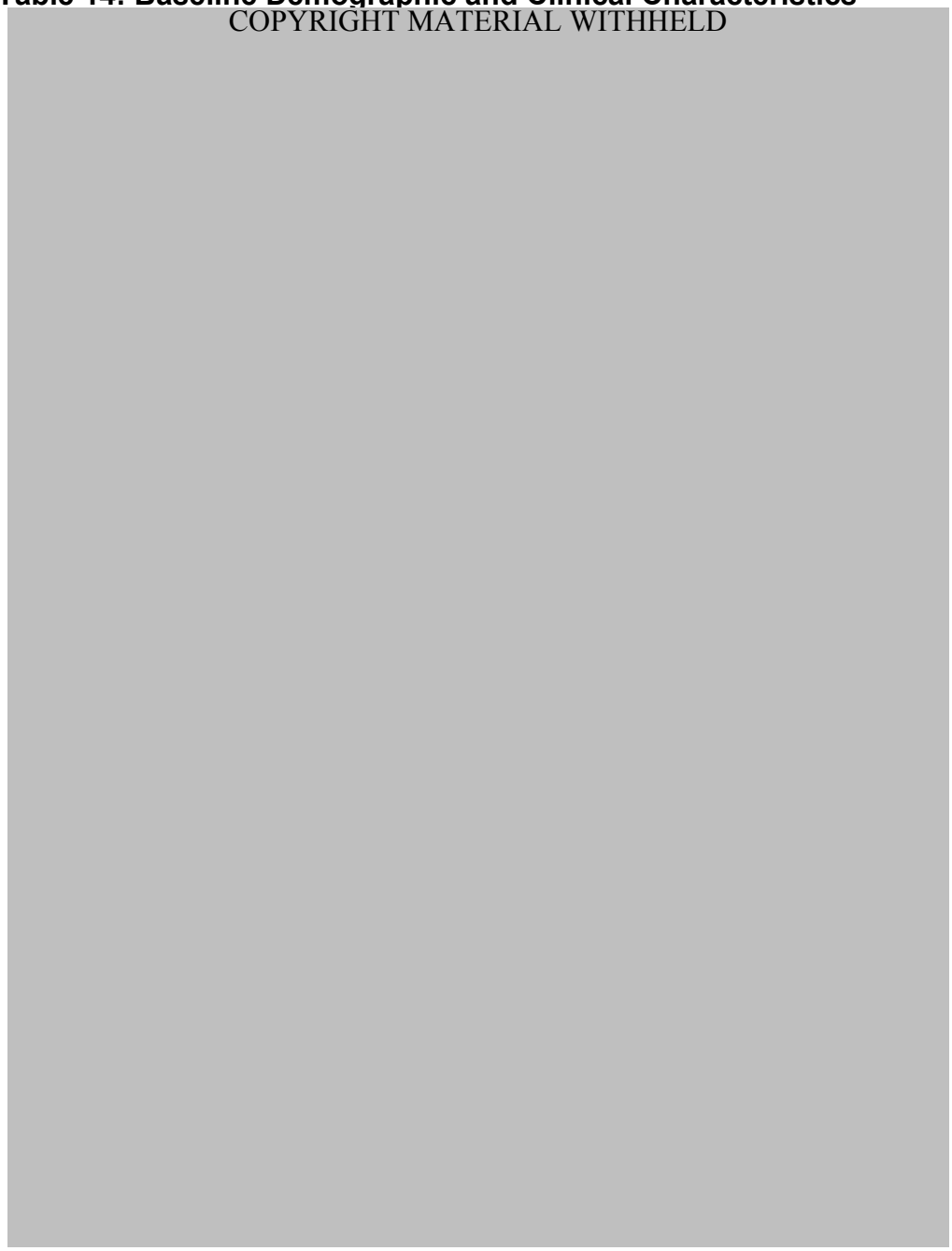
Statistical analysis plan was not prespecified.

Results
Three hundred seventeen subjects were randomized, of whom 154 were assigned to treatment with briakinumab and 163 were assigned to treatment with methotrexate.

Of 163 assigned to MTX group, 118 (72%) subjects discontinued the study. Of these, 95 (58%) subjects discontinued due to lack of efficacy and 10 (6%) subjects due to AEs (of which 5 were SAEs). 5 (3%) subjects withdrew consent. Three (2%) subjects each were lost to followup, violated the protocol or had other reasons discontinued the study, respectively.
Of 154 subjects assigned to receive briakinumab, 48 (31%) subjects discontinued the study. The most frequent reason was lack of effect in 22 (14%). Detailed information regarding subjects discontinued due to AEs was not provided.

Seventeen subjects in the methotrexate group required and increase in the dose to 20mg per week at week 10, and 100 subjects required and increase in the dose to 25mg per week at week 16.
Baseline demographic and clinical characteristics are presented in Table 14 below.

Table 14: Baseline Demographic and Clinical Characteristics



Efficacy
At week 24, 81.8% of subjects in the briakinumab and 39.9% of subjects in the methotrexate group reached a 75% improvement in PASI score.

At week 52, 66.2% of subjects in the briakinumab group and 23.9% of subjects in the methotrexate group reached a 75% improvement in PASI score.

At week 24, 80.5% of subjects in the briakinumab group and 34.4% of subjects in the methotrexate group met the criterion of a score of 0 to 1 on PGA scale.

At week 52, 63.0% subjects in the briakinumab group and 20.2% in the methotrexate group met the criterion of a score of 0 to 1 on PGA scale.

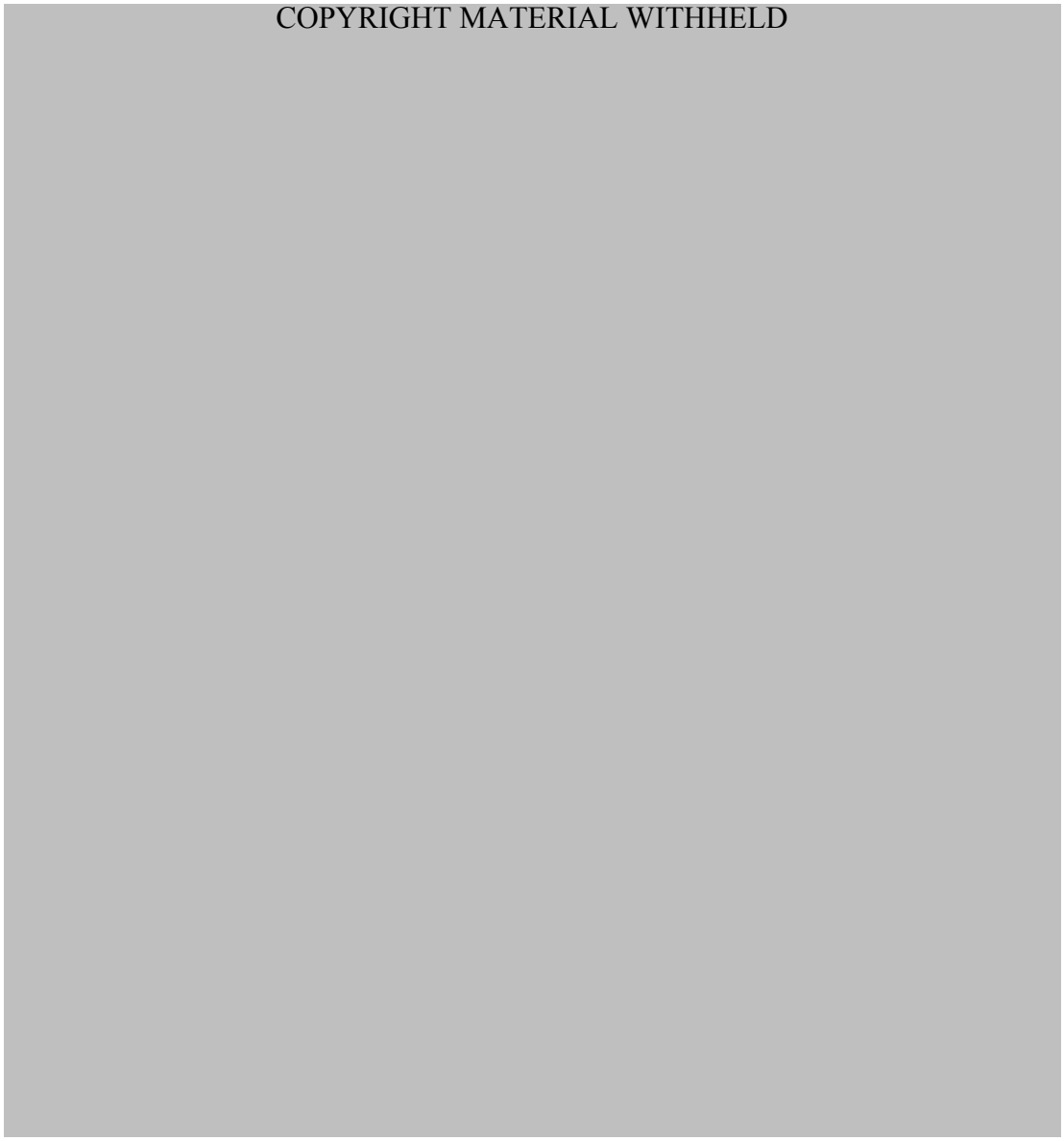
Of note is that only 45 (28%) of 163 subjects in MTX group completed the study. The most frequent reason for discontinuation was lack of effect [95 (58%) of subjects].

No subject-level efficacy data was included to allow independent assessments of the results

Safety
Safety evaluation was performed on data from population which included all subjects who received at least one dose of a study drug. Adverse events during the 52 weeks were evaluated.

One subject from the methotrexate group died from esophageal rupture. No additional information regarding this case of death was provided.
A total of 22 subjects were discontinued due to adverse events, 12 in the briakinumab and 10 in the methotrexate treatment group. Of these adverse events, 10 were serious adverse events (5 in the briakinumab and 5 in the methotrexate group). A total of 24 subjects reported 31 SAEs. Fourteen subjects (19 SAEs) were in briakinumab and 10 (12 SAEs) were in MTX group. Detailed information regarding AEs requiring subject discontinuations and SAEs was not provided.

Seven subjects had infections characterized as serious adverse events. Four of serious infections were in the briakinumab group (legionella infection with candidemia and septic shock, osteomyelitis, herpes zoster, and tonsillitis) and 3 were in the methotrexate group (2 cases of diverticulitis and one case of drug induced hepatitis). No additional information reading cases of infections was provided.
Cancer was diagnosed in 3 subjects in the briakinumab group (breast cancer, breast intraductal carcinoma and prostate cancer).
Sixteen subjects (9.8%) in the methotrexate group had liver-related adverse events. Of these subjects, 2 (1.2%) discontinued the study drug. No additional information regarding these AEs was provided. Adverse events are presented in the Table 15 below.



Source: Original publication

In MTX group 10 subjects reported SAEs: 2 events of diverticulitis and one of increased hepatic enzymes, hepatitis, esophageal rupture, intestinal polyp, sacroiliitis, erythrodermic psoriasis, vertigo, angioedema, urticaria, and intermittent claudication.

In briakinumab group the following SAEs were reported: 2 events of fistula and one event of septic shock, gastrointestinal hypomotility, legionella infection, candidiasis, ankle fracture, intermittent claudication, constipation, breast cancer, osteomyelitis, prostate cancer, breast neoplasm, herpes zoster, tonsillitis, hyperthyroidism, intervertebral disc protrusion, jaw fracture and anaphylactic reaction.

No additional information regarding these SAEs was provided.

This study has the following limitations:

1. This was randomized active controlled study. Without the placebo arm, the efficacy of the study drug cannot be accurately determined.
2. Oral dosage form of methotrexate was used. Therefore, the safety and efficacy of subcutaneously administered MTX in the population of subjects with moderate psoriasis could not be determined.
3. The source of MTX was not specified.
4. Complete safety database was not provided.
5. Information regarding the effects of study drug dose, duration of dosing, or subjects' disease severity on the frequency and severity of AEs was not provided.
6. Statistical analysis plan was not prespecified.
7. No subject-level efficacy data was included to allow independent assessment of the results.

Conclusion: The design and conduct of this study were not adequate to provide the evidence that the benefits of methotrexate in subjects with moderate to severe psoriasis outweigh the risks.

5.3.2.5 Treatment of psoriasis with recombinant human LFA3-antibody fusion protein: a multi-center, randomized, double-blind trial in a Chinese population. Yan et al. Eur J Dermatol. 2011: vol.21 (5): 737-43.

Trial objective
To evaluate efficacy and safety of injectable recombinant human LFA3-antibody fusion protein compared to methotrexate, in the treatment of moderate to severe chronic plaque psoriasis.

Trial design
This was multi-center, randomized, double-blind, active control, parallel group trial.

Study population
Inclusion criteria

1. 18 to 65 years of age
2. Weight of 40kg to 85kg
3. Chronic plaques psoriasis lasting not less than 6 months and in stable period, with BSA of 10% or PASI score of ≥12.
4. Female subjects of child-bearing potential who had negative pregnancy test and agree to use contraceptive measures.

Exclusion criteria
Subjects who fulfilled the following criteria were excluded:

1. Skin diseases potentially interfering with assessment of psoriasis (active or development stage of erythrodermic psoriasis, psoriatic arthritis, guttate psoriasis, pustular psoriasis).
2. Treatment with investigational drugs, biologic preparations or immunosuppressants in the past 3 months
3. Received treatment with high dose of glucocorticoids, vitamin D, or coal tar, or phototherapy in the past 2 weeks
4. Allergy to methotrexate
5. History of serious illnesses
6. History of serious diseases of heart, liver, kidney, and other vital organs, and the hematological and endocrine systems
7. Pregnant or breastfeeding
8. Serious, refractory, focal or systemic, acute or chronic infections in the past 3 months
9. HCV antibody positive, HbsAg positive or HIV antibody positive
10. Laboratory parameters, such as transaminases, higher than 1.5-fold upper limit of normal range.
11. Malignant tumors or with a family history of tumors.

Study visits and procedures
Subjects received study drug for 12 weeks and were followed up for additional 8 weeks after the last dose.

Study drug administration
Subjects were randomly assigned to treatment with rhLFA3-IgFP (15mg/week) and orally administered the blank dummy methotrexate once per week or methotrexate at the dose of 7.5mg/week and intramuscularly injected blank dummy rhLFA3-IgFP.

Low dose of MTX was used during the conduct of this study. Recommended dose for the treatment of severe, recalcitrant psoriasis is 10mg/week to 25mg/week. Safety and efficacy information obtained from this study is therefore limited.

Safety monitoring
The following safety evaluations were performed

- Vital signs: temperature, heart rate, respiratory rate(at baseline, Week 1; 2; 4; 6; 8; 12; 16; 20):
- Laboratory evaluations included: CBC, urinalysis, liver and renal function tests (at baseline, Week 1; 2; 4; 6; 8; 12; 16; 20).

The following evaluations were performed at baseline and at Week 12:

- Chest X-ray
- ECG

- Urine pregnancy test in female subjects of childbearing potential only
- HbsAg, HCV and HIV antibodies

Efficacy and endpoint measures
Efficacy measures included the following: PASI, PGA, Dermatology life quality index (DLQI), Visual Analogue Scale (VAS) and Quality of life Assessment (SF-36).

PASI was determined prior to and at 2; 4; 6; 8; 12; 16; and 20 weeks after the treatment. The rates of PASI decrease by 50%, 75% and 90% were calculated. PASI decrease of less than 50% was deemed as inefficacy.

PGA was measured on 7-point scale and each point was classified as: 0 full recovery, 1 near-full recovery; 3 mild /moderate; 4 moderate; 5 moderate/severe; and 6 severe.

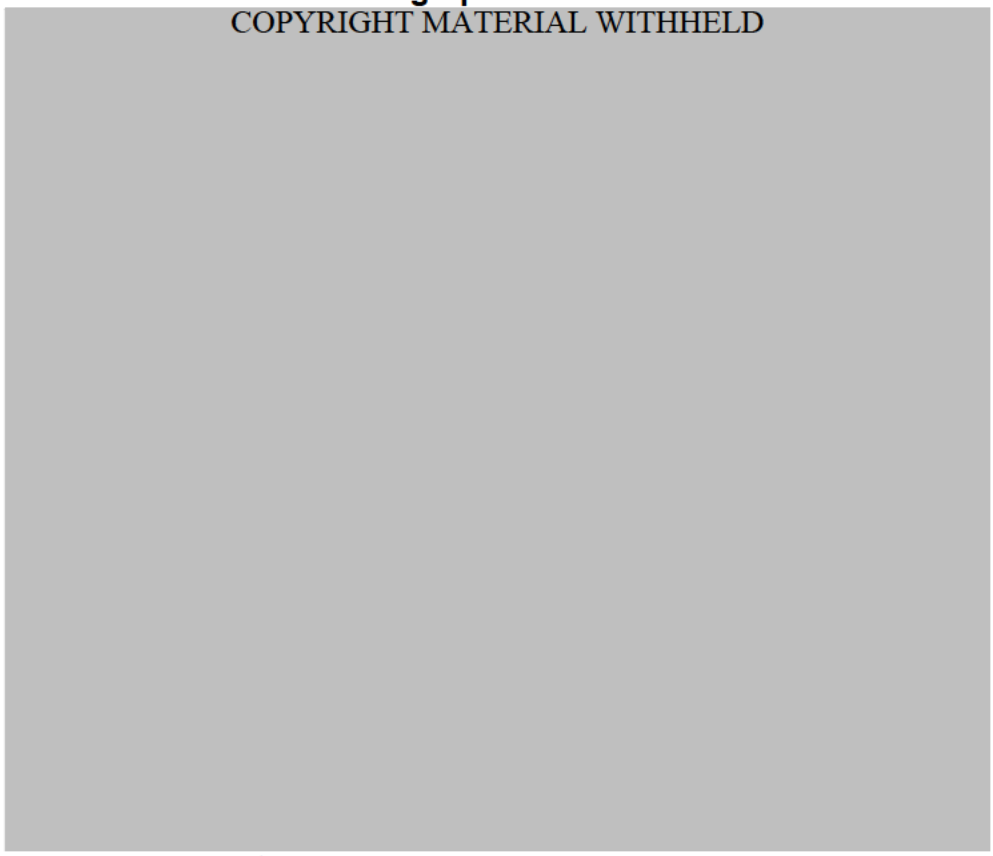
Statistical analysis plan was not prespecified.

Results
A total of 212 subjects were randomized, of whom 107 to rhLFA3-IgFP group and 105 subjects to the methotrexate group. One hundred ninety two subjects completed the trial, of whom 100 from the rhLFA3-IgFP group and 92 subjects from the methotrexate group.

In the methotrexate group, 11 (12.38%) subjects were discontinued, 2 due to elevated liver enzymes, one with headache and 8 lost to followup. No additional information regarding discontinuations due to AEs was provided.

Seven subjects (6.54%) from the rhLFA3-IgFP group discontinued. Of these, six subjects were lost to followup and one subject was discontinued due to leukocytopenia. Additional 2 subjects were excluded from the rhLFA3-IgFP group, one was found to be HbsAg positive at 5 day after the treatment, and one was found to be receiving glucocorticoids at 2 weeks before the treatment. The baseline characteristics of subjects who completed the trial are presented in Table 16 below.

Table 16: Baseline Demographic and Disease Characteristics



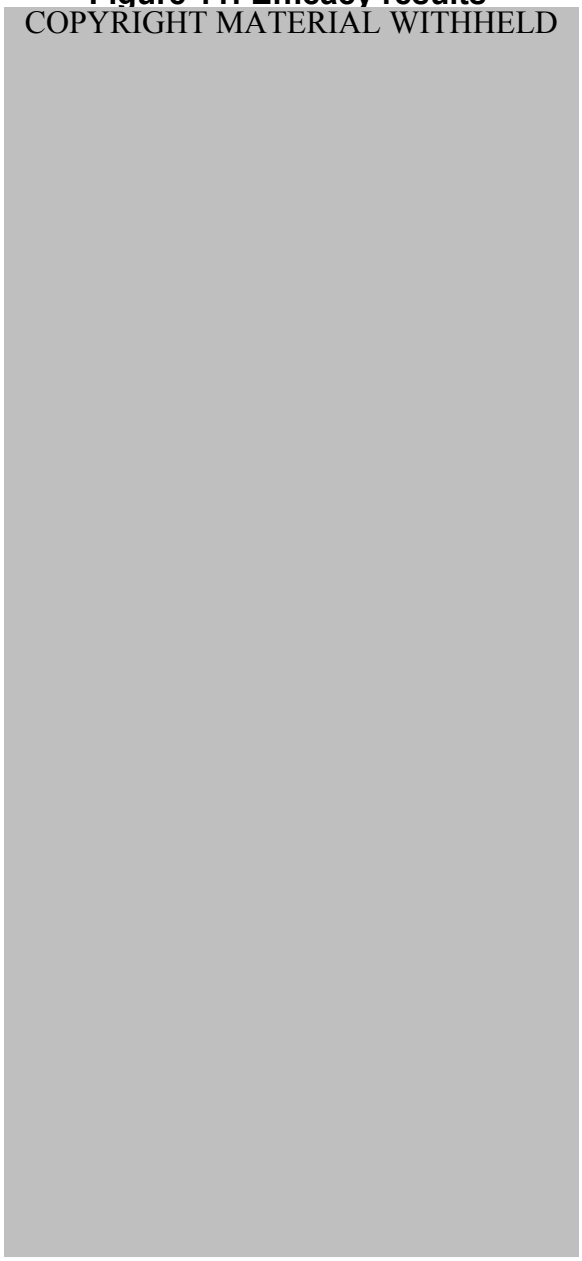
Source: Original publication
Experimental group: rhLFA3-IgFP group ; Control group: methotrexate group

Efficacy
After 6 weeks of treatment, the number of subjects who achieved PASI 75 and PASI 90 in the MTX group was 6 (5.7%) and 2 (2%) respectively.
Number of subjects who achieved PASI 75 and PASI 90, in the rhLFA3-IgFP group, was 6 (5.6%) and 2 (1.9%) respectively.

After 12 weeks of treatment, number of subjects who achieved PASI 75 and PASI 90, in the MTX group, was 29 (29%) and 7 (7%) respectively.
Number of subjects who achieved PASI75 and PASI90, in the rhLFA3-IgFP group, was 22 (21%) and 8 (7.5%) respectively.

At 8 weeks after discontinuation of treatment (Week 20 of the trial) the number of subjects who achieved PASI75 and PASI90 in the methotrexate group was 27 (26%) and 11 (%) respectively.
The number of subjects who achieved PASI 75 and PASI 90 in the rhLFA3-IgFP group was 36 (34%) and 17(16%) respectively. Efficacy results are presented in Figure 11 below.

Figure 11: Efficacy results



Source: Original publication
Experimental group: rhLFA3-IgFP group; Control group: methotrexate group

The authors concluded that PASI 75 scores differed insignificantly between treatment groups.

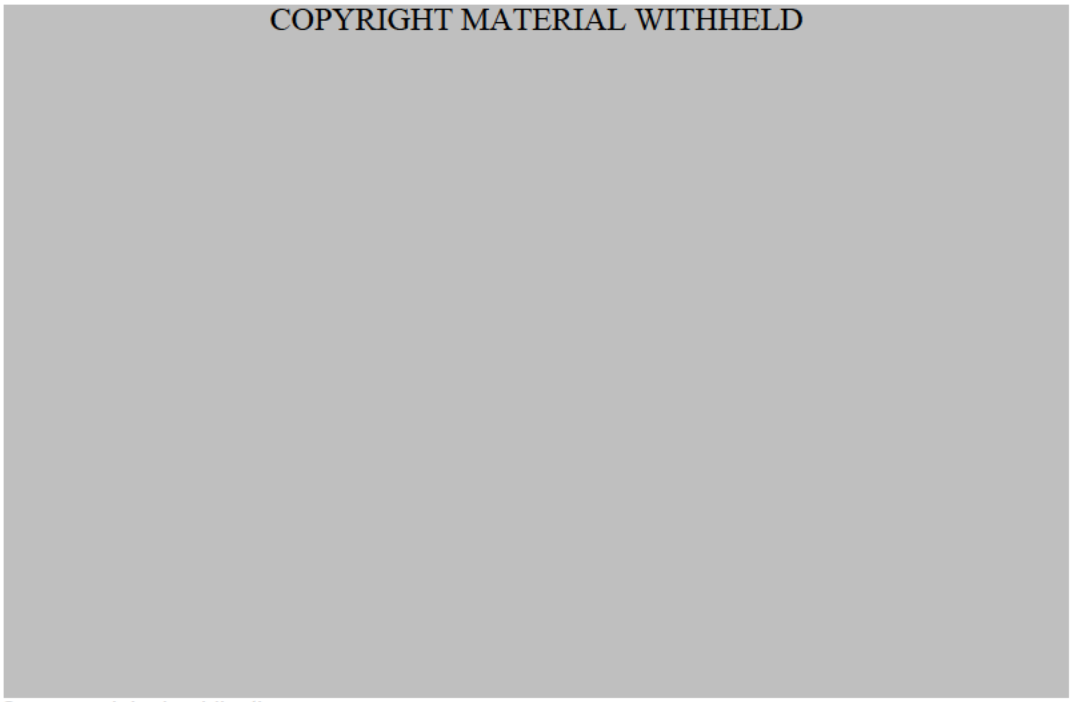
Safety
No deaths or serious adverse events were reported during the conduct of the trial.

In the methotrexate group the most frequent reported adverse events were: elevated liver enzymes, nausea, fatigue (6.67%) respectively; drowsiness (5.7%) and dizziness (4.76%).

In the rhLFA3-IgFP group the most frequently reported adverse events were: arthralgia (5.61%); elevated liver enzymes, fever injection site pain scleroma, dizziness and headache (1.87%) respectively.

The most frequently reported adverse events are presented in the Table 17 below.

Table 17: Adverse Events



Source: original publication
Experimental group received rhLFA3-IgFP
Control group received MTX

Complete safety database was not presented. No information was provided regarding relationship between study drug, drug dose, duration of dosing, and subjects' disease severity on the frequency and severity of adverse events.
Safety information obtained from this study is of limited value due to exposure to low dose (7.5mg/week) of MTX. Higher doses on MTX were not explored.
In the treatment of psoriasis, the approved MTX labeling recommends the starting MTX dose of 10mg/week that can be titrated up to 25mg/week. Exposure to adequate doses of MTX was not evaluated.

This study has the following limitations:

- This is active controlled study. Without the placebo arm, the efficacy of the study drug cannot be accurately determined.

- Primary efficacy endpoint and timepoint of efficacy evaluation were not prespecified.
- Statistical analysis plan was not prespecified.
- No subject-level efficacy data was included to allow independent assessment of the results.
- MTX used was in a dosage form for oral administration. Source of MTX was not provided.
- Safety and efficacy information obtained from this study is of limited value due to exposure to doses lower then recommended by approved MTX labeling.

Conclusion: The design and conduct of this study were not adequate to provide the evidence that the benefits of methotrexate in subjects with moderate to severe psoriasis outweigh the risks.

5.3.2.6 A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. A.B. Gottlieb et al. BJD 2012, 167, p 649-657.

Trial objective
To evaluate etanercept plus methotrexate vs. etanercept monotherapy in subjects with moderate to severe plaque psoriasis who had not failed prior methotrexate or tumor necrosis factor-inhibitors therapy.
Trial design
This was a randomized, double blind, placebo-controlled, multicenter study.

Study population
Inclusion criteria
1. Subjects 18 years of age and older
2. Stable moderate to severe plaque psoriasis for ≥6 months, psoriasis involving ≥10% of BSA, a PASI ≥10 at screening and baseline, ad were candidates for systemic therapy or phototherapy.
3. Adequate hematological, renal and hepatic functions, was required.
4. Serum AST and ALT levels had to be within normal limits at screening.

Exclusion criteria
Subjects who fulfilled the following criteria were excluded:
1. Active guttate, erythrodermic, or pustular psoriasis or other skin conditions at screening that would interfere with study evaluation.
2. Concurrent significant medical conditions.
3. active Common Terminology Criteria (CTC) for Adverse Events version 2.0 grade ≥ 2 infection within 30 days of screening;
4. History of significant methotrexate toxicity or total cumulative methotrexate exposure > 1000 mg (unless grade ≥IIIb liver injury has not occurred)

5. Use of ultraviolet (UV) B therapy
6. Topical cyclosporin or calcineurin inhibitors, class III through VII topical corticosteroids (permitted on the scalp, axillae, and/or groin), or topical vitamin A or D analogues within 14 days of screening.
7. Psoralen or UVA therapy, systemic psoriasis therapy (including methotrexate) oral retinoids, class I or II topical corticosteroids, dithranol, cyclophosphamide, sulfasalazine, or intravenous or oral calcineurin inhibitors within 28 days of screening.
8. If subjects had received a TNF blocking agent or other biologics within 3 months or interleukin (IL)-12 or IL-23 inhibitors within 6 months of study initiation.
9. Subjects were excluded if they had experienced a clinically significant AE with prior use of methotrexate or experienced lack of efficacy or a clinically significant AE with prior use of a TNF-blocker.

Study visits and procedures
Four hundred seventy eight subjects were randomized in 1:1 ratio to receive etanercept +placebo (239 subjects) or etanercept +methotrexate (239 subjects), for 24 weeks.

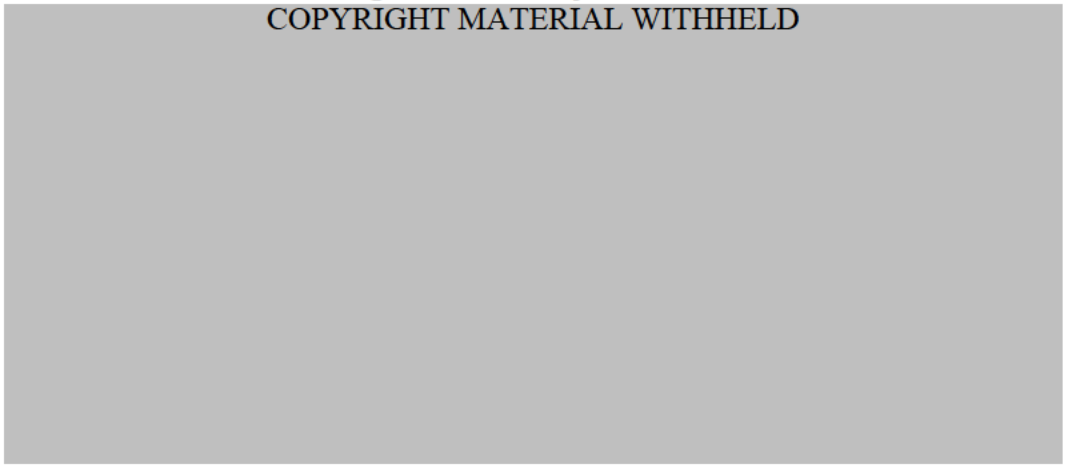
Study drug administration
Subjects were treated with study drug for 24 consecutive weeks as follows:

- Etanercept 50 mg subcutaneously twice weekly and placebo 6 capsules per week, for 12 weeks, followed by treatment with etanercept 50 mg once weekly plus 6 capsules of placebo for an additional 12 weeks.

or

- Etanercept 50 mg subcutaneously twice weekly plus oral methotrexate 15mg per week [titrated from 7.5 mg (weeks 1–2) to 10 mg (weeks 3–4) to a maximum of 15 mg or the maximum tolerated dose (not to exceed 15mg/week (weeks 5–12)] for 12 weeks, followed by 12 week treatment with etanercept 50mg once weekly plus methotrexate at the dose of 15mg per week or at the maximum tolerated dose (not to exceed 15mg/week). Treatment schematic is presented in Figure 12 below.

Figure 12: Study schema



Source: Original publication BIW, twice weekly; ETN, etanercept; MTX, methotrexate; PBO, placebo; QW, once weekly.

Safety monitoring

Safety monitoring during the study was not specified. Other than live function test (LFT) evaluation, no additional monitoring was described. Frequency of LFT evaluations was not specified.

Efficacy and endpoint measures

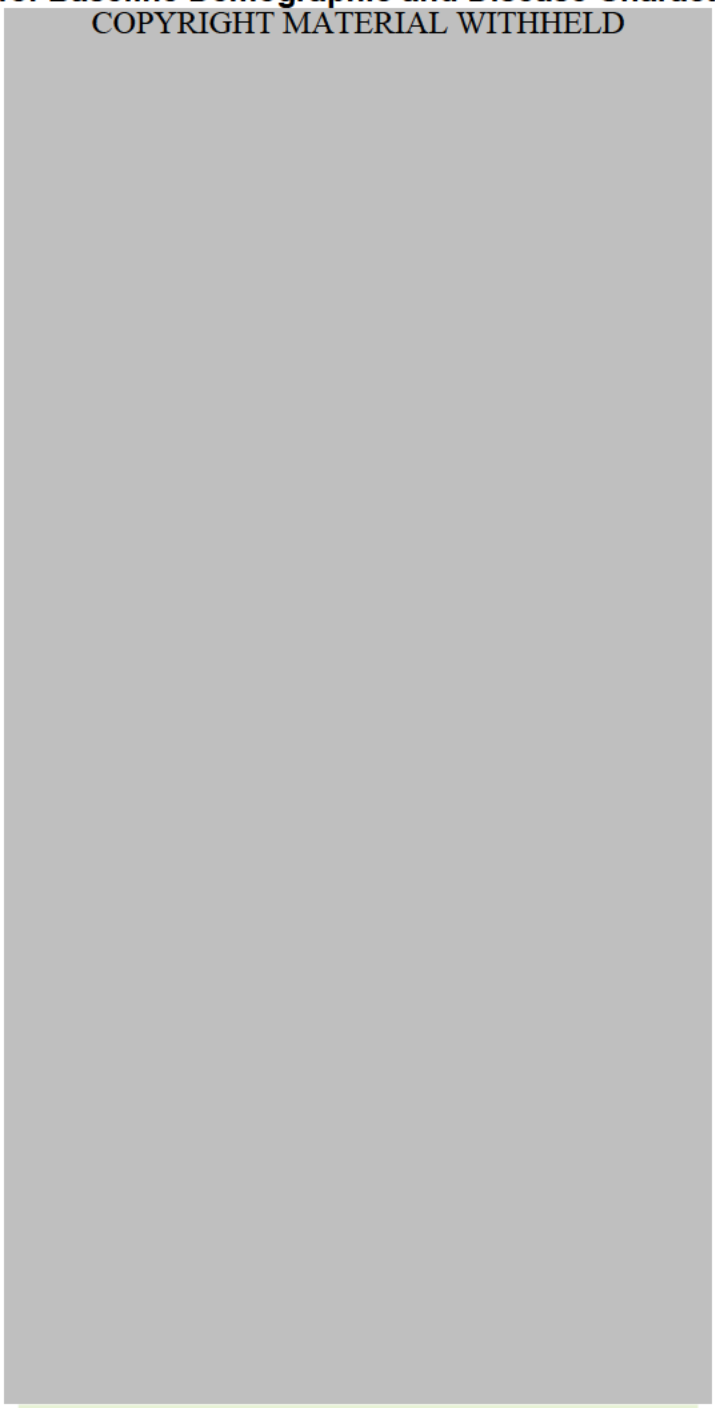
Efficacy assessments were performed at screening, at baseline, and every 4 weeks thereafter throughout the study.

The primary endpoint was the proportion of subjects achieving PASI 75 from baseline at week 24.

Results

Four hundred seventy eight subjects were randomized. Baseline demographic and disease characteristics are presented in the Table 18 below.

Table 18: Baseline Demographic and Disease Characteristics

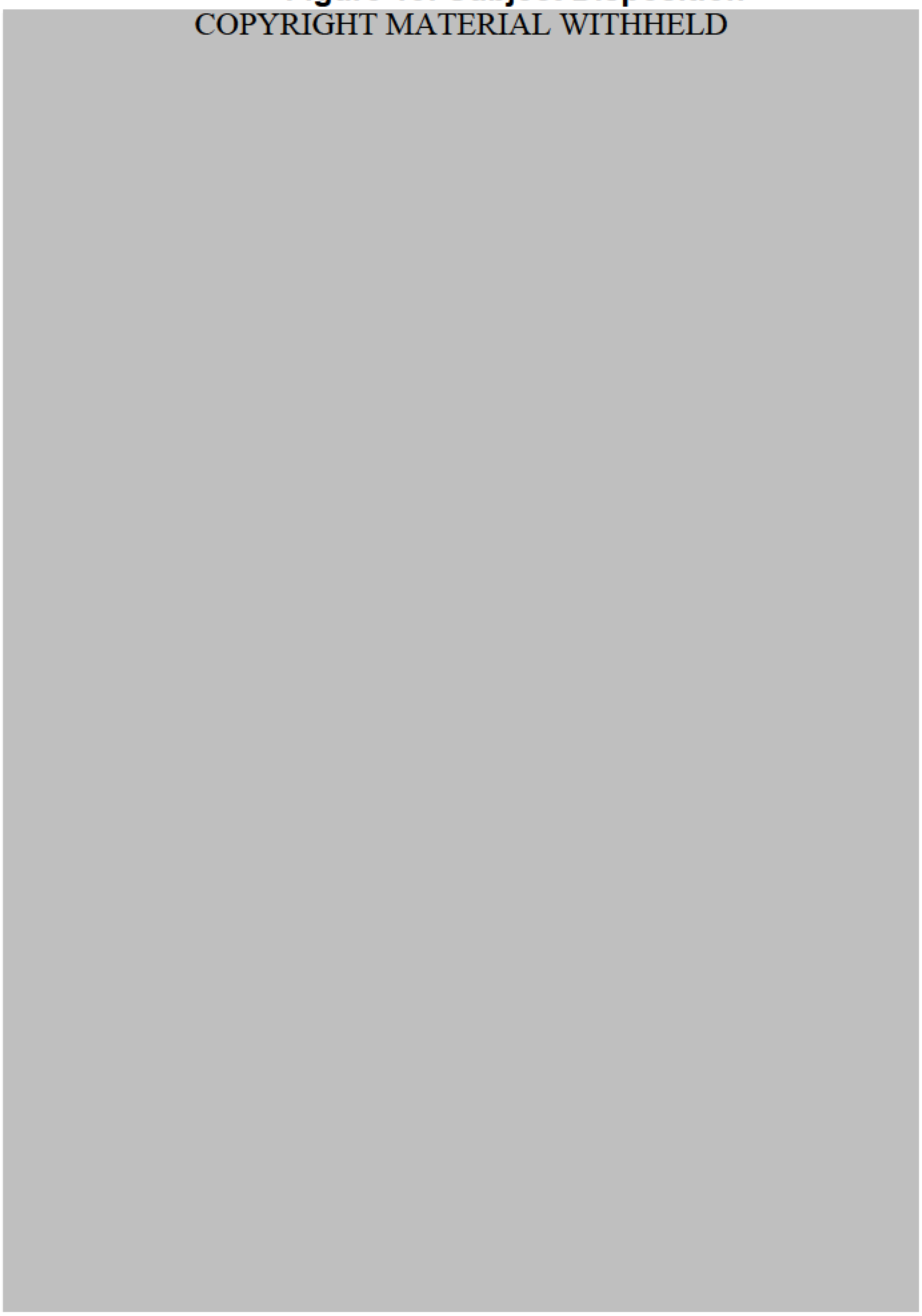


Source: Original publication

Four hundred seventy eight subjects were randomized and 417 subjects completed the trial. Sixty one subjects discontinued the trial, 28 from etanercept/methotrexate group and 33 from etanercept/placebo group. Reasons for discontinuation were as follows: Adverse events (15), lost to follow up (14), noncompliance (11), consent withdrawal (9),

subject ineligibility (6), disease progression (3), other (2). One additional subject in the etanercept/placebo group did not complete the trial due to disease progression, which was also reported as AE. Subject disposition is presented in Table Figure 13 below.

Figure 13: Subject Disposition

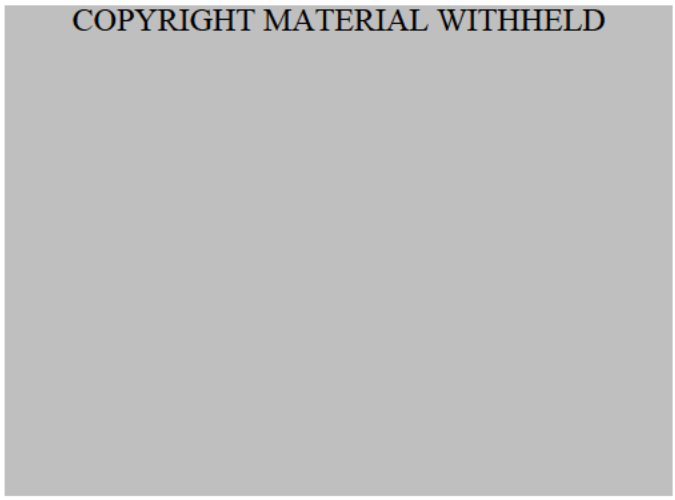


Source: Original publication. ALT (alanine aminotransferase); AST (aspartate aminotransferase);
[a] Represents all adverse events leading to study withdrawal.

Efficacy
Efficacy analyses were performed using the Intent to Treat (ITT) set (all randomized subjects).
Missing post-baseline data were imputed using last observation carried forward for primary analysis of all efficacy endpoints. Sensitivity analyses were performed using nonresponder imputation (NRI) for missing data and observed cases for all efficacy endpoints.

At week 24, PASI 75 response was 77.3% in the etanercept + methotrexate group and 60.3% in etanercept + placebo group. Efficacy results are presented in Figure 14 below.

Figure 14: Proportion of Subjects with Improvement in PASI of ≥50%, ≥75% or ≥90% from Baseline to Weeks 12 and 24.



Source: Original publication
PASI, Psoriasis Area and Severity Index

Safety
Sixteen subjects discontinued due to AE, 10(4.2%) in the etanercept + methotrexate group and 6 (2.5%) in etanercept + placebo group. None of the AEs leading to discontinuation was considered to be SAE or due to infection. More subjects in etanercept + methotrexate group had increased hepatic transaminases, 7 (2.9%) then in etanercept + placebo group, 4 (1.7%).

This study has the following limitations:

- MTX was used in combination with etanercept, therefore efficacy and safety of MTX alone could not be determined.
- Safety monitoring was not described; therefore information obtained during the conduct of this study is of limited value in determining safety profile of MTX in the treatment of moderate to severe psoriasis.

Conclusion: The design and conduct of this study were not adequate to provide the evidence that the benefits of methotrexate in subjects with moderate to severe psoriasis outweigh its risks.

Scientific publications: "Supportive evidence for the efficacy of MTX in moderate-to-severe" psoriasis

Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. M Akhyani et al.JEADV 2010, 24, 1447-1451.

This was randomized open label trial. Thirty eight adult subjects with chronic plaque psoriasis, with disease severity based on PASI score of >10, were randomized to receive treatment with oral MTX (7.5mg/week titrated up to 20mg/week) or mycophenolate mofetil (MMF, 2g/day) for 12 weeks with 12 weeks of follow-up. Eighteen subjects were randomized to MTX group and 20 to MMF group. Efficacy outcome measure was 75% (PASI 75) and 90% (PASI 90) reduction in PASI score at Week 12.

Efficacy results: PASI 75 was achieved by 73.3% of subjects in MTX group and by 58.8% of subjects in MMF group at week 12. PASI 90 was achieved by 26.7% of subjects in MTX group and by 11.8% of subjects in MMF group, at Week 12.

Safety: 12 (80%) of subjects in MTX group had nausea and 5 had elevation of liver enzymes.

The Combination of Etanercept and Methotrexate Increases the Effectiveness of Treatment in Active Psoriasis Despite Inadequate Effect of Methotrexate Therapy Claus Zachariae et al. Acta Derm Venereol 2008, 88: 495-501.

This was randomized open label trial. Fifty nine subjects with active plaque psoriasis with disease severity of at least 10% of body surface area involvement and PASI score of 8 were randomized to receive 24 weeks of etanercept plus MTX (MTX tapered and discontinued during first 4 weeks of trial) or etanercept with continued MTX. Etanercept was given 50mg twice weekly for 12 weeks and 25mg twice weekly for remaining 12 weeks. MTX dose was at least 7.5mg. The primary efficacy variable was the proportion of subjects who were "clear" (score of 0) or "almost clear" (score of 1) on the Physician Global Assessment scale at week 24. Twenty eight subjects were in etanercept with MTX taper group and 31 subjects in etanercept with continuous MTX group.

Efficacy results: 66.7% of subjects in etanercept with continuous MTX group achieved "clear or almost clear" and 37% of subjects in etanercept with tapering MTX achieved this endpoint.

Safety: A total of 101 adverse events were reported. Of these 7 SAE were reported (3 infections, pustular psoriasis, heart insufficiency, atrial fibrillation and vomiting) and were all considered related to the study treatment. Three subjects discontinued due to adverse events in etanercept/MTX taper group and none in combination group.

Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicenter prospective randomized controlled clinical trial. S. Fallah Arani et al. British Journal of Dermatology 2011 164, pp855-861.

This was randomized, open label trial. Sixty subjects with moderate to severe psoriasis (PASI score of 10) were randomized to receive oral fumarates (30 subjects; starting with 30mg and increased to 120mg) or oral MTX (30 subjects; 5mg/week increased to 15mg/week) for 16 weeks with 4 weeks of followup. The primary efficacy endpoint was the difference in mean change from baseline in PASI score after 12 weeks of treatment.

Efficacy results: After 12 weeks of treatment, the mean PASI score decreased from 14.5±3 at baseline to 6.7±4.5 in subjects treated with MTX, whereas it decrease from 18.1±7 to 10.5±6.7 in subjects treated with fumarates.

Safety: Four subjects from MTX group discontinued due to adverse events of whom 2 because of elevation of liver enzymes and one due to recurrent angina.

Methotrexate-betamethasone weekly oral pulse in psoriasis. Mamji Gupta et al., Journal of Dermatological Treatment, 2007, 18: 291-294.

This was randomized, open label trial. Forty subjects with psoriasis (plaque type:36 and erythrodermic :4) with the PASI score >10 and body surface area of 10%, were randomized to receive oral weakly dose of 15mg of MTX plus 3mg of betamethasone (GMT) or 15mg of MTX, until PASI score reduced by 95-100% from the baseline. Efficacy was defined as: the number of pulses needed to clear the psoriasis lesions completely, time taken to clear the lesions completely and duration of remission.

Efficacy results: MTX +BMT treatment required 4.1±0.28 pulses and 27.13±2.39 days to clear the lesions, with remission period lasting 91.78±14.19.days. MTX alone needed 4±1 pulses and 33±5.61 days to clear the lesions, with a remission period lasting on 20.3±2.5 days.

Safety: 5 subjects in MTX+BMT group and one in MTX only group had elevated liver enzymes after 4-5 pulses that returned to normal after discontinuation of treatment.

Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-sever plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). J. Baker et al. British Journal of Dermatology 2011, 165, pp1109-1117.

This was randomized, open label trial. Eight hundred sixty eight subjects with psoriasis with at least 10% BSA and PASI ≥12 were randomized (3:1) to receive infliximab 5mg/kg (at weeks 0; 2; 6; 14; 22) or MTX 15mg/week (with a dose increase to 20mg at week 6 if PASI response was <25%) for 22 weeks. The primary efficacy endpoint was PASI75 response at week 16.

Efficacy results: 78% of subjects in infliximab group and 42% in MTX group achieved PASI75 at week 16.

Safety: Up to week 16, 6% of infliximab treated subjects and 2% in MTX treated subjects reported SAEs. Severe, life-threatening SAEs were experienced by 5% of infliximab subjects and <1% of MTX subjects.

Methotrexate/narrowband UVB phototherapy combination vs. narrowband UVB phototherapy in the treatment of chronic plaque-type psoriasis – a randomized single-blinded placebo-controlled study. R. Mahajan et al. JEADV 2010, 24, 595-600

This was randomized, patient-blinded trial. Forty subjects with chronic plaque-type psoriasis (BSA >10%) were randomized to receive either MTX/NBUVB phototherapy or placebo/NBUVB until achieving more than 75% reduction of PASI score or up to 6 months, whichever was earlier. Oral MTX dose was 0.5mg/kg once weekly with maximum of 30mg/week. NBUVB therapy was administered three times per week. Primary endpoint was reduction in PASI.

Efficacy results**:** Mean number of weeks needed to achieve PASI75 was 7.57±3 weeks in combination therapy group and 11.42±4.98 weeks in phototherapy only group. Mean number of phototherapy sessions required to achieve PASI75 was 17.47±6.62 in combination therapy group and 35.72±17.05 in phototherapy only group. The mean time to relapse in combination group was 7±2 weeks and in phototherapy group was7.2±4.38 weeks.

Safety: 7 subjects in combination group and 12 subjects in phototherapy group experienced AEs. Most common AE was itching after phototherapy. Nausea was reported by 3 subjects in combination group.

Benefits and adverse drug experiences during long-term methotrexate treatment of 248 psoriatics. A. Nyfors. Danish Medical Bulletin, Vol. 25, October 1978, pp. 208-211.

This was retrospective analysis of 248 subjects with severe psoriasis who underwent treatment with methotrexate. Subjects were divided in 3 groups depending on cumulative MTX dose and duration of treatment:
Group 1: 88 subjects with mean cumulative MTX dose of 1733mg and mean treatment of 26 months

Group 2: 68 subjects with mean cumulative MTX dose of 3940mg and mean treatment of 52 months
Group 3: 92 subjects with mean cumulative MTX dose of 2287mg and mean treatment of 32 months

Efficacy: 52% of subjects had complete clearing of psoriasis, and 38% had 90-99% clearing of psoriasis.

Safety: All subjects had at least one liver biopsy. The average duration of MTX therapy was 37 months (range 3-105 months).
MTX was temporarily discontinued in 116 subjects for the following reasons: clearing 32, nausea 30, liver cirrhosis 16, lack of cooperation 10, ineffective therapy 9, recurrence of duodenal ulcer 2, thrombocytopenia 2, alcohol abuse 2, leukopenia 1, pyelonephritis 1, hyperthyroidism 1, gall bladder colic 1, headache1, wanted pregnancy 1, increased caries 1.
Two subjects developed transient bilateral basal pulmonary infiltrates and 4 developed unilateral transient basal pulmonary infiltrates.

The following malignancies were diagnosed: 1 ovarian cancer, 1 breast cancer, 1 pancreatic cancer, 1 lung cancer, 1 esophageal cancer, 10 basal cell epitheliomas and 5 squamous cell carcinomas.

Conclusion regarding above described studies: Above discussed studies did not involve either randomization, blinding or used methotrexate in combination with other treatments. Therefore, these studies did not provide evidence of safety and efficacy of methotrexate in the treatment of moderate to severe psoriasis.

6 Review of Efficacy

Efficacy Summary

In support of indication of moderate to severe psoriasis, the applicant did not conduct any efficacy and safety studies, instead the applicant submitted study reports available in the public domain. Efficacy results of each study report were presented in section **5.3 Discussion of Individual Studies/Clinical Trials.**

Five out of six randomized, double blind studies compared methotrexate therapy to an active control. Authors of these studies concluded the following:

- There was no significant difference in efficacy between methotrexate and cyclosporine (Heydendael et al)
- Cyclosporine was more effective than methotrexate (Flystrom et al)
- Briakinumab (unapproved monoclonal antibody against IL-12 and IL-23) showed to be more effective than methotrexate (Reich et al.),

- LFA-3IgFP (unapproved recombinant human Lymphocyte Associated Antigen 3 – antibody fusion protein) did not differ significantly (Yan et al) from methotrexate.
- In the study by Gottlieb et al, methotrexate was used in the combination with etanercept; therefore safety and efficacy of methotrexate alone were not evaluated.
- In a single study that included a placebo arm (Saurat et al.), methotrexate was more effective then placebo in the treatment of subjects with moderate to severe psoriasis. However, statistical analysis comparing methotrexate to placebo was not prespecified.

Taking into consideration that most of the studies used active control for comparison to MTX, none of the studies provided subject-level data to allow independent efficacy assessment, this reviewer finds that the design and conduct of studies were not adequate to provide the evidence of effectiveness of methotrexate in the treatment of subjects with moderate to severe psoriasis.

7 Review of Safety

Safety Summary

The assessment of local and systemic safety for Otrexup was based on two PK trials, one device usability study and the safety information provided in the published studies submitted by the applicant.

Adequate clinical and laboratory (hematology, serum chemistry) were performed during the conduct of all three clinical studies conducted by the applicant. No clinically significant differences from baseline to the final visit, in physical examination, vital signs and laboratory evaluations, were identified. ECG tracings were performed at the baseline visit only in one of three studies, therefore no comparison to the ECG tracing at the end of study visit could be done.

There was one death and one serious adverse event in three clinical studies conducted by the applicant. These two adverse events were considered by the investigator to be unrelated to methotrexate treatment.

To support safety of Otrexup in the treatment of moderate to severe psoriasis the applicant submitted published literature. No new safety signals were reported in any of published study reports. However, because the complete safety database was not available for any of published study reports, no conclusions regarding safety of MTX in the treatment of moderate to severe psoriasis could be made. Therefore, determination if the benefit of Otrexup therapy outweighs the risk in subjects with moderate to severe psoriasis could not be made.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety results from two PK studies conducted by the applicant is discussed below. Safety information obtained in study MTX-11-002, a single dose device usability study, is also presented in this section.
In addition, safety information reported in published articles submitted by the applicant is discussed below.

7.1.2 Categorization of Adverse Events

For the studies conducted by the applicant, adverse events were classified by body system and preferred term using the Medical Directory of Regulatory Affairs (MedDRA) classification 6.1, and summarized by incidence, severity, and causality. Applicant's categorization of events was assessed by comparing the verbatim terms to preferred terms used by investigators. This reviewer considered adverse events that could be coded into two or more categories.

In published literature, classification and categorization of AEs was not specified. This information is presented as it appears in published study reports.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety information from two PK studies and one safety device usability study, conducted by the applicant, was presented separately for each study.

Because the studies were conducted under varied conditions, safety information from published study reports was presented with discussion of each study in the section 5.3 Discussion of Individual Studies / Clinical Trials. Analysis or pooling of safety data across studies could not be performed. In this section, discussion will be focused on global evaluation of safety results presented in published literature.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Studies conducted by the applicant

Two PK studies and one device usability study were conducted by the applicant. MTX doses and duration of exposure and demographic characteristics were adequate for the purpose of these studies.

7.2.1.2 Studies from the published literature submitted by the applicant

MTX doses and dosing regimen varied widely between studies. In the study by Yan et al., a fixed does of 7.5mg/week was administered, while adjustment of dose from 7.5mg up to 25mg/week was allowed in the study by Saurat et al. The majority of studies followed dose adjustment schedule to a maximal dose of 15mg to 25mg once a week. Therefore, the exposure at appropriate doses, with the exception of the study by Yan et al, was adequate.

The duration of dosing wearied from 12 weeks to 52 weeks. In the study by Reich et al., dosing with study drug was of 52 weeks in duration, however only 45 out of 163 subjects in MTX group completed 52 weeks of dosing.
In the study of Gottlieb et al., the duration of dosing was of 24 weeks. However, MTX was dosed in combination with etanercept; therefore long-term safety of MTX alone cannot be determined from the information provided.

Demographic characteristics of subjects varied widely between studies. Most of studies were conducted in Europe or Europe and Canada. Only study by Gottlieb et al. included subjects from the US. Study by Yan et al. was conducted in China. The majority of subjects were male and white (with the exception of study by Yen et al. were all subjects were Asian and in studies by Heydendael et al. and Flystrom et al., race was not specified).
The effects of race and sex on efficacy and safety of MTX were not evaluated in any of published studies submitted by the applicant. Therefore, no conclusions could be drawn regarding the effects of race and sex on safety and efficacy of MTX in the treatment of subjects with moderate to severe psoriasis.

7.2.2 Explorations for Dose Response

The applicant conducted two PK studies and one single dose device usability study. No safety and efficacy trials were conducted by the applicant. Therefore, no exploration for dose response was performed.

In the five out of six published studies, MTX was titrated from the starting dose (5mg to 15mg) to the maximal dose of (15mg to 25mg) per week. In the study by Yan et al. only dose of 7.5mg/week was administered. No analysis regarding dose response was performed in any of the studies.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this application.

7.2.4 Routine Clinical Testing

The safety evaluations were performed during the conduct of two PK studies and one single dose device usability study. The following evaluations were performed at screening and at the end of the study visits: Vital signs (BP, pulse rate), physical examinations, injection site reactions, and clinical laboratory evaluations (serum pregnancy test, hematology, biochemistry, HCV Ab, HIV Ab, HbsAg, and urinalysis,). A 12-lead ECG, and urine drug and alcohol screen, were performed at screening visit only. Monitoring for AEs was done throughout the duration of studies.

In study a single dose device usability study MTX-11-002, vital signs were performed during all visits and physical examination was performed at screening. No laboratory or ECG evaluations were performed during the conduct of this study.

The choice and frequency of laboratory and cardiac evaluations was adequate to assess the safety of the product for the short duration of study drug administration performed during two PK studies.

Information on safety clinical testing and its adequacy, during the conduct of studies reported in published literature, wearied widely. This information is discussed separately for each publication in section **5.3 Discussion of Individual Studies/Clinical Trials.**

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1 Deaths Reported in Studies Conducted by the Applicant

There was one death reported during the conduct of MTX -11-003 study.

Subject #001-030, a 79 year old male with the past medical history of: rheumatoid arthritis; myocardial infarction; coronary artery disease; CHF; ventricular ectopy; angina pectoris; s/p pacemaker insertion; palpitations; hypertension; Crohn's disease; gastrointestinal bleed; anemia; drug induced lupus; COPD; peptic ulcer disease. Subject was randomized to MTX at 25mg/week and received a single dose of the study drug prior to the event. According to a family member, three days after receiving the study drug, the subject developed jaw and chest pain and died. The cause of death was ruled by the coroner as myocardial infarction due to subject's cardiac history. An autopsy was not performed. The adverse event on myocardial infarction that resulted in death was reported as SAE. The investigator concluded that this adverse event was unrelated to the study drug.

Taking into consideration that the subject had underlying history of coronary artery disease and cardiac arrhythmias as well as a single exposure to the study drug, it is reasonable to conclude that this case of death was not related to the exposure to the study drug.

7.3.1.1 Deaths Reported in Published Studies Submitted by the Applicant

One death (esophageal rupture) was reported in published study by Reich et.al. This death was in a subject who was in the MTX treatment group. The author of this publication did not provid any information regarding this case of death. No assessment of causality to the study drug exposure was provided. Therefore, it is not possible to assess if the AE of death is related to the exposure to the MTX.

7.3.2 Nonfatal Serious Adverse Events

Given the different sources used to analyze safety data, discussion adverse events will be organized based on the originating source of data: Applicant's conducted studies or published scientific literature.

7.3.2.1 Nonfatal Serious Adverse Events Reported in Studies Conducted by the Applicant

There were two SAEs reported during the conduct of study MTX-11-002 and MTX-11-003: a sick sinus syndrome reported by the same subject who took part in both studies, therefore counted as two events. Subject was randomized to 15mg/week of MTX. At the time of the event, the subject completed the treatment and follow-up periods and was in the 30-day SAE reporting follow-up period for both studies. Narrative of this SAE is presented below.

Subject #001-008, 72 year old male with the past medical history of: rheumatoid arthritis, coronary artery disease, s/p stent placement, sinus bradycardia, 1st degree AV

block, hyperlipidemia, hypertension, atrial fibrillation, intermittent angina, deep venous thrombosis, asthma. The subject presented in the emergency room following syncope. He was diagnosed with a sick sinus syndrome. The subject underwent placement of a ventricular-inhibition-rate response pacemaker. The investigator concluded that this AE was unrelated to the study drug.

This reviewer agrees with the assessment of the investigator that this adverse event was not related to the study drug. No changes in labeling are recommended based on the report of this AE.

7.3.2.2 Nonfatal Serious Adverse Events Reported in Published Literature Submitted by the Applicant

No SAEs were reported during the conduct of studies by Heydendael et al., Flystrom et al., and Yan et al.

In the study by Saurat et al., one SAE (hepatitis) was reported in the MTX group. No additional information regarding this SAE was provided.

In the study by Reich et al. 12 SAEs were reported by 10 subjects in the MTX group. SAEs included the following: Increased hepatic enzymes, Esophageal rupture, intestinal polyp, Sacroiliitis, Erythrodermic psoriasis, Vertigo, Angioedema, Urticaria and Intermittent claudication. Authors did not provide any information regarding these SAEs. No relationship to the study drug, dose, and duration of treatment was provided.

In the study by Gottlieb et al., in the combination group (MTX + etanercept) 2 subjects reported 3 SAEs: lumbar stenosis, synovial cyst and bacterial pneumonia. Due to treatment with combination of MTX and etanercept, and due to lack of any additional information, it is not possible to determine the relationship of SAE and the study drug administration.

Three out of six studies reported SAE in the MTX treatment groups. However, no detailed information regarding these adverse events was provided and therefore the assessment of relationship between these AEs and the exposure to the study drug cannot be made.

7.3.3 Dropouts and/or Discontinuations

Discussion regarding dropout and discontinuations is presented based on the originating source of data: studies conducted by the applicant or published scientific literature.

7.3.3.1 Dropouts and/or Discontinuations in Studies Conducted by the Applicant

In the study MTX-10-001, 38 subjects were randomized and 36 subjects received study drug. Two subjects discontinued the study before receiving the study drug. All subjects who received the study drug completed the study.

In the study MTX-11-002, 101 subjects were enrolled into the study. No subject discontinued the study.

In the study MTX-11-003, 50 subjects were randomized. One subject discontinued the study prior to receiving study drug. Two subjects discontinued the study due to adverse events (death and rheumatoid arthritis) after receiving the first dose of the study drug.

7.3.3.2 Dropouts and/or Discontinuations in Published Literature Submitted by the Applicant

No subject was discontinued during the conduct of the study by **Flysrom** et.al.
The following are dropouts and discontinuations in the MTX group reported in the individual studies:

Heydendael et al.: 12 (28%) out of 43 subjects in the MTX group, discontinued the study. All subjects discontinued due to AEs (elevated LFTs).

Saurat et al.: 6 (5.4%) out of 110 subjects in the MTX group, discontinued the study, and all were due to AEs. No further information was provided regarding these subjects. In the placebo group, 5 (9.4%) discontinued the study (one due to AE and 4 due to lack of efficacy.

Reich et al.: 118 (72%) out of 163 subjects in the MTX group, discontinued the study. The most frequently reported reasons for discontinuation were: lack of efficacy 95 (58%); adverse events 9 (6%); withdrew consent 5 (3%) and 3 (2%) of each: lost to followup, protocol violation and other reasons.

Yan et al.: 11(12%) out of 105 subjects in the MTX group, discontinued the study. Of these 3 (3%) discontinued due to AEs (2 subjects had elevated LFTs, one with headache) and 8 (8%) due to being lost to followup.

Gottlieb et al.: 28 (12%) out of 239 subjects in the MTX + etanercept group discontinued the study. All discontinuations were due to AEs. No further information was provided.

The proportion of subjects in the MTX group that discontinued the study varied between the studies: from 5% to 72%. Discontinuations due to AEs ranged from 3% to 28%. The high variability of discontinuations can be explained by differences in study duration, size of study population, dose and dosing regimen. Detailed information regarding discontinuation due to AEs was not provided in any of published studies.

The dose response and time dependency of the dropouts and drug-demographic, drug-disease, and drug-drug interactions could not be assessed due to lack of information.

7.3.4 Significant Adverse Events

7.3.4.1 Significant Adverse Events Reported in Studies Conducted by the Applicant

During the conduct of two PK and one device usability study, no additional significant adverse events were identified.

7.3.4.2 Significant Adverse Events Reported in Published Literature Submitted by the Applicant

Complete and detailed information regarding subject discontinuations and AEs was not provided in any of the published study reports. Therefore, significant adverse events could not be identified or assessed.

7.3.5 Submission Specific Primary Safety Concerns

There are no new safety concerns regarding the current application.

7.4 Supportive Safety Results

7.4.1. Common Adverse Events

Common adverse events are presented by the source of data: from studies conducted by the applicant and from studies from published literature submitted by the applicant.

7.4.1.1 Common Adverse Events Reported in Studies Conducted by the Applicant

Study MTX-10-001
Thirty eight subjects were randomized and 36 completed the study. Two subjects discontinued from the study prior to receiving the first dose of the study drug.

A total of 6 treatment emergent adverse events (TEAE) were reported by 4 (11.1%) subjects.

In treatment A group (Otrexup SC injection with the device): 2 subjects reported AEs: one subject had nasopharyngitis and one had maculopapular rash (of the forearm).
In treatment B group (marketed MTX administered SC using needle and syringe): three subjects reported 4 AEs: one subject had injection site erythema and injection site hematoma, one subject had maculopapular rash and one subject had hypertension.

In treatment C (); No TEAEs were reported.

One subject reported AEs of maculopapular rash during the treatment A and B, considered not to be related to the study drug. Two AEs (injection site erythema and hematoma) reported in a single subject were considered drug related. All other reported AEs were considered not related to the study drug treatment.

Study MTX-11-003
Fifty subjects were randomized and 47 completed the study. Two subjects discontinued the study after the first dose of the study drug. A total of 5 (10.2%) subjects experienced at least one TEAE (myocardial infarction, sick sinus syndrome, nausea, fatigue, and rheumatoid arthritis). Two (4.1%) subjects discontinued the study due to a TEAE: one subject receiving 10 mg of MTX (rheumatoid arthritis) and one subject receiving 25mg of MTX (myocardial infarction that resulted in death).

Two (4.1%) subjects experienced a SAE (myocardial infarction that resulted in death and sick sinus syndrome). Both of these SAEs were considered not related to the study drug.
One AE of nausea was considered drug related. All other AE were considered not related to the study drug.
No injection site reaction occurred during the study. No clinically significant changes in laboratory values were reported.
No new safety signals were identified during the conduct of this study.

Study MTX-11-002
A total of 104 subjects were screened and 101 subjects were enrolled into the study. No subject discontinued the study.

No deaths were reported during the conduct of this study. One subject in 25mg MTX group reported SAE of sick sinus syndrome that was considered by the investigator to be severe and unrelated to the study drug. This SAE was discussed above in the section **7.3.2.1 Nonfatal Serious Adverse Events Reported in Studies Conducted by the Applicant.**

A total of 3 AEs were reported by two subjects. One subject in 20mg MTX group reported two AEs: headache and exostosis. Headache was mild in severity and considered related to the study drug.

Common adverse events reported in studies **MTX-10-001; MTX-11-003** and **MTX-11-002** are summarized in the Table 19 below.

Table 19: Common Treatment Emergent Adverse Events

Adverse Event by System Organ Class and Proffered Term	**Protocol #** Number of Subjects (%)		
	MTX-10-001 36 (%)	**MTX-11-003** 49 (%)	**MTX-11-002** 101 (%)
Gastrointestinal disorders		**1 (2.0)**	
Nausea		1 (2.0)	
General disorder and administration site condition	**1(2.8)**	**1 (2.0)**	
Fatigue	1 (2.8)	1 (2.0)	
Injection site erythema	1 (2.8)		
Injection site hematoma			
Infection and infestations	**1 (2.8)**		
Nasopharyngitis	1 (2.8)		
Musculoskeletal and connective tissue disorders		**1 (2.0)**	**1 (1.0)**
Exostosis		1 (2.0)	1 (1.0)
Rheumatoid arthritis			
Nervous system disorder			**1 (1.0)**
Headache			1 (1.0)
Skin and subcutaneous tissue disorders	**1 (2.8)**		
Rash maculopapular	1 (2.8)		
Vascular disorders	**1 (2.8)**		
Hypertension	1 (2.8)		

Source: Applicant's submission

7.4.1.2 Common Adverse Events in Studies from Published Literature Submitted by the Applicant

Common adverse events that were reported across all clinical studies were: Gastrointestinal (nausea), Infections, Nasopharyngitis, Elevation of Liver Enzymes, and Fatigue. All these adverse events are described in the approved MTX labeling.

7.4.2 Laboratory Findings

Laboratory evaluations were performed in two PK studies conducted by the applicant. No abnormal laboratory values were reported.

In the published studies submitted by the applicant, the most frequently reported abnormal laboratory values were increased liver function tests that ranged from 3% (Gottlieb et.al.) up to 28% (Heydendael et.al.). The differences in rate of abnormal LFTs

can be explained by differences in dose, duration of dosing, and size of the study population.

Current MTX labeling adequately describes hepatotoxicity in the BOXED WARNING and the PRECAUTION, Organ System Toxicity and Laboratory Tests sections.

7.4.3 Vital Signs

No clinically significant vital sign changes were reported during the conduct of two PK studies and one device usability study conducted by the applicant.

No clinically significant vital sign changes were reported in the published literature submitted by the applicant.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed only at the screening of study MTX-10-001. There were no clinically significant abnormalities reported in any of subjects enrolled in this study. Since that ECG was not performed at the end of treatment, no comparison to the baseline ECG could be made.

No ECG monitoring was performed during the conduct of published studies submitted by the applicant.

7.4.5 Special Safety Studies/Clinical Trials

No additional special safety studies were conducted during the development of Otrexup.

7.4.6 Immunogenicity

Not applicable, as the drug is not a therapeutical protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events was not evaluated due to short duration of studies conducted by the applicant.
Dose dependency for adverse events analysis was not conducted in any of published study reports submitted by the applicant.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events could not be evaluated due to short duration of studies conducted by the applicant. Time dependency for adverse events analysis was not conducted in any of published articles submitted by the applicant.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Drug-Disease interaction was not performed by the applicant. Studies conducted by the applicant were of short duration and not designed to evaluate drug-disease interactions.

7.5.5 Drug-Drug Interactions

No drug-drug interaction evaluations of Otrexup were conducted by the applicant. Current labeling adequately addresses drug-drug interactions in **PRECATIONS, Drug Interaction** and **WARNINGS** sections.

7.6 Additional Safety Evaluations

No additional safety evaluations were performed by the applicant.

7.6.1 Human Carcinogenicity

No human carcinogenicity evaluations of Otrexup were conducted by the applicant. **PRECATIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** section of labeling describes instances of malignant lymphoma occurring during treatment with low dose oral methotrexate. Current labeling adequately addresses human carcinogenicity and no changes in labeling are recommended.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy evaluations of Otrexup were conducted by the applicant.

7.6.3 Pediatrics and Assessment of Effects on Growth

No evaluations in pediatric population or assessment of effects on growth of Otrexup were conducted by the applicant.
Methotrexate is currently approved for the indication of treatment of “severe recalcitrant

disabling psoriasis that is not adequately responsive to other forms of therapy" administered by **oral**, **IM** or **IV** routes. Safety and efficacy for this indication has not been established in children.
The current application (Otrexup, NDA 20-4824) provides for the following changes for the psoriasis indication:
1. New route of administration: SC.
2. New indication: "Otrexup is indicated for treatment of **moderate** or severe **psoriasis**".
Because the applicant seeks approval for a new indication and new route of administration, this application is required under PREA to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The applicant has requested for a full waiver in children 0 to 17 years. The applicant claims that the product does not represent a meaningful therapeutic benefit over the available already marketed generic products. This reviewer agrees with granting a waiver, but disagrees with the applicant's reasoning or justification.

Methotrexate has the potential for serious toxic reactions (which can be fatal). Methotrexate labeling carries Boxed WARNING for the following:

• METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.
• DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS
• PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES
• Methotrexate causes hepatotoxicity, fibrosis and cirrhosis
• Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis which may occur at any time during therapy and at low doses.
• Hemorrhagic enteritis and death from intestinal perforation may occur
• Malignant lymphomas
• Occasionally fatal skin reactions
• Potentially fatal opportunistic infections

Furthermore, per current MTX labeling, periodic liver biopsy is recommended during the treatment of patient with psoriasis:
"In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams."

Based on the above safety information for the use of methotrexate, the safety concerns posed by the drug outweigh the potential benefits of treatment in pediatric psoriasis. Therefore, it is the opinion of this reviewer that full waver of studies in pediatric population with psoriasis should be granted for safety reasons, and DDDP plans to label the product accordingly.

The Pediatric Review Committee considered this application on 6/5/2013. The PeRC recommendation concurred with the Division recommendations to restrict this product to use in patients 18 years of age and older.

For the Section **8.4 Pediatric Use**, the following wording is recommended:

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established**.**

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Drug abuse potential, withdrawal and rebound of Otrexup were not evaluated. Based on the mode of action, there is no reason to assume that there is a potential for abuse or dependency of Otrexup.

Overdose with methotrexate have been reported with oral and parenteral dosage forms and with all routs of administration. Current labeling adequately addresses overdose with methotrexate.

7.7 Additional Submissions / Safety Issues

There were not additional safety issues.

8 Postmarket Experience

Otrexup is not a marketed product therefore there is no postmarketing experience available. However, postmarketing data for the methotrexate used in the treatment of psoriasis available within its original NDA 11719 and NDA 08085 along with all subsequent, associated safety reports and published literature. The safety profile observed during the development of the Otrexup is consistent with that of the Methotrexate Sodium Preservative Free and Methotrexate Tablet, and product labeling is adequate to communicate risks to patients and prescribers.

9 Appendices

9.1 Literature Review/References

1. Methotrexate for Psoriasis, A New Therapeutic Schedule. Gerald D. Weinstein, Phillip Frost. Arch Dermatol. 1971; 103(1): 33-38.

2. Methotrexate versus Cyclosporine in Moderate-to-Severe Chronic Plaque Psoriasis. Vera M.R. Heydendael et al. N Engl J Med 2003; 349:658-65.

3. Methotrexate vs. cyclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. B. Flystrom et al.; BJD, 2008; 158, pp116-121.

4. A 52-Week Trial Comparing Briakinumab with Methotrexate in Patients with Psoriasis. Kristian Reich et al. N Engl J Med 2011; 365:1586-96.

5. Treatment of psoriasis with recombinant human LFA3-antibody fusion protein: a multi-enter, randomized, double-blind trial in a Chinese population. Heng Yan et al. Eur J Dermatol 2011; 21(5): 737-43

6. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. A.B. Gottlieb et al. BJD 2012; 167, pp 649-657.

7. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). J.H. Saurat et al. BJD 2008; 158, pp558-566.

8. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. M. Akhyani et al. JEADV 2010, 24, 1447-1451.

9. The Combination of Etanercept and Methotrexate Increases the Effectiveness of Treatment in Active Psoriasis Despite Inadequate Effect of Methotrexate Therapy. Claus Zachariae et al. Acta Derm Venereol 2008; 88: 495-501.

10. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis; a multicenter prospective randomized controlled clinical trial. S. Fallah Arani. BJD 2011. 164, pp855-861.

11. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial. J. Varker et al. BJD 2011 165, pp1109-1117.
12. Methotrexate/narrowband UVB phototherapy combination vs. narrowband UVB phototherapy in the treatment of chronic plaque-type psoriasis- a randomized

single-blinded placebo-controlled study. R. Mahajan et al. JEADV 2010, 24, 595-600.

13. Benefits and adverse drug experiences during long-term methotrexate treatment of 248 psoriatics. A. Nyfors. Danish Medical Bulletin. October 1978, Vol. 25 No.5, pp 208-211.

14. Methotrexate-betamethasone weekly oral pulse in psoriasis. Ramji Gupta, Sarthak Gupta. Journal of Dermatological Treatment, 2007; 18: 291-294

15. Guidelines of care for the management of psoriasis and psoriatic arthritis. Alan Menter et al. Journal of American Academy of Dermatology. Vol 61, No.3, pp: 451-485.

8 Labeling Recommendations

The applicant submitted proposed labeling in the form that complies with Physician's Labeling Rule. Professional and patient labeling, as well as carton and container labels, were reviewed by DMEPA and DDDMAC. Labeling negotiations are ongoing at the time of closure of this review. This reviewer recommends the following specific labeling changes and/or additions to the proposed Otrexup labeling.

From the applicant proposed:

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

NDA 20-4824 was not presented to the Dermatology Drug Advisory Committee because no safety issues were identified during the review. Current application does not present novel issues which would warrant advisory committee input.

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/s/

SNEZANA TRAJKOVIC
08/30/2013

TATIANA OUSSOVA
09/20/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204-824
Priority or Standard	Standard
Submit Date(s)	December 14, 2012
Received Date(s)	December 14, 2012
PDUFA Goal Date	October 14, 2013
Division / Office	DPARP / OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	August 19, 2013
Established Name	Methotrexate Auto-Injector
(Proposed) Trade Name	Otrexup™
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Antares Pharma
Formulation(s)	Solution for injection
Dosing Regimen	Subcutaneous injection
Proposed Indication(s)	Rheumatoid Arthritis (RA); Polyarticular Juvenile Idiopathic Arthritis (pJIA); [Moderate and Severe Psoriasis – see separate review]
Intended Population(s)	RA: adults pJIA: 2 years of age and older

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
December 14, 2012	December 14, 2012	SD-1	Original application
January 25, 2013	January 25, 2013	SD-3	Labeling
March 12, 2013	March 12, 2013	SD-4	Response to the deficiency/comments noted in the 74-day filing letter; revised labeling
April 8, 2013	April 8, 2013	SD-6*	Clinical information ("white paper") to support claim of moderate psoriasis*
April 10, 2013	April 10, 2013	SD-7	(b) (4)
May 7, 2013	May 7, 2013	SD-8	Response to IR of April 30, 2013
May 23, 2013	May 23, 2013	SD-10	Response to DMEPA IR of May 17, 2013
June 4, 2013	June 4, 2013	SD-11	Revised Form 356h
June 7, 2013	June 7, 2013	SD-13	Revised labeling (b) (4)

**Note*: Submission SD-6 was not reviewed in this document, and is listed for information purposes only. Please refer to the reviews performed by the Division of Dermatology and Dental Products for further details.

RECOMMENDED REGULATORY ACTION

NDA/Supplements: _X_ Approval

____ Complete Response

Other Action: ____

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this application.

1.2 Risk Benefit Assessment

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for Methotrexate (MTX) Injection, a drug/device combination consisting of a single-use, prefilled auto-injector intended for subcutaneous (SC) administration. The application references three applications for methotrexate: NDA 11-719 for Methotrexate Injection EQ 50 mg base/2mL from Hospira, ANDA 40-632 for Methotrexate Preservative-Free Injection from Bedford, and NDA 08-085 for Methotrexate Tablets from Dava Pharmaceuticals. The proposed Trade Name for the product is Otrexup, and the PDUFA date is October 14, 2013.

MTX is a folate analog metabolic inhibitor currently indicated for the treatment of neoplastic diseases, severe psoriasis, rheumatoid arthritis (RA), and polyarticular-course juvenile rheumatoid arthritis (JRA), which is now called polyarticular juvenile idiopathic arthritis or pJIA. For the treatment of neoplastic diseases, methotrexate is currently labeled for administration by the oral, intramuscular (IM), intravenous (IV), intrathecal (IT), and intra-arterial (IA) routes, for psoriasis by the oral, IM, and IV routes, for RA by the oral and IM routes, and for pJIA by the oral, IM and SC routes.[1] The originator products were approved in the 1950s, and generics are also available for both oral tablets and parenteral formulations. This will be the first instance of an auto-injector formulation.

The proposed product will be supplied in doses of 10 to 25 mg in 5 mg increments. Because it is intended as a convenience formulation for self or caregiver use in the home setting, the applicant's proposed indications for this product are limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. However, the product is bioequivalent to parenteral methotrexate administered either IM or SC. Given the higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it seems appropriate to limit the indications to RA, pJIA, and psoriasis as proposed by the sponsor rather than broadening the label to neoplastic diseases.

The proposed doses (from 10 mg to 25 mg in 5 mg increments) will cover most of the currently recommended doses for treatment of psoriasis and RA, but will not adequately

1 *Note*: The current labeling for the parenteral product does include SC administration for JRA. Therefore, this product does not represent a new route of administration for this condition, although it does represent a new route of administration for adults with RA and patients with psoriasis.

cover dosing for the entire pJIA population in children, which is typically dosed by mg/m^2 in doses starting at about 5 mg. Although the oncology indications are not being sought by the applicant, the proposed doses also do not adequately cover dosing for these conditions, which extend far higher by the IV route and may require leukovorin rescue. Issues with dosing raised by the limitations imposed by the product will necessitate limitations for use in the Dosing and Administration section of this product. This product will also be the first instance of Physicians Labeling Rule (PLR) labeling for a methotrexate product, necessitating differences between the labeling for this product from those of currently marketed originator and generic methotrexate products despite the fact that there is no particular advantage for use of this product over other products other than convenience. These differences will be minimized whenever possible.

The applicant has also proposed to extend the current indication for psoriasis from symptomatic control of “severe, recalcitrant, disabling psoriasis” to “moderate psoriasis”, which requires a risk/benefit assessment for the newly proposed dermatological indication beyond an assessment of risk/benefit for the use of methotrexate by the subcutaneous route in the home setting. Therefore, the application was administratively split to provide for review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP). This review focuses on the RA and pJIA indications in DPARP. For discussions of the psoriasis indication, please see separate reviews by the Division of Dermatology and Dental Products.

No clinical trials were performed to support this application. Support for approval of this application is based on:

1. The Agency’s previous findings of the safety and effectiveness of methotrexate in patients with RA, JRA (pJIA), and psoriasis, including Agency’s previous findings of the safety and effectiveness of SC administration in patients with JRA.
2. A BA study (and MTX-11-003) in adults that supports efficacy with SC administration in patients with RA and psoriasis because it showed equal or greater bioavailability of the proposed MTX auto-injector product administered SC when compared to systemic exposure with orally administered MTX tablets.
3. Literature reviews that support the safety and efficacy of SC administration of methotrexate for these conditions and for the age groups for which they are currently approved. The literature supports SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and improvements in efficacy when administered SC or IM vs orally at similar doses, particularly when the doses are above 15 mg. The safety review of the literature and of the studies provided to this application did not reveal any new safety signals that would require additional labeling beyond those already labeled in the reference products.
4. A BE study (MTX-10-001) in adults that showed bioequivalence between this auto-injector product administered SC in either the abdomen or the thigh and the approved injectable product administered with a needle and syringe either by the SC or IM route.

The applicant also performed an actual use labeling study (MTX-11-002) and a labeling and human factors study (MTX-11-004) to support the labeling and use of the proposed product, demonstrating that patients and caregivers could be taught to successfully administer the product.

The studies submitted by the applicant to support this application are briefly summarized below.

- Study MTX-10-001 was a single dose bioequivalence study that compared systemic methotrexate exposure following SC administration with the proposed auto-injector device, with administration using a needle and syringe by either the IM route in the outer thigh or the SC route in the abdominal wall. Systemic exposure following administration by all three routes of administration was bioequivalent based on 90% confidence intervals (CI).
- Study MTX-11-003 was a single dose bioavailability study that compared systemic methotrexate exposure following SC administration of MTX using the proposed auto-injector device in the thigh and the abdominal wall, and with a similar dose following oral administration. The results demonstrated bioequivalence between the two SC injection sites using the auto-injector device. Bioavailability following SC administration with the auto-injector was higher than following oral administration, particularly at higher dose levels at and above 15 mg.
- Study MTX-11-002 was a multicenter, open-label, single-dose actual human use study that evaluated the ability of RA patients to self-administer the proposed MTX auto-injector after training. After training, all patients were able to perform a successful SC self-injection of study drug and completed all essential tasks successfully.
- Study MTX-11-004 was stated to have been a simulated-use, summative, usability testing, Human Factors study. As a simulated use study, it not involve administration of active drug or use of the device with a needle, and as such did not use a placebo device. The study is stated to have been designed to evaluate whether the device could be used by representative users (patients, caregivers, and healthcare providers [i.e., nurses]) under simulated use conditions “without generating patterns of failures that could result in negative clinical impact to patients or injury to device users”. Specifically, the study purported to test whether the instructions for use are adequate such that patients can use the device in an un-coached setting at home. However, this was not the case. All patients and caregivers received specific training in the use of the device, and the only participants who did not receive this training were the nurse participants. As a result, the study actually evaluated the entire training set and not specifically labeling comprehension of the instructions for use. That stated, with some reservations, the study appeared to show that the entire training set provides adequate instructions to allow appropriate use of the device.

The Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) is triggered by this application for the RA [and psoriasis] indication[s], for which this product would represent a new route of administration. With respect to the RA indication, pJIA is

considered the pediatric form of RA, and the injectable product is already approved and labeled for use in children with pJIA. Therefore, the PREA requirements for RA are satisfied by the Agency's previous findings of safety and effectiveness for JRA (pJIA). Please refer to Section 2.6.2, Pediatric Issues, for further details.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for Methotrexate (MTX) Injection, a drug/device combination consisting of a single-use, prefilled auto-injector containing sterile, preservative-free MTX and intended only for subcutaneous (SC) administration. These characteristics make the product sufficiently different from the reference parenteral vial product(s) that the 505(b)(2) route is appropriate.

Methotrexate Tablets have been marketed since December of 1953 (NDA 08-085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX is approved as an injection (NDA 11-719; approved 1959; Hospira) for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intrathecal (IT) administration. Form 356h that accompanied the application referenced the generic Methotrexate Injection EQ 50 mg base/2mL (NDA 11-719; Hospira), which is listed in the Orange Book as a reference listed drug (RLD) and was the originator for the generic methotrexate injectable products (Table 3). However, due to the shortage of the Hospira Methotrexate Preservative Free drug product, the clinical studies for this application used Methotrexate Sodium Preservative Free from Bedford (ANDA 40-632, approved on August 12, 2005), which is also listed in the Orange Book as an RLD. Therefore, the application also needed to reference this product. Further, one of the clinical studies also used Methotrexate Tablets manufactured by Dava Pharmaceuticals as a comparator. Therefore, the Division informed Antares that the application should also reference NDA 08-085 for Methotrexate Tablets (Table 4). Antares sent in a revised Form 356h referencing all three products on June 6, 2013.

MTX is a folate analog metabolic inhibitor. It is currently approved for the following indications when administered by the routes as shown below:

Indication	Route
Neoplastic diseases	oral, IM, IV, IA, IT
Adults with severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy	oral, IM, IV
Adults with rheumatoid arthritis (RA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral
Polyarticular-course juvenile rheumatoid arthritis (JRA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral, IM, SC

* First line therapy for RA and JRA, as defined in the Indications and Usage section of the labels, includes full dose Non-steroidal anti-inflammatory agents (NSAIDS).

Polyarticular-course juvenile rheumatoid arthritis (JRA) is now called polyarticular juvenile idiopathic arthritis or pJIA, JIA being the more up-to-date classification terminology used to describe what used to be called JRA. Therefore, the newer terminology of pJIA is used in this application instead of the older terminology of JRA, except when specifically referring to the existing labeling or indications for marketed and approved products.

The prescribing information (PI) for MTX includes a Boxed Warning regarding the serious risks and limitations of use. The Pediatric Use sections for both the oral tablets and the injectable products state that "the safety and effectiveness [of methotrexate] in pediatric patients have been established only in cancer chemotherapy and in polyarticular course juvenile rheumatoid arthritis", i.e., RA and psoriasis do not currently carry pediatric indications.

The proposed product will be supplied in doses of 10 to 25 mg in 5 mg increments. Because it is intended as a convenience formulation for self or caregiver use in the home setting, the applicant's proposed indications for this product are limited to RA, pJIA, and psoriasis, and do not include treatment of neoplastic diseases. However, the product is bioequivalent to parenteral MTX administered either IM or SC. Given the higher dosing used for most of the oncology indications and the fact that this product can only be administered by the subcutaneous route, it seems appropriate to limit the indications to RA, pJIA, and psoriasis as proposed by the sponsor rather than broadening the label to neoplastic diseases.

The proposed doses (from 10 mg to 25 mg in 5 mg increments) will cover most of the currently recommended doses for treatment of psoriasis and RA, but will not adequately cover dosing for the entire pJIA population in children, which is typically dosed by mg/m^2 in doses starting at about 5 mg. Although the oncology indications are not being sought by the applicant, the proposed doses also do not adequately cover dosing for these conditions, which extend far higher by the IV route and may require leukovorin rescue. Issues with dosing raised by the limitations imposed by the product will necessitate limitations for use in the Dosing and Administration section of the PI for this product.

This product will also be the first instance of labeling in Physicians Labeling Rule (PLR) format for a MTX product, thereby resulting in some differences between the labeling for this product from those of currently marketed originator and generic methotrexate products despite the fact that there is no particular advantage for use of this product over other products other than convenience. Despite the formatting differences inherent in PLR, the Division will try to minimize these differences as much as possible. When and if the originators are updated to PLR labeling, most of those differences should disappear, although several may remain because of the fact that this is a drug/device combination.

The applicant has proposed to extend the current indication for psoriasis from symptomatic control of severe, recalcitrant, disabling psoriasis to moderate psoriasis, which requires a risk/benefit assessment for the newly proposed dermatological indication beyond an assessment of risk/benefit for the use of MTX by the

subcutaneous route in the home setting. Therefore, the application was administratively split to provide for review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Dermatology and Dental Products (DDDP). This review focuses on the RA and JIA indications in DPARP. For discussions of the psoriasis indication, please see separate reviews by the Division of Dermatology and Dental Products.

2.1 Product Information

The proposed product is drug-device combination consisting of a single-use, single-dose, pre-filled, auto-injector fitted with a 27-gauge, ½ inch needle [full length] that delivers a fixed volume of 0.4 mL per injection as a sterile, preservative-free solution (Figure 1). Antares proposes that the device will contain the following MTX doses: 10, 15, 20, or 25 mg of MTX (concentrations of (b) (4), respectively). The needle is protected before use by a needle safety guard and a 'soft needle shield' that are built into the removable safety cap (shown in the figure below with a "1"). The product also includes a removable safety at the end opposite to the needle that prevents triggering of the device (marked as "2" in the figure), and a clear viewing window to allow direct visualization of the methotrexate in the syringe. Sharps protection is provided by the collar (shown in Figure 1 as 'needle end') that, when pressed against the skin to trigger the injection depresses to provide an exposed needle length of [at least] 2.5 mm, and when pressure is withdrawn re-extends beyond the needle and locks in place to prevent future needle sticks.

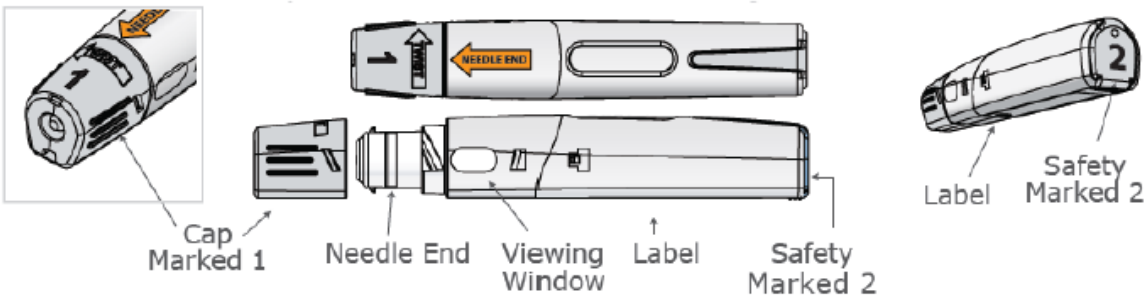

Figure 1. Representative schematic of the proposed device

Source: F1, p5; Module 3.2.P.1; description-and-composition.pdf

2.2 Tables of Currently Available Treatments for Proposed Indications

Methotrexate is a folic acid analogue that inhibits production of DNA, RNA, and proteins. Because it is structurally similarity to folate, MTX binds and inhibits the enzyme dihydrofolate reductase (DHFR), thereby preventing the formation of tetrahydrofolate, which is essential for purine and pyrimidine synthesis. Other approved folate analog metabolic inhibitors include trimethoprim, pyrimethamine, and pemetrexed.

The labeling for MTX for the treatment of adult rheumatoid arthritis (RA) and polyarticular juvenile rheumatoid arthritis (i.e., pJIA) reflects the treatment paradigms that were in place when the products were approved in the 1950s and over the following 20-30 years, whereas the treatments available these conditions have changed dramatically in the last ~20 years and additional information regarding the use of MTX for these conditions has also become available. As a result, the current labeling for the approved products is somewhat dated. Further, the current labeling is confusing with respect to the approved routes of administration for each indication. Although the originator labeling will not change with this application, the labeling for this product will reflect how MTX falls within the current treatment paradigms and modalities for these conditions.

The classes of therapies for RA and pJIA include non-steroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids, conventional disease-modifying anti-rheumatic drugs (DMARDs); and biologic DMARDs. DMARDS slow or prevent structural progression of the disease. In the last several decades, MTX has emerged as the most widely accepted traditional DMARD because of its potency and well understood long-term effects. NSAIDs, which formerly were considered a core therapy, are now considered adjunctive therapy. Additionally, a number of highly effective biologicals have been approved that can be used alone or in combination with MTX, allowing individual tailoring of treatment to fluctuations in disease activity and drug-related toxicities.

Biologic DMARDs have revolutionized the treatment of RA over the past two decades. There are currently 10 small molecules (Table 1) and 9 biologic products (Table 2) approved for the treatment of RA.

Polyarticular juvenile idiopathic arthritis (pJIA) is a category of juvenile idiopathic arthritis (JIA), formerly called Juvenile Rheumatoid Arthritis (JRA). pJIA is similar to adult RA with articular manifestations being predominant. The prevalence of JIA has been estimated to be between 57 and 220 per 100,000 children younger than 16 years of age, with pJIA affecting approximately 2 to 17% of children with JIA. There are multiple biologic products currently FDA approved for the treatment of pJIA, two TNFα-inhibitors: adalimumab (Humira) and etanercept (Enbrel); one targeting the IL-6 signaling pathway: tocilizumab (Actemra); and one targeting T-cell co-stimulatory signaling pathway: abatacept (Orencia). The other TNF-inhibitor, infliximab (Remicade), was not shown to be effective in the treatment of pJIA, possibly because of the higher rate of immunogenicity and clearance than observed in adults.

Table 1. Approved small molecule products for the treatment of RA in the United States1

	Product	NDA	Sponsor	Year of Approval[2]
1	Sulfasalazine (AZULFIDINE)	7-073	Pfizer	1950
2	Methotrexate sodium (METHOTREXATE SODIUM)	8-085 (PO) 11-719 (IV)	Multiple	1953 1959

3	Hydroxychloroquine (PLAQUENIL)	9-768	Sanofi-Aventis	1955
4	Prednisone	Many ANDAs	Multiple	1955
5	Azathioprine (IMURAN)	16-324	Prometheus Labs	1968
6	Penicillamine (CUPRIMINE)	19-853	Aton	1970
7	Auranofin (RIDAURA)	18-689	Prometheus Labs	1985
8	Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE)	50-715 50-625	Novartis	1995 1990
9	Leflunomide (ARAVA)	20-905	Sanofi-Aventis	1998
10	Tofacitinib (XELJANZ)	203-214	Pfizer	2012

1 Other formulations (e.g., solutions) are not included in this table. Steroids and NSAIDs are approved for reduction of the signs and symptoms of RA; however, they are not included in this table.

2 The initial approval of these small molecules may have not been for RA.

Table 2. Approved biologic products for the treatment of RA in the United States

	Product	BLA (sponsor)	Year Approved for RA[1]	Characteristics	ROA
1	Infliximab (REMICADE®)	103772 (COBI)	1999	Monoclonal antibody (TNF inhibitor)	IV
2	Etanercept (ENBREL®)	103795 (Immunex)	1998	Fusion protein (TNF inhibitor)	SC
3	Anakinra (KINERET®)	103950 (Amgen)	2001	Human IL-1 receptor antagonist (IL-1 inhibitor)	SC
4	Adalimumab (HUMIRA®)	125057 (Abbott)	2002	Monoclonal antibody (TNF inhibitor)	SC
5	Abatacept (ORENCIA®)	125118 (BMS)	2005	Fusion protein (costimulation modulator – inhibits T-cell activation)	IV
6	Rituximab (RITUXAN®)	103705 (Genentech & Biogen Idec)	2006	Monoclonal antibody [anti-CD20 (B-cell depleter)]	IV
7	Golimumab (SIMPONI®)	BLA 125289 (COBI)	2009	Monoclonal antibody (TNF inhibitor)	SC
8	Certolizumab Pegol (CIMZIA®)	BLA 125160 (UCB)	2009	Fab fragment conjugated to PEG (TNF inhibitor)	SC
9	Tocilizumab (ACTEMRA®)	125276 (Roche)	2010	Monoclonal antibody (Il-6 receptor inhibitor)	IV

1 Infliximab was originally approved in 1998 for Crohn's Disease and rituximab was originally approved for non-Hodgkin's Lymphoma in 1997. Certolizumab Pegol was originally approved for Crohn's disease in 2008.

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate is available as oral tablets in multiple strengths and as an injectable solution (both preservative-free and with a preservative) in several strengths. Proprietary and generic forms are available. Many of the products are labeled as the sodium salt, which is an incorrect statement. There are no products in an auto-injector presentation, as is the proposed drug product. The Orange Book listings for injectable (Table 3) and oral (Table 4) MTX products are shown below. Two NDA products, NDA 08-085 for MTX tablets from Dava Pharmaceuticals, and NDA 11-719 for injectable MTX from Hospira, and one ANDA, ANDA 40-621 for preservative-free injectable MTX from Bedford, are listed as RLDs and are referenced in this application. Referenced products are shown in **Bold** font.

Table 3. Orange Book listing of Methotrexate injectable products as of 1/10/2013

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A089341	AP	Yes	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	BEDFORD
A040632		**Yes**	**INJECTABLE; INJECTION**	**EQ 1GM BASE/VIAL**	**METHOTREXATE SODIUM PRESERVATIVE FREE**	**BEDFORD**
A089342		Yes	INJECTABLE; INJECTION	EQ 200MG BASE/8ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	BEDFORD
A089343	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	BEDFORD
A089340	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	BEDFORD
A090029	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A090039	AP	No	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A090039	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	EBEWE PHARMA
A040266	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/VIAL	METHOTREXATE PRESERVATIVE FREE	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
A040263	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM	FRESENIUS KABI USA
N011719	**AP**	**Yes**	**INJECTABLE; INJECTION**	**EQ 1GM BASE/40ML (EQ 25MG BASE/ML)**	**METHOTREXATE SODIUM PRESERVATIVE FREE**	**HOSPIRA**
N011719	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ	METHOTREXATE SODIUM	HOSPIRA

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
				25MG BASE/ML)		
A040716	AP	Yes	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040768	AP	Yes	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A040767	AP	Yes	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	MYLAN INSTITUTIONAL
A201529	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201530	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 200MG BASE/8ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 250MG BASE/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A201529	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	ONCO THERAPIES LTD
A200171	AP	No	INJECTABLE; INJECTION	EQ 100MG BASE/4ML (EQ 25MG BASE/ML)	METHOTREXATE PRESERVATIVE FREE	PHARMACHEMIE BV
A040843	AP	No	INJECTABLE; INJECTION	EQ 1GM BASE/40ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040853	AP	No	INJECTABLE; INJECTION	EQ 250MG/10ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV
A040850	AP	No	INJECTABLE; INJECTION	EQ 50MG BASE/2ML (EQ 25MG BASE/ML)	METHOTREXATE SODIUM PRESERVATIVE FREE	PHARMACHEMIE BV

Table 4. Orange Book listing of Methotrexate oral products as of 1/10/2013

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A040385		No	TABLET; ORAL	EQ 10MG BASE	TREXALL	BARR
A040385		Yes	TABLET; ORAL	EQ 15MG BASE	TREXALL	BARR
A081099	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	BARR
A040385		No	TABLET; ORAL	EQ 5MG BASE	TREXALL	BARR
A040385		No	TABLET; ORAL	EQ 7.5MG BASE	TREXALL	BARR
N008085	**AB**	**Yes**	**TABLET; ORAL**	**EQ 2.5MG BASE**	**METHOTREXATE SODIUM**	**DAVA PHARMS INC**

Appl No	TE Code	RLD	Dosage Form	Route Strength	Proprietary Name	Applicant
A081235	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	MYLAN
A040054	AB	No	TABLET; ORAL	EQ 2.5MG BASE	METHOTREXATE SODIUM	ROXANE

2.4 Important Safety Issues With Consideration to Related Drugs

NA

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency had multiple pre-submission interactions with Antares between 2009 and 2012, including several meetings with CDER and CDRH to discuss the requirements for an NDA submission (pre-IND: 2/5/2009, End-of-Phase 2: 9/13/2011, pre-NDA: 11/2/2012), one set of post-meeting Written Responses (2/10/2012), one response to an email request regarding CMC issues (5/14/2012), and one meeting with CDRH to discuss a possible IDE submission for the proposed auto-injector product (4/25/2012).

The intended route of administration for this product is via subcutaneous (SC) injection. While the Dosage and Administration section of the reference MTX product allows for IM or SC dosing as an alternative to oral dosing for polyarticular course JRA, the labeling for adult RA includes only oral administration and is otherwise ambiguous as to the appropriate route of administration. For psoriasis, the oral, IM and IV routes are represented in the labeling, but the SC route is not. Therefore, the Division stated that Antares' proposal for dosing via the SC route would be considered a new route of administration that would need to be supported by clinical information including relative bioavailability data and clinical data supporting safety and efficacy of subcutaneous administration. Antares was asked to bridge between the SC, IM, and oral routes of administration as well as provide clinical data, which could be satisfied by submission of published literature rather than conducting new efficacy and safety trials. The applicant was told that the new route of administration would likely trigger PREA, and that the entire age range of 0-16 years would need to be addressed. [pIND meeting 2/5/2009]

With submission of the NDA, Antares has requested extending the indication for psoriasis from symptomatic control of severe, recalcitrant, disabling psoriasis to moderate psoriasis, which will require a risk/benefit assessment for the proposed dermatological indication. (b) (4)

At the pre-NDA meeting in November 2012, Antares specifically asked whether the proposed clinical development plan would support an indication (b) (4) in addition to severe psoriasis, and the Division responded that to obtain an indication of (b) (4), Antares would need to provide substantial evidence of effectiveness of MTX in patients with this condition because it is unlikely that the literature would provide sufficient clinical support for this indication. Because Antares proposed a new

indication that might require clinical support, a 74-day comment was generated to indicate that the applicant will need to remove this indication from the proposed labeling, and to submit revised labeling that matches the approved indication for the reference MTX injection products. In response, Antares submitted a white paper and additional literature, which they claim support the extended indication. Following this submission, the NDA was administratively split to accommodate substantive reviews in two review divisions. This review focuses on the RA and pJIA indications conducted in DPARP. For the psoriasis indications, please refer to separate reviews conducted by the Division of Dermatology and Dental Products (DDDP).

2.6 Other Relevant Background Information

2.6.1 Trade Name

Antares has requested a proposed Trade Name of Otrexup™ for the product, which was reviewed by the Office of Surveillance and Epidemiology (OSE) and found to be acceptable.

It is important to note that Antares has previously called the proposed auto-injector device by the names 'Vibex™' and 'Medi-Jet™'. However, the company has not requested consideration of either of these names as part of the Trade Name for the product. Because Antares referred to these names in the studies and throughout the application, the names appear in this review when referring to the MTX auto-injector product used in the submitted studies. Whether these two product names imply any differences in the auto-injectors used in the studies is not stated, but this does not appear to be the case.

2.6.2 Pediatric Issues

Methotrexate is currently approved for the indication of treatment of rheumatoid arthritis when administered by **oral** route; for the indication of JRA (pJIA), when administered by **oral**, **IM** or **SC** routes, and for the indication of severe recalcitrant disabling psoriasis when administered by **oral**, **IM** or **IV** routes. The application therefore triggers the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) for the indications of RA and severe psoriasis, for which this is a new route of administration. Additionally, the applicant has proposed a new indication of moderate psoriasis, which also triggers PREA as a new indication. The addition of an auto-injector to an injectable MTX, making this a drug/device combination, does not trigger PREA as this change is not considered to be a new dosage form.

The RA indication triggers PREA because the RA indication is not labeled for SC dosing. However, RA is an adult disease, and pJIA is its pediatric counterpart. Pediatric assessments for RA are therefore performed in children with pJIA down to 2 years of age, the lowest age that pJIA can be diagnosed. For these indications, the applicant has asked for a waiver for children ≤6 years because dosing [for pJIA] is

based on body surface area (BSA) and the proposed product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight. This is based on the fact that the lowest proposed dose for this product of 10 mg is only appropriate for children starting at about 7-8 years of age and around 28 kg (62 pounds). However, DPARP disagrees with this waiver request. As a 505(b)(2) application, the applicant has relied on the Agency's previous findings of safety and effectiveness by the SC route in children with pJIA for the injectable formulation in pJIA. Once the links have been provided for this drug to the reference products, and since the reference parenteral products are already labeled for SC administration in patients with JRA (pJIA), PREA is satisfied and the pediatric assessment is considered complete for children 2 years of age and older. The Dosage and Administration Section of the label will reflect the limitations for dosing below 10 mg and for increments that cannot be accommodated with the product's available dosing. A waiver is appropriate for patients under 2 years of age because the disease does not exist.

With regard to the psoriasis indications, the applicant has asked for a waiver in children 0 to 17 years because the product does not present a meaningful therapeutic benefit over the available already marketed generic products. DDDP agrees with granting of a waiver but disagrees with the applicant's reasoning or justification. The current labeling states that the safety and efficacy of MTX for psoriasis have not been established in children. Further, MTX has the potential for serious toxic reactions (which can be fatal), and the labeling carries a BOXED WARNING for multiple safety concerns. Additionally, periodic liver biopsy is recommended during the treatment of patients with psoriasis. As a result, DDDP believes that the safety concerns posed by the drug outweigh the potential benefits of treatment in pediatric psoriasis. Therefore, DDDP plans to grant a full waver of studies in the pediatric population with psoriasis for safety reasons, and will label the product accordingly.

Both Divisions discussed their recommendations with the Pediatric Review Committee (PeRC) on June 4, and PeRC concurred with the recommendations stated above.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No ethical or data integrity issues were noted during the review of this application.

3.2 Compliance with Good Clinical Practices

The applicant has stated that the studies submitted to this NDA were conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulation, and were in compliance with Good Clinical Practice Guidelines. The protocols and informed consent documents were reviewed by Institutional Review Boards for each center prior to initiation of the study.

3.3 Financial Disclosures

Financial disclosure forms were submitted and reviewed for the two biopharmaceutical studies. No issues were noted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

There were no significant review issues noted in this application noted by either the ONDQA (CMC) reviewer, Dr Shaw, or by the CDRH reviewer. The company has provided stability data and requested 24 months expiry dating. The CMC reviewer agrees.

Functionality testing specifications for the device are as follows:

A) Viewing Window as received: Not obstructed

B). Needle Shield: Strips with safety cap removal

C) Device triggers: Ram released

D) Exposed needle length: ≥2.5 mm

E) Lock Out Function: Collar lock out

F) Viewing window, post-triggering: Obstructed

The specifications also call for a delivery time of (b) (4), which is adequate.

In terms of needle exposure, 2.5 mm is short enough to avoid IM injection, and this is acceptable. Since the product is bioequivalent between IM and SC dosing, no clinical issues are raised if an IM injection were to occur.

4.2 Clinical Microbiology

No microbiological issues were noted in the application. The drug substance is sterile (b) (4) filling of the syringe. Both processes are performed at (b) (4) and sterility assurance monitoring processes are in place to assure and maintain sterility.

4.3 Preclinical Pharmacology/Toxicology

The only pharmacology/toxicology information submitted with this application was a toxicology report for qualification of leachables and extractables in the product, including data for seven organic compounds and three metals. The data were reviewed by

pharmacology/toxicology team, who came to the conclusion that there are no nonclinical concerns related to the safety qualification of the impurities, leachables, and extractables in the proposed product.

4.4 Clinical Pharmacology

The clinical pharmacology of this product was assessed in 2 open-label, randomized, 3-way crossover phase 2 studies (Study MTX-10-001 and Study MTX-11-003). The studies are discussed within Section 5.3.1 of this review, and brief summaries are presented below.

Study MTX-10-001 was a single dose bioequivalence study that compared systemic methotrexate exposure following SC administration with the proposed auto-injector device, with administration using a needle and syringe by either the IM route in the outer thigh or the SC route in the abdominal wall. Systemic exposure following administration by all three routes of administration was bioequivalent based on 90% confidence intervals (CI).

Study MTX-11-003 was a single dose bioavailability study that compared systemic methotrexate exposure following SC administration of MTX using the proposed auto-injector device in the thigh and the abdominal wall, and with a similar dose following oral administration. The results demonstrated bioequivalence between the two SC injection sites using the auto-injector device. Bioavailability following SC administration with the auto-injector was higher than following oral administration, particularly at higher dose levels at and above 15 mg.

4.4.1 Mechanism of Action

NA. No new information was submitted with this application.

4.4.2 Pharmacodynamics

NA. No new information was submitted with this application.

4.4.3 Pharmacokinetics

See Section 5.3.1 of this review for details of the BA/BE studies performed for this application.

5 Sources of Clinical Data

No clinical trials were performed for this application. The application includes a literature review summarizing the safety and effectiveness of SC administration, and a development program that included two clinical pharmacology studies and two use and

handling studies. The Division does not consider any of these studies to be clinical trials for the purposes of exclusivity determination. The program was discussed over multiple interactions with the Agency. Clinical pharmacology was assessed in two open-label, randomized, 3-way crossover studies (MTX-10-001 and MTX-11-003) designed to compare systemic exposure when dosed subcutaneously (SC) via the proposed MTX auto-injector with SC and IM dosing via a needle and syringe (MTX-10-001) and to compare SC administration with the proposed MTX auto-injector dosed in the abdomen and thigh with oral administration (MTX-11-003). Safety and usability was assessed in one open-label, single-dose study (MTX-11-002) in RA patients, and usability and handling of the device was assessed in one simulated use study using a dummy device (MTX-11-004).

5.1 Tables of Studies/Clinical Trials

Table 5. Studies Submitted to the Application

Study	Type	Design	Product	Doses (mg)	N
Clinical Pharmacology studies					
MTX-10-001	BE	R, OL, MC, 3-way crossover in subjects ≥18y with RA on treatment with MTX	Vibex MTX SC MTX SC abd wall MTX IM outer thigh	10, 15, 20, or 25 10, 15, 20, or 25 10, 15, 20, or 25	R 38 C 36
MTX-11-003	BA	R, OL, 3-way crossover in subjects ≥18y with RA on treatment with MTX	Oral MTX Vibex MTX SC abd Vibex MTX SC thigh	3 weekly doses	R 49 C 47
Use and handling studies					
MTX-11-002	AHU	OL, MC, SD single-arm in subjects ≥18y with RA	Vibex MTX SC abd wall	10, 15, 20, or 25	R 101 C 101
MTX-11-004	User study	Two one-on-one sessions (1 wk apart) to evaluate training on use of the device based on the IFU, device label, and HCP training script	Vibex MTX placebo	1st Session: training 2nd Session: Evaluation of simulated device use	50 RA 15 Lay caregivers 17 HCP

AHU = (Actual human use) device handling and use study; R = randomized; C = completed; IFU = information for use; HCP = health care professional

Note: 'Medi-Jet™' and 'Vibex™' are names that Antares has previously used to refer to their proposed auto-injector device and/or drug/device combination product. However, Antares has not proposed to use either as part of the Trade Name. Because Antares referred to these names in the studies and throughout the application, they also appear in this review when used by the company to refer specifically to their proposed methotrexate auto-injector.

Source: synopses-indiv-studies.pdf

5.2 Review Strategy

The studies submitted to the application were reviewed along with the literature supports submitted to the application.

5.3 Discussion of Individual Studies/Clinical Trials

The applicant submitted published literature to support efficacy and safety of SC dosing for JRA and psoriasis, but did not perform any clinical trials for this application. Two clinical pharmacology studies were performed, along with two use and handling studies.

5.3.1 Clinical Pharmacology Studies

Clinical pharmacology was assessed in 2 open-label, randomized, 3-way crossover phase 2 studies (Study MTX-10-001 and Study MTX-11-003).

5.3.1.1 Study MTX-10-001

Initiation Date:	January 17, 2011
Completion Date:	May 31, 2011
Investigation Sites:	(b) (4)
Bioanalytical Laboratory:	(b) (4)

Study MTX-10-001 was an open-label, single-dose, 3-way crossover PK study that compared systemic MTX exposure following SC administration with the proposed MTX auto-injector ["Vibex"] device, with administration of preservative-free MTX using a needle and syringe by either the IM or the SC route in 36 subjects ≥18 years with RA who were on methotrexate treatment for at least 3 months prior to the study. The study was performed at two clinical sites in the United States. The comparator product used in this study was Methotrexate Sodium Preservative Free from Bedford (ANDA 89-340, approved on September 16, 1986), which is listed in the Orange Book as an RLD.

Inclusion criteria included: stable on concomitant medications for 3 months; no medical conditions or medications that would interfere with study outcomes; chest x-ray within 6 months; use of a highly effective form of contraception for females of child-bearing potential; and capable of understanding and following the protocol instructions and

requirements. Exclusion criteria included: pregnant or lactating females; chronic or acute renal disease; history of malignancy except basal/squamous cell carcinoma; any clinically significant disease that might interfere with the study; considering surgical procedures during the study; acute illness within 7 days; donated blood or plasma within 56 days; history of excessive alcohol consumption or drug abuse; administration of an investigational compound within 3 months; taking medications known to affect the PK of MTX; or unable to follow instruction in English or comply with the study procedures. Subjects were to be withdrawn for any medical reason determined by the investigator, although after returning to good health or after the adverse event resolved and was found to be not related to study drug, a subject could return to complete the study.

On three successive weeks, the subjects were randomized to receive weekly doses of methotrexate 10, 15, 20 or 25 mg, depending upon which dose matched the patient's current dosing regimen. Treatments included SC administration with the Vibex device in the abdominal wall, or administration using a needle and syringe by either the SC route in the abdominal wall or the IM route in the outer thigh (*vastus lateralis*).

The study population was primarily female (69.4%) and white (97.2%), with a mean age and weight of 62.1 years and 83.5 kg, respectively [p43, mtx-10-001-report-body.pdf].

There were no deaths and no serious adverse events (SAEs). A total of 4 subjects had 6 treatment-emergent adverse events (TEAEs) during the study, including two subjects with a maculopapular rash (one subject twice and one subject once), one subject with nasopharyngitis, one subject with injection site erythema and hematoma after the 25 mg SC dose with a needle and syringe, and one subject one subject with worsening hypertension. All AEs resolved except the worsening hypertension, which was a continued problem at the time of database lock.

PK parameters are shown in Table 6 and shown graphically in Figure 2 and Figure 3. Systemic exposure following administration by all three routes of administration was bioequivalent based on 90% confidence intervals (CI) for the geometric LS means.

Table 6. MTX-10-001, Dose-normalized PK parameters, PK pop

Parameter Mean (SD)	Vibex MTX	Needle and syringe	
	SC	SC	IM
N	36	36	36
C_{max} (ng/mL/mg)	21.43 (8.31)	22.38 (10.26)	23.37 (7.19)
T_{max} (hr)	1.24 (0.48)	1.32 (0.64)	1.24 (0.85)
½ life (hr)	3.57 (0.69)	3.59 (0.66)	3.51 (0.68)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	118.14 (42.30)	122.63 (40.65)	116.71 (41.39)

Source: T8, p52; mtx-10-001-report-body.pdf

Table 7. MTX-10-001, Geometric LS Means and Comparisons, PK pop

Parameter	Vibex MTX	Needle and syringe		Ratio (90% CI)
	SC	SC	IM	[Vibex to Needle and Syringe]
AUC_{0-24} (ng•hr/mL/mg)	111.3	115.7		96.22 (92.3, 100.3)
			110.1	101.14 (97.1, 105.4)
AUC_{0-inf} (ng•hr/mL/mg)	112.6	117.0		96.24 (92.3, 100.3)
			111.2	101.28 (87.2, 105.6)
C_{max} (ng/mL/mg)	20.2	20.9		96.76 (87.9, 106.5)
			22.5	89.79 (81.6, 98.8)

Source: T8, p52; T9, p53; T10, p54; mtx-10-001-report-body.pdf

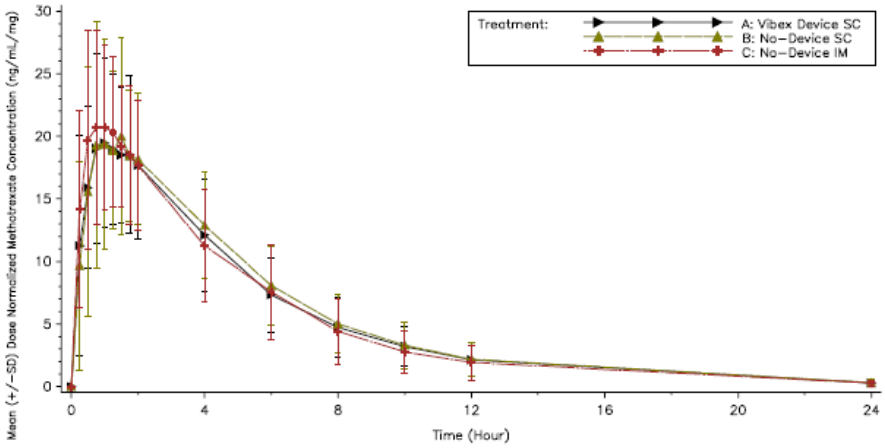

Figure 2. MTX-10-001, Mean dose-normalized MTX concentration vs time, by treatment, original scale, PK pop

Source: F1, p49; mtx-10-001-report-body.pdf

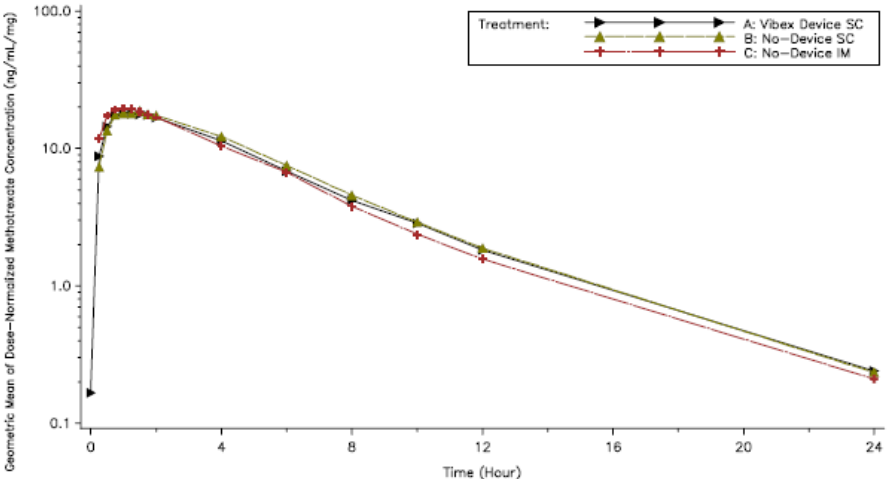

Figure 3. MTX-10-001, Geometric mean dose-normalized MTX concentration vs time, by treatment, log scale, PK pop

Source: F2, p50; mtx-10-001-report-body.pdf

Conclusion

This open-label PK study demonstrated bioequivalence between MTX delivered SC using the proposed auto-injector, SC using a needle and syringe, and IM using a needle and syringe. It therefore supports interchangeability of dosing administered using the proposed device SC in the abdomen with dosing administered either IM and SC using other parenteral forms of MTX.

5.3.1.2 Study MTX-11-003

Initiation Date: May 2, 2012

Completion Date: July 26, 2012

Investigation Sites: (b) (4)

Bioanalytical Laboratory: (b) (4)

Study MTX-11-003 was open-label, single dose, 3-way crossover bioavailability study that compared systemic MTX exposure following SC administration using the proposed auto-injector ["Vibex"] device in either the thigh or the abdominal wall with a similar dose following oral administration in 50 patients ≥18 years with RA who were on methotrexate treatment for at least 3 months prior to the study. The study was performed at four clinical sites in the United States. The comparator product used in this study was Methotrexate Tablets manufactured by Dava Pharmaceuticals Inc. (NDA 08-085, approved on December 7, 1953), which is listed in the Orange Book as an RLD.

Inclusion criteria included: stable on concomitant medications for 3 months; no medical conditions or medications that would interfere with study outcomes; chest x-ray within 6 months; use of a highly effective form of contraception for females of child-bearing potential; and capable of understanding and following the protocol instructions and requirements. Exclusion criteria included: pregnant or lactating females; aspartate aminotransferase, or bilirubin >3x the ULN; chronic or acute renal disease; history of malignancy except basal/squamous cell carcinoma; any clinically significant disease that might interfere with the study; considering surgical or dental procedures during the study; acute illness within 7 days; positive for HIV, HbSAg, or Hepatitis C antibodies; donated blood or plasma within 56 days; history of excessive alcohol consumption or drug abuse; administration of an investigational compound within 3 months; taking medications known to affect the PK of MTX, or unable to follow instruction in English or comply with the study procedures. Subjects were to be withdrawn for any medical reason determined by the investigator, although after returning to good health or after the adverse event resolved and was found to be not related to study drug, a subject could return to complete the study.

On three successive weeks, the subjects were randomized to receive weekly doses of methotrexate 10, 15, 20 or 25 mg, depending upon which dose matched the patient's current dosing regimen. Treatments included SC administration using the Vibex MTX device in either the thigh or the abdominal wall with a similar dose following oral administration.

The study population was primarily female (63.3%) and white (89.9%), with a mean age and weight of 61.4 years and 86.5 kg, respectively [p44, mtx-11-003-report-body.pdf].

One subject experienced an SAE of myocardial infarction that resulted in death. Subject 001-030, on MTX 25 mg, was a 79 year old male with a history of RA ((b) (6)), hypertension, CHF, MI ((b) (6)), and coronary artery disease. (b) (6) days after he received his first dose of study drug he developed jaw and chest pain, and subsequently died in his sleep the next day. The coroner ruled the cause of death to be MI, although an autopsy was not performed.

One subject experienced an SAE of sick sinus syndrome (Subject 001-008, 72 year old male, MTX 15 mg), which was severe but considered unrelated to study drug and resolved by the end of the study. One subject (MTX 10 mg) discontinued due to a

TEAE of worsening rheumatoid arthritis on the same day as the first dose of study drug. Two other subjects experienced a TEAE, including one subject with nausea and one subject with fatigue.

PK parameters are shown in Table 8 and Table 9, and shown graphically in Figure 4 through Figure 8. The results demonstrate bioequivalence between the two SC injection sites using the proposed MTX auto-injector device. However, bioavailability was higher following SC administration with the proposed device than following oral administration, particularly at the higher (20 and 25 mg) dose levels at which a plateau of systemic exposure is reached (Figure 4).

Table 8. MTX-11-003, Dose-normalized PK parameters for SC injection routes

Parameter Geometric LS Mean	Vibex MTX		Ratio (90% CI)
	SC abdomen	SC thigh	
N	49	47	
C_{max} (ng/mL/mg)	20.5	17.8	115.63 (108.83, 122.86)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	133.9	129.1	101.82 (99.39, 104.31)

Source: T12, p61; mtx-11-003-report-body.pdf

Table 9. MTX-11-003, Geometric LS Means and Comparisons by Dose Level, PK pop

Parameter	Oral	Vibex MTX		Ratio (90% CI) [Vibex to Oral]
		SC abdomen	SC thigh	
MTX 10 mg				
$AUC_{0\text{-}24}$ (ng•hr/mL/mg)	1223.7	1507.6		123.20 (115.7, 131.2)
			1441.5	117.80 (110.5, 125.6)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	1246.9	1537.3		123.29 (115.8, 131.3)
			1470.3	117.91 (110.7, 125,9)
C_{max} (ng/mL/mg)	247.2	242.5		98.11 (85.3, 112.8)
			178.4	72.17 (62.6, 83.2)
MTX 15 mg				
$AUC_{0\text{-}24}$ (ng•hr/mL/mg)	1752.0	1994.0		113.82 (106.1, 122.1)
			1992.7	113.74 (106.1, 122.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	1786.6	2039.7		114.17 (106.3, 122.6)
			2040.6	114.22 (106.3, 122.7)
C_{max} (ng/mL/mg)	349.4	266.8		76.35 (70.0, 83.3)
			259.9	74.38 (68.2, 81.1)
MTX 20 mg				
$AUC_{0\text{-}24}$ (ng•hr/mL/mg)	1927.2	2501.8		129.81(118.4, 142.3)
			2542.1	131.90 (120.3, 144.6)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	1949.7	2539.8		130.27 (118.8, 142.9)
			2581.8	132.42 (120.7, 145.3)
C_{max} (ng/mL/mg)	440.4	410.4		93.18 (78.7, 110.3)
			385.7	87.57 (74.0, 103.6)

Parameter	Oral	Vibex MTX		Ratio (90% CI) [Vibex to Oral]
		SC abdomen	SC thigh	
MTX 25 mg				
AUC_{0-24} (ng•hr/mL/mg)	1987.8	2887.5		145.26 (130.5, 161.5)
			2708.6	136.26 (122.2, 152.0)
AUC_{0-inf} (ng•hr/mL/mg)	2012.4	2933.9		145.80 (131.1, 162.2)
			2745.3	136.42 (122.4, 152.0)
C_{max} (ng/mL/mg)	423.5	491.4		116.02 (98.6, 136.5)
			395.9	93.47 (79.1, 110.5)

Source: T9, p55; T10, p57; mtx-11-003-report-body.pdf

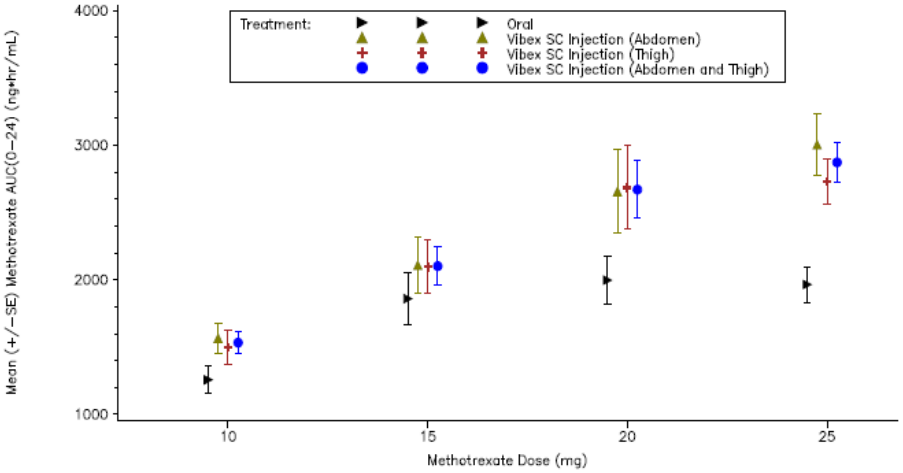

Figure 4. MTX-11-003, Plot of mean AUC0-14 (ng•hr.mL) by dose group and treatment, PK pop

Source: F3, p18; clinical-overview.pdf

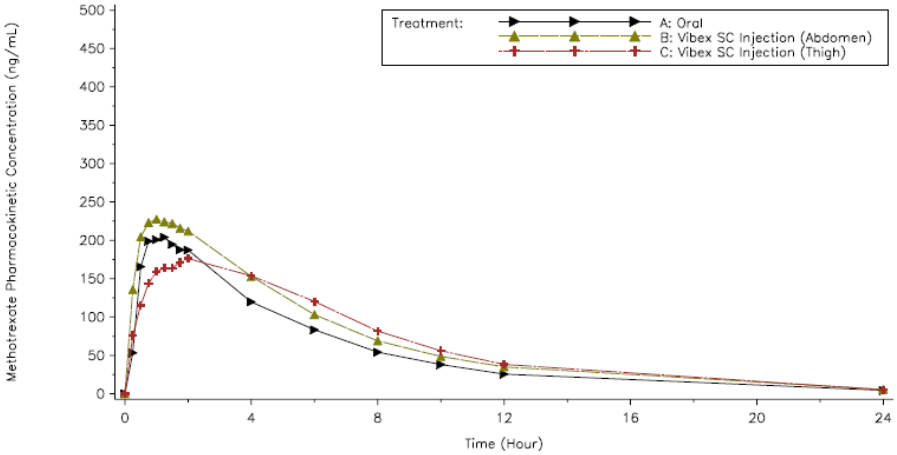

Figure 5. MTX-11-003, Mean MTX concentration vs time, by treatment, original scale, PK pop, MTX 10 mg dose group

Source: F1, p46; mtx-11-003-report-body.pdf

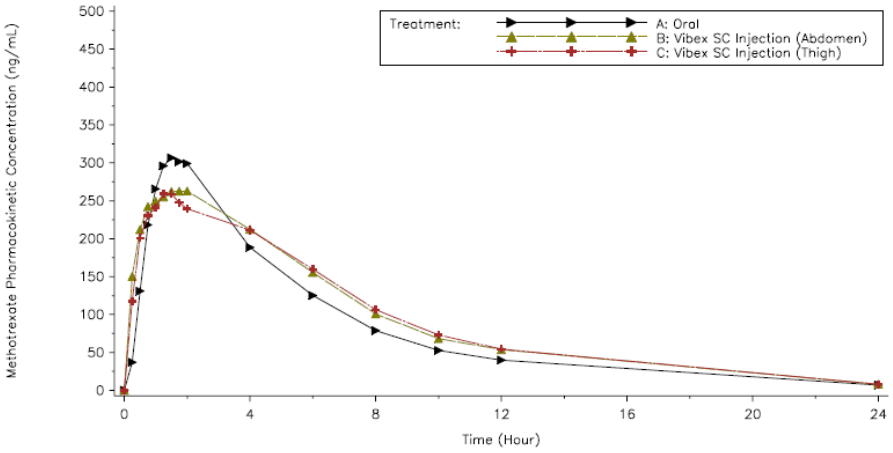

Figure 6. MTX-11-003, Geometric mean MTX concentration vs time, by treatment, PK pop, MTX 15 mg dose group

Source: F2, p47; mtx-11-003-report-body.pdf

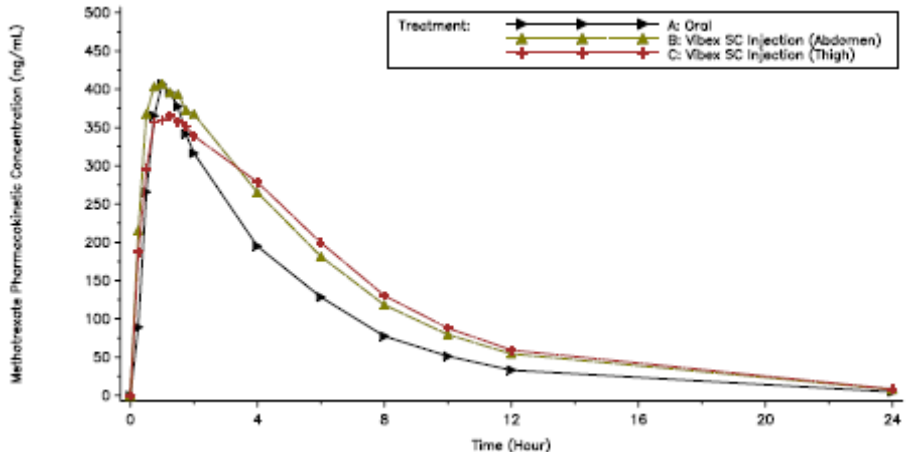

Figure 7. MTX-11-003, Geometric mean MTX concentration vs time, by treatment, PK pop, MTX 20 mg dose group

Source: F3, p47; mtx-11-003-report-body.pdf

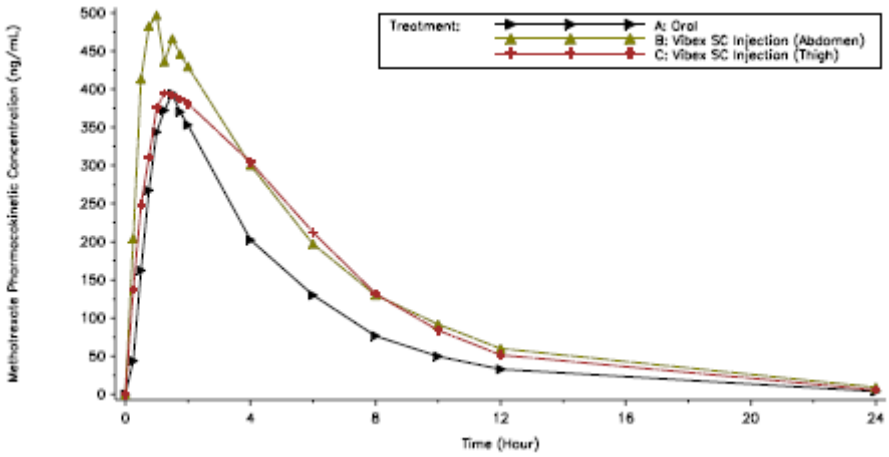

Figure 8. MTX-11-003, Geometric mean MTX concentration vs time, by treatment, PK pop, MTX 25 mg dose group

Source: F4, p48; mtx-11-003-report-body.pdf

Conclusion

This open-label PK study demonstrated bioequivalence between methotrexate delivered SC using the proposed MTX auto-injector either in the abdomen or the thigh. The study therefore supports interchangeability of abdominal wall and thigh sites for SC injection in the labeling.

The study did not demonstrate bioequivalence between administration using the proposed MTX auto-injector SC and oral administration. Subcutaneous dosing was associated with a linear increase in systemic exposure with progressively higher doses, whereas oral dosing with progressively higher doses was associated with non-linear systemic exposure resulting in a plateau of systemic exposure at doses above 15 mg orally. This finding was not unexpected, given the known limitations of oral methotrexate dosing with progressively higher doses imposed by saturation of gut absorption. Given this phenomenon, IM or SC dosing provides a viable alternative approach to increasing oral doses of MTX above 15 mg with resultant increases in GI side effects.

5.3.2 Device Usability Studies

Two use and handling studies were performed to evaluate the ability of patients to follow the instruction set and use the device (MTX-11-002), and usability of the device (without medicine or a needle) in a simulated use setting (MTX-11-004).

Comment: It should be noted that, while they may have been requested by the Agency and may provide some informative results, these studies are not appropriate for and will not be described in the labeling for this product. They do not meet the requirements of a clinical trial, and will not be listed as studies essential to the application.

5.3.2.1 Study MTX-11-002

Study MTX-11-002 was a multicenter, open-label, single-dose, phase 2 study that evaluated the ability of adult patients with RA to use of the Vibex MTX auto-injector device and its associated instructions after having received training in the use of the product.

The study was conducted at 8 clinical sites in the United States between May and July of 2012. The report states that the protocol was reviewed by the (b) (4) (b) (4) was conducted in accord with the Declaration of Helsinki and applicable Good Clinical Practice guidelines, and appropriate informed consent was obtained prior to initiation of any study procedures.

Patients had to have been on MTX therapy for at least 3 months prior to enrollment, and were assigned to a dose of study MTX based on their baseline MTX dose. The study included a screening visit, a single training and treatment visit, and a follow up visit. The study report states that primary objective was to assess the usability of the device after standardized training by site personnel and review of the written instructions. The study also served a role in evaluating device reliability and robustness. At the End-of-Phase 2 (EOP2) meeting (September 13, 2011), the Agency had recommended that device reliability and robustness data be collected after actual use in at least 100 patients. This study fulfilled that recommendation. However, from the Agency's perspective the main reason for a study such as this one is to assess whether the training program and Instructions for Use (IFU) are adequate to assure that patients with RA can learn to self-administer a dose. Regardless of the study objective, it is entirely possible that all could have been met via a study that did not include administration of active drug to patients.

Training consisted of standardized verbal instructions (version 1.9, included as Appendix B of the study report), a demonstration of the proper use of the device, and review of the written patient instructions (version 1.9, included as Appendix C of the study report). Comparison shows that the written IFU that were provided to patients were very similar [although not identical] to the proposed IFU submitted with the application, and the standardized verbal instructions also are similar. Differences include that the IFU included drawings whereas the final IFU includes pictures, and the instruction set only included injection into the abdomen rather than either the abdomen or thigh.

After the training and an assessment of the injection site, patients were asked to independently self-administer a dose of MTX SC via the Vibex device using the written instructions (IFU) for guidance. Site personnel observed the self-injection attempt and recorded the outcomes on an Essential Tasks questionnaire. Elements of the questionnaire included: SC administration by the patient; SC injection was intentional; injection was administered in the appropriate location on the abdomen; patient removed cap marked "1"; patient removed cap marked "2"; patient held device at injection site, patient confirmed that the window as obstructed). After the injection, patients rated injection site pain using a visual analog scale (0-100 mm VAS) and completed an ease of use questionnaire. Used devices were collected and inspected to confirm delivery.

Negative outcomes were reviewed with the patients, and patient comments and observations were collected. After a post-dose injection site assessment and vital signs, patients were discharged with follow-up the following day. The primary endpoint was successful SC self-injection, which was defined as intentional SC self-injection administered by the patient in an appropriate location on the abdomen; and the device functioned appropriately as determined by inspection of used devices, including confirmation that the window was obstructed, the ram was released, and the needle guard no longer retracted.

A total of 101 RA patients were enrolled at 8 sites in the United States, and 101 completed the study. A total of 12 (11.9%), 54 (53.5%), 31 (30.7%), and 4 (4%) patients were classified as American College of Rheumatology RA classification Stage I, II, III, and IV, respectively, and 10 (9.9%), 59 (58.4%), 31 (30.7%), and 14 (1%) patients were classified as being in functional status Class I, II, III, and IV, respectively. Most (n=81, 80.2%) had previous experience with SC injections, and most (n=83, 82.2%) had experience with self-injection devices, of whom 31 (30.7%) had previous experience with an auto-injector device.

All patients were able to perform a successful SC self-injection of study drug and completed all essential tasks successfully, regardless of radiographic disease stage or functional status. All devices functioned appropriately, as confirmed by site personnel. The study report states that 98% of patients found the device easy to use and 100% of patients found the instructions and training clear and easy to follow. Most (94%) patients answered all 5 training confirmation questions correctly, indicating a high level of understanding of the standardized training and written instruction set.

One patient in the 20 mg MTX group experienced a TEAE of headache immediately after self-injection, one patient in the 25 mg group experienced an SAE of sick sinus syndrome, and one patient in the 20 mg MTX group experienced a TEAE of exostosis. There were no injection site AEs, and the most commonly reported pain value was 1 mm on the VAS (Day 1 mean 3.6, range 0-72; Day 2 mean 1.4, range 0-21).

Conclusion

This single dose study in RA patients demonstrated that patients can learn to use the proposed auto-injector device and perform a successful auto-injection after a scripted training demonstration following a script that is similar to and based on the proposed IFU. There were no local reactions to subcutaneous injection of methotrexate with the proposed device, and there were no issues with device functioning or device failures. The study therefore supports use of the device in RA patients, although it does not specifically demonstrate that the proposed IFU and device are adequately labeled. Please refer to results of study MTX-11-004 for further details.

5.3.2.2 Study MTX-11-004

Study MTX-11-004 was a training device-only study that did not involve the administration of MTX or the use of a device with placebo or a needle. The study is

stated to have been a summative, simulated-use, usability testing and design validation (Human Factors) study to evaluate the proposed Vibex MTX auto-injector device and its associated documentation, including the IFU, on-device label, and health care provider (HCP) training script. The study report states that the objective was to assess whether the device could be used by representative users under simulated use conditions without generating patterns of failures that could result in negative clinical impact to patients or injury to device users. In other words, one of the main reasons for this study was to assess whether the training program and IFU were adequate.

Comments about the design of the proposed study were provided by CDRH at the EOP2 meeting on September 13, 2011. The study was conducted by (b) (4), in January 2012.

Study Design

The study included two sessions spaced one week apart. The week between sessions was intended to be reflective of the intended once-weekly dosing interval and to assess the impact of training decay in those participants who received training in Session 1. Seventy-five individuals were recruited, including 17 RA patients, 16 lay caregivers, and 17 healthcare professionals (nurses). Healthcare professional participants participated in Session 2 only, but all others participated in both Sessions 1 and 2. Session 1 (Day 1) was a **training session** in which participants watched an in-person demonstration according to the HCP script, had the opportunity to practice with a resettable demonstration device, and were then observed performing one successful simulated injection. Session 2 (Day 8) included no training; participants simulated a single injection using a commercial-quality dummy device (identical to the commercial device but with no needle). The IFU was available for reference in both sessions.

Since a training session was part of the study design for all but experienced healthcare professionals (nurses), this study was not designed to be a label comprehension study in that it was not designed to directly evaluate whether patients and caregivers could appropriately follow and use the IFU without further training. Rather, the study evaluated the entire instruction set, including a training session and the IFU itself. Since the training script was not included in the study report, it was requested in an IR dated April 30, 2013, and provided in a submission dated May 7, 2013. The script covered the following areas: review of the injector parts, how to check the injector to make sure that it is viable and not expired, selecting and preparing the skin site for injection, preparing the injector for use, how to perform an injection, and the labeling on the injector (which is stated to be the same as that in the IFU). As such, the training script was based on the proposed IFU, but also included more information than is provided in the IFU.

The primary evaluation criteria for the study were 1) the participant's ability to deliver a successful injection to the patient, and 2) the medication was delivered without potential for harm to the patient or caregiver. The study evaluated the participant's ability to complete each task in the injection process, as documented in the IFU, with ten critical tasks identified and evaluated:

- inspection of the contents of the syringe

- location of the appropriate injection site
- removal of the cap (1)
- removal of the safety (2)
- griping the device in hand
- placement of the needle end perpendicular to and directly against the injection site
- firm pushing of the needle end into the injection site to trigger the device
- holding for 3 seconds after hearing the audible “click”
- removal of the device from the injection site
- visual confirmation that the viewing window is occluded.

Study Population

The RA patients included: 13 females and 4 males; ages: n=5 45-54y, n=5 55-64y, n=7 ≥65y; 13 required help to grip or open things; 7 had tender joints of whom 5 had tender hand joints; with 0-11 (average = 2) swollen joints [0-10, average = 1, hand joints]. Of the 17 RA patients recruited, 9 had no experience with self-injections, 5 had experience with a syringe injection, and 3 had experience with an auto-injector.

The lay caregivers included: 14 females and 2 males; ages: n=1 25-34y, n=7 45-54y, n=4 55-64y, n=4 ≥65y. Of the 16 lay caregivers, 7 had experience injecting others and 9 did not.

The professional caregivers included: 17 females, no males; ages: n=1 18-24y, n=1 25-34y, n=2 35-44y, n=8 45-54y, n=4 55-64y. Of the 17 professional caregivers, 11 had experience auto-injectors and 6 did not. For most (n=7), the experience was based on insulin injections, with one each for migraine medications, enoxaparin, and epinephrine. Other than auto-injector experience, the medical training and experience of these caregivers was not stated in the report. This was requested in an IR dated April 30, 2013, and submitted on May 7, 2013. All of the professional caregivers were registered nurses (RNs) and two were nurse practitioners, and their experience with SC injections varied from 1x to 30x per week.

Results

Overall, the study report states that 81 of the 83 trials were successful; however, two were unsuccessful (1 patient, 1 health care professional), of which one event raises concern about the training device and one event was raises concern about a safety issue.

- One healthcare professional (RN) failed to deliver a successful injection after she pointed the needle end of the device toward her own hand. The study report notes that she initially appeared to be overwhelmed by the IFU, stating that she would need further instruction to use the device. However, the report also states that when

given a second device, she read the IFU and was able to follow the step-by-step directions and deliver a successful injection.

This report raises the concern that the two ends of the device are not clearly enough distinguished such that accidental injection into the hand will be prevented.

- One RA patient (participant #4) delivered an incomplete injection because she held the device at the injection site for less than 1 second. The report states that the patient was startled by the click, but immediately realized that she had done it wrong and was able to complete a simulated injection using a second device.

The report also states that the reason that the patient was startled by the click is that "the training device did not make any sound", whereas the commercial-quality dummy device did. Starting with participant #5, training Session 1 was modified such that the moderator demonstrated the use of the device using a commercial-quality dummy device rather than with a trainer device, to allow participants to become familiar with the sound. However, this also raised the concern that the trainer and the actual device differ in a substantive way regarding the lack of presence of a "click" with use of the trainer device. Further, health care professional will not have a commercial-quality dummy device available for training. Therefore, the modification of the training Session 1 created an artificial environment that no longer mimicked the training that might occur in the health care professional's office setting.

To resolve issues with the trainer device brought up by the study results, in an IR dated April 30, 2013, Antares was asked to state whether the trainer device was modified, and to explain any differences in the clicking sound between the trainer and the live device. Antares responded on May 7, stating that:

> "The Otrexup demonstrator (demo) is designed so an audible "click" is made when the Otrexup demo is triggered. The Otrexup demo "click" sound is very similar to the real Otrexup device "click", but the Otrexup demo "click" is slightly softer (i.e. not quite as loud).
>
> The mechanism by which the click sound is generated in both the Otrexup demo and the real Otrexup device is the same. Both the Otrexup demo and the real Otrexup device make a "click" when the device is triggered, and in both cases this is accomplished by the "release of a spring". However, the type of spring, latch and trigger used are different between the two devices in order to allow resetting of the Otrexup demo. In the real Otrexup device a standard compression spring is being released when the Otrexup device is triggered – which results in the "click" sound. In the Otrexup demo a flat leaf spring is being released when the device is triggered – which results in the Otrexup demo "click" sound. A flat leaf spring is used in the Otrexup demo because the Otrexup demo has to be re-settable so it can be reused for multiple training as applicable, whereas the real Otrexup device is only used one time i.e. disposable.
>
> In addition, the bushing, lock ring and ram have been removed from the Otrexup demo as the dose deliver mechanism is not required in the Otrexup demo unlike the Otrexup device."

To evaluate the trainer, the actual device, and the instruction set in the IFU, TIFU and on the devices labeling, and to further understand the similarities and differences between the trainer and the actual device, examples of the trainer and live devices were requested and evaluated by the clinical review team as well as reviewers in ONDQA and CDRH. Please see the Section 9.2 of this review for further details.

Table 10 shows the task-by-task results including most of the critical steps and several safety steps that had not been identified as critical but were nonetheless important. The two missing so-called critical steps not included in this table were removal of the device from the injection site and visual confirmation that the viewing window was occluded. However, those steps are far less important than the three additional steps that are included, i.e., hand in front of the needle, potential needle stick post injection, and device failures.

Success rates for IFU comprehension questions are shown in Table 11. Most individuals were able to answer the comprehension questions correctly.

In a submission dated May 22, 2013, the applicant responded to an IR from the Division of Medication Error Prevention and Analysis (DMEPA) and stated that no placebo was used in the device in this study and there were no cases of accidental firing during the study. DMEPA raised this as a concern because multiple participants were noted to not leave the auto-injector in place for the full 3 seconds as stated in the proposed labeling instructions. Since no placebo was used, the study did not evaluate whether the full simulated injection was received [pooling of liquid would have been noted during the simulation if the full injection was not received]. However, the actual use study (MTX-11-002) demonstrates that patients could learn to use the device and successfully administer injections, so this is not a significant issue.

Table 10. MTX-11-004, Task-by-task results of successful steps

Step	Successful step	
	n (n=89)[1]	%
Inspected the window prior to injection	86	96.6
Removed the safety	89	100.0
Removed the cap	89	100.0
Selected the proper injection location	88	98.9
Held device properly for injection[2]	87	97.8
Injected the entire dose (>3 sec. and proper force)	86	96.6
Gripped device properly for injection	89	100.0
Locked the white needle guard	87	97.8
Recognized a full injection[3]	85	95.5
Because of red indicator	*81*	
Because heard click	*3*	
Because held for 3 sec.	*1*	
Hand in front of needle during injection[4]	1	1.1
Potential needle stick post injection	0	0.0
Device failure	0	0.0

1 Includes the two separate trials for patients and lay caregivers, one trial for professional caregivers, and 6 additional trials (some participants were given a new device during their first trial if they had confusion operating the device or performed a step incorrectly).
2 Holding the device properly means that the participant held the device with the needle end pointed downward at a 90° angle to the injection site.
3 All injection steps except "recognized a full injection" were measured objectively by the Study Monitor. This was a subjective measure based upon participant responses.
4 Note: This error was committed by the same participant (Nurse # 13) described under incomplete injection performances. It was the only safety-related use error observed.

Source: T2, p10; mtx-11-004.pdf

Table 11. MTX-11-004, Success Rates for Yes/No IFU Comprehension Questions

According to the IFU, is it OK to…	**Correct Response**	**Number Correct (*n* = 82*)**	**Percentage rate (%)**
Use the device if the contents look slightly yellow?	Yes	74	90
Use the same location for each injection?	No	71	87
Inject next to your naval (within 2 inches)?	No	77	94
Twist the cap to remove it?	Yes	80	98
Remove device from the injection site after 2 seconds?	No	81	99
Call your doctor if you inject and do not see red in the window?	Yes	74	90
*Includes the responses from patients and lay caregivers during Sessions one and two (minus one lay caregiver who did not have time to respond during session one) plus the professional caregivers.			

Source: T3, p12; mtx-11-004.pdf

Conclusion

This was a summative, simulated-use, so-called usability testing and design validation (Human Factors) study. Since a training session was part of the study design for all but experienced healthcare professionals (nurses), this study was not designed to be a label comprehension study in that it was not designed to directly evaluate whether patients and caregivers could appropriately follow and use the IFU when presented to them without further training. Rather, the study evaluated the entire instruction set, including a training session based on the IFU as well as the IFU itself. The study provides insight into two issues with the proposed trainer device and the proposed instructions for use. One patient was startled by the "click" of the commercial-quality dummy device because, according to her, the trainer device was not associated with a click. However, this is not the case. One healthcare giver did not follow the directions and inappropriately handled the device such that she could have received a needle stick in the hand. This is a safety issue pointing to the need to explore whether additional safeguards need to be put into place to prevent similar instances in the clinical setting.

6 Review of Efficacy

6.1 Efficacy Summary

Support for approval of this application is based on the Agency's previous findings of safety and effectiveness of MTX in patients with RA and JRA [and psoriasis], published literature to support efficacy and safety of SC dosing for RA, pJIA, [and psoriasis], and a bioavailability study (MTX-11-003) that supports the effectiveness of SC MTX by demonstrating higher systemic exposure dose for dose when MTX is administered SC than orally, particularly as doses extend above 15 mg. Support also comes from a bioequivalence study (MTX-10-001) that showed bioequivalence between the proposed product injected into either the abdomen or the thigh with both SC and IM injection using a needle and syringe. Please see Section 5.3 for details of these studies.

The published literature to support efficacy and safety of SC dosing for RA and pJIA that was submitted to the application was reviewed and is outlined in the next section of this review, Section 6.2. Please refer to the reviews from the Division of Dermatology and Dental Products for discussion of the psoriasis indication. The literature supports SC administration as an alternative to oral or IM administration of MTX, with higher systemic exposure and improvements in efficacy when administered SC or IM vs orally in similar doses, particularly in doses above 15 mg. It therefore supports the use of the proposed product as a convenience alternative to using a needle and syringe for at-home self or caregiver injection of methotrexate.

The applicant also submitted two use and handling studies that are reviewed in Section 5.3.2 and have some implications for appropriate labeling of the instructions for use.

6.2 Indications

This section reviews the literature submitted with the application to support use of the proposed product for the RA and pJIA indications.

The sponsor conducted Medline and Embase literature searches. Only papers in English or English translations of systematic reviews, meta-analyses, randomized controlled trials, and treatment guidelines were included, where the MTX interventions were administered chronically by the SC, IM, parenteral, or oral routes, the disease was RA/JRA, and the endpoints were safety, efficacy, PK, or human pharmacology.

6.2.1 Rheumatoid Arthritis (RA)

6.2.1.1 Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune (i.e., immune self-tolerance) disorder of unknown etiology characterized by symmetric, erosive synovitis

that results in progressive joint destruction, deformity, and physical disability. Disability from RA can have a profound impact on patients and families, resulting in major economic loss and more than 9 million physician visits and over 250,000 hospitalizations annually. The wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints are the most frequently involved joints. Extra-articular manifestations include fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities. Despite therapy, the course for most patients is chronic and fluctuating. RA occurs more frequently in females (2-3:1) and affects between 0.5 to 1% of the adult population worldwide, and 0.7-1.3% of the adult population in the United States. Genetic factors play a role in the disease and its severity, with alleles that confer the greatest risk located within the major histocompatability complex (MHC). In addition, environmental factors such as cigarette smoking increase the risk for developing the disease (RR = 1.5-3.5). Self-reactive T cells drive the chronic inflammatory response, with CD4+ T cells playing an important role along with activated B cells and macrophages. TNF-α is a pivotal cytokine in the pathobiology of synovial inflammation, upregulating adhesion molecules on endothelial cells, promoting the influx of leukocytes into the synovial microenvironment, activating synovial fibroblasts, and stimulating angiogenesis, pain receptor sensitizing pathways, and osteoclastogenesis. [ACR 2002; Shah 2012]

The clinical diagnosis of RA is largely based on signs and symptoms of chronic inflammatory arthritis, with laboratory and radiographic results providing important supplemental information.

Classification criteria developed jointly by American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010 help to distinguish patients at the onset of disease with a high likelihood of evolving into a chronic disease with persistent synovitis and joint damage, thereby helping to identify patients who would benefit from early introduction of disease-modifying therapy.

Medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional disease-modifying anti-rheumatic drugs (DMARDs); and biologic DMARDs. DMARDS slow or prevent structural progression of the disease. In the last several decades, NSAIDs, which formerly were considered a core therapy, are now considered adjunctive and MTX has emerged as the DMARD of choice for the treatment of RA. Additionally, a number of highly effective biologicals have been approved that can be used alone or in combination with MTX, allowing individual tailoring of treatment to fluctuations in disease activity and drug-related toxicities.

6.2.1.2 Literature Review

The applicant summarized the literature with respect to SC MTX treatment of RA and other rheumatic diseases, as well as the literature with respect to IM MTX treatment. The literature for SC MTX treatment included including two randomized controlled trials [Braun 2008, Parker 2004] and multiple other studies and clinical reports. Dosages of

SC MTX ranged from 5 mg to 30 mg once a week. Most studies were 6 to 12 months in duration. The MTX SC use literature is summarized below.

Arthur AB, et al, 1999

These authors reviewed their experience with the safety, efficacy, and practicality of self-administered parenteral gold or MTX in RA and psoriatic arthritis patients at a clinic in Canada between 1992 and 1995. Forty patients (27 women) who were improved and stable on parenteral medication were taught to self-administer their medication. Patients were assessed for disease activity and outcome measures at the time of referral and every 3 months. Variables included tender and swollen joint count, erythrocyte sedimentation rate (ESR), pain visual analog score (VAS), and Health Assessment Questionnaire (HAQ).

Sixty-five percent of patients performed self-injection and 35% received injections at home from a partner. The mean active joint count and ESR remained stable during self-injection, and 70% continued self-injection after a mean of 34 months. Side effects of self-injection included superficial irritation at the injection site in 2 patients and dosing error in 2 patients with no adverse effects. Clinic visits were reduced from weekly to once every 12 weeks in patients on MTX. Satisfaction surveys identified time saving and convenience as major benefits.

The authors concluded that with basic instruction and close supervision, self-injection of antirheumatic drugs is safe, practical, and effective in selected patients.

Arthur V, et al, 2001 and 2002

These authors conducted a 13-week study in the UK to compare the safety and efficacy of methotrexate administered by intramuscular and subcutaneous routes, and to teach patients to self-administer methotrexate subcutaneously. It appears that they reported on the study twice, once in a letter to the editor in 2001, and again as a stand-alone paper in 2002.

Eight patients (6 females, 2 males; 4 RA, 2 psoriatic arthritis, 1 Wegener's granulomatosis, and 1 polymyositis) with a mean age 43 and a mean disease duration of 11 years 4 months were enrolled. Variables of disease activity were measured at week 1 and week 13. Nurse specialists administered weekly IM MTX at weeks 1 to 3 and weekly SC MTX at weeks 4 to 6, and serum MTX levels were measured 1 hour after each administration. During weeks 4 to 6, patients were given instruction for self-administration by practical demonstration and with the addition of written information, during weeks 7 to 9 patients self-administered (pre-drawn) MTX by SC injection under supervision and during weeks 10 to 12 the participants self-administered the (pre-drawn) MTX at home. At week 13 patients returned to the clinic.

No significant differences were noted between SC and IM MTX administration with respect to pain, fatigue, early morning stiffness, tender joints, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) levels. PK analysis revealed no significant difference in serum levels between IM and SC injections. The authors concluded that self-administration of SC MTX is effective for patients with reasonable dexterity.

Bakker et al, 2010

This study was part of a 2-year, prospective, randomized, open-label, multi-center trial conducted in the Netherlands that compared two methotrexate regimens to evaluate the utility of "tight control" in RA patients who had a disease duration of <1 year and were naïve to DMARDs and glucocorticoids. Patients in the tight control arm of the trial were evaluated in this study. MTX was initiated at 7.5 mg/week orally and increased by 5 mg/week until remission, a maximum tolerable dose was reached, or a maximum dose of 30 mg/week was reached. Remission was predefined using the criteria of swollen joint count = 0, and 2 of 3 of the following: tender joint count ≤ 5, ESR ≤ 20 mm/h, and VAS ≤ 20 mm). Patients not attaining remission or reaching the maximum tolerable oral dose were switched to the equivalent SC dose. The change in the patient's 'disease activity score in 28 joints' (DAS28)[2] was evaluated after 1 month on SC MTX and compared with the average monthly change in DAS28 in the preceding 3 months. If the predefined goal of remission at the subsequent visit was not met, cyclosporine therapy was added.

Of 151 patients enrolled, 57 were switched from oral to SC MTX (21 due to AEs on mean oral dose of 25 mg/week, and 36 due to lack of efficacy at a maximum dose of 30 mg/week). After 1 month on SC MTX, the mean decrease in DAS28 was 0.30 points ($p < 0.05$), with similar results regardless of the reason for switching. Over the 4-month evaluation period, the decrease in DAS28 was 0.5 points ($p < 0.01$), with similar results for patients switching because of AEs (0.4 points, $p > 0.05$) and lack of efficacy (0.6 points, $p < 0.001$) (Figure 9). Following the switch to SC MTX, 36 patients responded (i.e., has an equal or better course of DAS28 compared to the preceding months) and 21 did not (cyclosporine treatment was added).

The authors concluded that switching from oral to SC MTX can provide further improvement at equivalent or higher doses once the maximum tolerated oral dose is reached.

2 DAS28 is a quantitative measure of disease activity used to clinically monitor the treatment of RA. There are several versions of DAS, but all measure the disease burden using the number of swollen or tender joints (up to 28), self-assessed patient global health on a VAS 0-100 scale, and either ESR or CRP. A formula is used to calculate the final score.

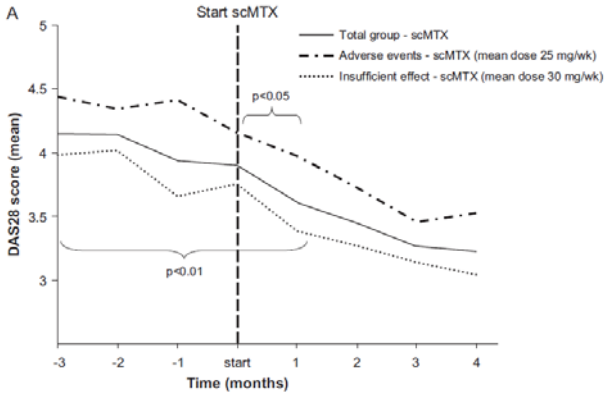

Figure 9. Bakker et al, 2010. DAS28 for patients switched to SC MTX.

Braun et al, 2008

This was a 6-month, multicenter, double-blind, randomized, placebo-controlled 2-arm trial comparing the clinical efficacy and safety of methotrexate administered either SC or orally in patients with RA. The trial was conducted in Germany between 2003 and 2005, and supported by medac GmbH.

MTX-naïve patients with active RA and a disease activity score in 28 joints (DAS28) of ≥4, were randomized 1:1 to: 15 mg subcutaneous MTX (one prefilled syringe containing 15 mg of MTX + 2 placebo tablets) or 15 mg of oral MTX (two 7.5-mg tablets of MTX + 1 prefilled syringe containing placebo). All patients took 5 mg of folic acid the day after their MTX dose. At week 16, patients who did not meet the ACR criteria for 20% improvement (ACR20) were switched from 15 mg orally to 15 mg SC, or from 15 mg SC to 20 mg SC, and continued for the remaining 8 weeks in a blinded fashion. The primary endpoint was the percentage of patients with an ACR20 response at week 24. Secondary endpoints included ACR50 and ACR70 responses as well as tolerability of SC versus oral treatment.

A total of 384 patients (median age 59 years, ~ 75% females, median time since diagnosis 2.1-2.5 months, median DAS28 6.1-6.3, and 125 [62%] RF positive) were enrolled: 194 in the SC group and 190 in the oral group.

At 24 weeks, the percentage of patients with ACR20 and ACR70 responses were 78% vs 70% ($p < 0.05$) and 41% vs 33% ($p < 0.05$) for SC vs. oral dosing, respectively, although the ACR50 at 24 weeks was not significantly different (SC 62% vs oral 59%). Patients with a disease duration ≥ 12 months had higher ACR20 response rates (SC 89% vs oral 63%). The number of swollen joints (SC 2 vs oral 3; $p = 0.04$), the number of tender joints (SC 3.5 vs oral 6; $p = 0.08$), median HAQ score (SC 0.4 vs oral 0.5), and median DAS28 (SC 3.3 vs oral 3.7) were lower in patients taking SC injections than in patients taking oral tablets.

After 16 weeks, 52 patients (14%) were classified as ACR20 non-responders and treatment was switched: 30 were switched from 15 mg orally to 15 mg SC, resulting in an ACR20 response in an additional 30% of patients at 24 weeks; and 22 were

switched from 15 mg to 20 mg SC, resulting in an ACR20 response in an additional 23% of patients at 24 weeks.

Tolerability was similar between treatments. Overall, 66% of SC MTX–treated patients reported an adverse event during the study, compared with 62% of oral MTX–treated patients. Similar percentages had SAEs. AEs of moderate severity with at least 3% incidence are shown in Table 12.

Table 12. Braun 2008. AEs of moderate severity with at least 3% incidence

AE	SC MTX (n=193)	Oral MTX (n=188)
Abdominal pain	17 (8.8)	20 (10.6)
Diarrhea	5 (2.6)	13 (6.9)
Dyspepsia	13 (6.7)	11 (5.9)
Loss of appetite	14 (7.3)	6 (3.2)
Nausea	32 (16.6)	23 (12.2)
Stomatitis	6 (3.1)	7 (3.7)
Vomiting	7 (3.6)	6 (3.2)
Increased ALT	3 (1.6)	8 (4.3)
Bronchitis	4 (2.1)	7 (3.7)
Headache	4 (2.1)	8 (4.3)
Nasopharyngitis	9 (4.7)	10 (5.3)

The authors concluded that SC injection of MTX is more effective than oral administration at the same dosage, suggesting that the increase in bioavailability with SC administration translates to superior efficacy over an equivalent oral dose.

Griffin & Erkeller-Yuksel, 2004

In a letter to the editor, these authors summarized prospective data from 22 patients with RA who were switched from a mean oral dose of 17.5 mg MTX to parenteral therapy (subcutaneous or intramuscular) at the same dose before consideration of addition of a biologic agent. Over a period of 6 months, significant reductions were found in swollen joint count ($p < 0.05$), tender joint count ($p < 0.01$), pain VAS ($p < 0.01$), patient's self-assessment VAS ($p < 0.02$), and physician's global assessment ($p < 0.02$). The HAQ did not change during this period. The authors recommended switching from oral to parenteral MTX before considering biological treatments.

Hameed et al, 2010

This is a retrospective report on 103 patients (30 males, 73 females; mean age 55 [range 20 to 83] years) who were switched from oral to SC MTX either for lack of efficacy (Group A, n=40; 32 RF positive) or intolerance (Group B, n=63; 48 RF positive) over a 12 month period of time at the Kingston Hospital HNS Trust, London, UK. Most patients (98%) in Group B had GI intolerance. Doses of MTX were not stated. Patients were followed for 3 months with no dropouts. In Group A, the mean DAS 28 improved from 4.8 on oral MTX to 4.2 in SC MTX ($p=0.006$, CI 0.9, 1.03), and 4 patients achieved

remission (DAS28 <2.6). In Group B, the mean DAS28 improved from 4.1 on oral MTX to 3.0 on SC MTX (p=0.0001, CI 0.9, 1.5), and 15 patients achieved remission. SC MTX was reported to be better tolerated than oral MTX, although no specifics were given.

Muller-Ladner et al, 2010

This was an open-label, prospective, within-patient controlled, multicenter study to determine the preference, satisfaction, usability and local tolerability of two SC administered MTX formulations of different concentrations. The study was performed at 16 centers in Germany between 2007 and 2008. The fist author received consulting and speaker fees (less than 10.000 USD) from medac GmbH, and 3 other authors are stated to have been employees of medac GmbH.

Patients received a dose of 20 mg of MTX SC for 6 weeks: 2 ml of a 10 mg/ml solution once weekly for 3 weeks, followed by 0.4 ml of a 50 mg/ml solution once weekly for another 3 weeks. Unfortunately, the study design did not incorporate a 2-way crossover, so all patients were switched in one direction only. The 1st and 4th injections were administered by study personnel, whereas the 2nd, 3rd, 5th, and 6th injections were self-administered. Questionnaires and visual analogue scales were used to document satisfaction, usability and local tolerability.

A total of 132 patients 18 to 75 years with active RA and a DAS28 >2.6 were enrolled. 93.0% of patients preferred the concentrated formulation vs. 2.3% who preferred the less concentrated formulation (95% CI: [87.1%; 96.7%] (p<0.0001). AEs were about equal between treatment groups. With regard to local tolerability, the more concentrated formulation is stated to have been slightly better tolerated, but no further details were provided.

Parker et al, 2004

This prospective, randomized crossover trial assessed the clinical utility of increasing the MTX dose from 20 mg/week to 25 mg/week either orally or SC in RA patients with active RA refractory to their current DMARD regimen. After ≥8 weeks of oral MTX at a dose of 20 mg/week, eligible patients were randomly assigned to receive 25 mg/week administered either SC or orally for 8 weeks and then crossed over to the alternate route for an additional 8 weeks. Patients were evaluated by blinded assessors using the modified HAQ, patient's global assessment, physician's global assessment, joint counts, and ESR.

Eight patients (5 females; 5 RF positive at study start) with median age of the patients was 47.5 years (range 34 to 78 years) and the median duration of disease activity was 15 years (range 8 to 20 years) were evaluated. Two patients had a significant response when MTX was administered SC. One of these patients showed no improvement after 8 weeks of oral MTX at 25 mg/week, but achieved an ACR20 improvement when crossed over to SC MTX. The other patient achieved an ACR50 while on SC MTX, but returned to her active baseline level when crossed over to oral MTX. Following

completion of the study, the patient switched back to SC MTX and achieved an ACR50 again.

The authors concluded that some patients with active RA who are taking 20 mg/wk or oral MTX may respond to 25 mg/wk if the route of administration is changed to SC injection.

Stamp et al, 2011

This was a 6-month study that evaluated the effects of switching from oral to SC MTX on red blood cell methotrexate polyglutamate (RBC MTXGlun) concentrations, disease activity, and adverse effects in patients with RA. It was conducted at the University of Otago, Christchurch, New Zealand, between 2005 and 2008, and was supported by the Health Research Council of New Zealand and Arthritis New Zealand.

Thirty patients (23 females, 7 males; mean age 51.8 years [range 32 to 70]; mean duration 7.7 years [range 0.75 to 21]; 87% RA positive) with inadequate disease control and/or intolerable adverse events while on a stable dose of weekly oral MTX were switched to SC MTX at their same dose and evaluated over 6 months. The median MTX dose was 20 mg/week (range 10 to 20 mg/week), and no patients had the dose changed during the study. All patients received 5 mg/week folic acid 3-4 days after MTX dosing. Disease activity was evaluated using swollen joint count, tender joint count, modified HAQ, physician global scores, and patient pain and global scores. A response was defined as a >0.6 reduction in DAS28 score.

Comparing week 0 with week 24, there was a trend toward improvement in DAS28 (3.27 vs 2.56, p = 0.064), with a mean change of 0.47 (range -1.5 to 5.19) in the 26 patients who had complete DAS28 scores. Improvements were noted in swollen joint count (p = 0.001), pain VAS (p = 0.014), patient's global score (p = 0.04), and modified HAQ (p = 0.03), but no improvements were noted in total joint count, patient fatigue, CRP, or ESR. Ten (10 of 26) patients had an improvement in their DAS28 score of >0.6 (responders), and 16 patients had an improvement of ≤0.6 (non-responders). Responders had a higher mean baseline DAS28 compared with non-responders (4.0 ± 0.4 vs 2.6 ± 0.3, p = 0.011), and all patients with a baseline DAS28 >3.0 were responders. Improvement in DAS28 was associated with an increase in RBC MTXGlu5 and MTXGlu3-5 concentrations. Furthermore, in the increase in MTXGlun occurred more rapidly in responders than in non-responders, suggesting that long-chain polyglutamates are important to the clinical effect of MTX.

Thornton et al, 2008

This was a prospective study to investigate the effectiveness of SC MTX in a cohort of patients with RA for whom oral MTX was ineffective or not tolerated. The study also assessed the need for treatment with a biologic agent in the event of failure of SC MTX. The study was conducted in the Rheumatology Clinic at Wexham Park Hospital, Slough, UK between 2004 and 2006.

Thirty consecutive clinic patients (26 females, 4 males; mean disease duration 15.3 years [range 2 to 46]) were recruited. The reasons for switching from oral MTX were

lack of efficacy (n=23) and intolerance (n=7). Patients were assessed at baseline, and at 3 and 6 months after switching to SC MTX. Efficacy endpoints included tender joint score, swollen joint score, patient's global assessment of disease activity, CRP, and DAS28 at each visit. Patients initiated SC MTX at a mean dose of 14.3 mg (range 7.5 to 17.5 mg). After 6 months of treatment, the mean dose was 19.9 mg (range 12.5 to 25 mg). The authors reported that 3 patients discontinued treatment at 3 months due to leucopenia (1) or poor compliance (2), and 2 stopped treatment at 6 months due to lack of efficacy (1) or nausea (1). Five reported minor side-effects: nausea (4), injection site reaction (1).

Compared with baseline, patients had with a mean reduction in DAS28 score of 2.34 at 3 months ($p < 0.001$) and 2.09 at 6 months ($p < 0.001$). Based on European League Against Rheumatism (EULAR) response criteria, 20 of 27 patients (74%) had a good response when evaluated at 3 months, and 13 of 25 patients (52%) maintained this at 6 months. Eleven patients met British Society of Rheumatology criteria for anti-TNF-α therapy at baseline, of whom 8 had a good response after 3 months of SC MTX, and none needed anti-TNF-α therapy at 6 months. Two of the 3 patients who failed to respond at 3 months required anti-TNF-α therapy at 6 months.

The authors concluded that the study provides evidence of the efficacy of SC MTX in controlling active RA in patients who fail to respond to, or are intolerant of, oral MTX, and that switching from oral to parenteral administration may suppress or delay the need for treatment with anti-TNF-α therapy.

6.2.1.3 Discussion

As requested by the Agency, the applicant has submitted bioequivalence data and published literature to support the SC route of administration in patients with RA. My review of the data presented supports the proposed dosing administered by the SC route for these patients. Further, my review of these data does not reveal any specific safety concerns with this route of administration beyond those already labeled. Study-10-001 showed bioequivalence between IM and SC administration of MTX, and Study MTX-11-003 showed higher bioavailability with IM and SC dosing than with oral doses above 15 mg. These data are consistent with clinical results of published studies, including two randomized controlled trials [Braun 2008, Parker 2004] and multiple other studies and clinical reports, suggesting equal or greater efficacy with SC dosing and no increase in safety concerns.

Parenterally administered MTX is also recommended for the treatment of RA in essentially all published treatment guidelines, including those from the American College of Rheumatology (ACR). [Singh, 2012] The updated ACR guideline recommends MTX as either first line monotherapy or in combination with other DMARDs prior to resorting to biologic DMARDS. DMARDs are now recommended for both early and established disease. Although the ACR guideline does not include recommendations with regard to the route of administration, SC administration is recommended by all of the other guidelines. [Pavy et al, 2006; Visser et al, 2009; Visser

& van der Heijde, 2009; Verstappen & Hyrich, 2010; Ataman et al, 2011; da Mota et al, 2012]

Therefore, based on the information presented by the applicant, the proposed SC route for administration of MTX in adults with RA is acceptable.

6.2.2 Polyarticular Juvenile Idiopathic Arthritis (pJIA)

6.2.2.1 Background and Terminology

Juvenile Idiopathic Arthritis (JIA), previously called Juvenile Rheumatoid Arthritis (JRA), is defined by the International League of Associations of Rheumatology (ILAR) as arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks and for which other known conditions are excluded. JIA is a heterogeneous condition that is relatively common in childhood, with an estimated prevalence of about 57 to 200 per 100,000 children younger than 16 years of age. While both result in arthritis, RA and JIA are considered different diseases even though they share the same pathophysiology and the armamentarium of drugs used to treat RA are generally used (with a few exceptions) for childhood forms as well.

JIA and JRA are terms used classify the forms of juvenile chronic arthritis, with JRA being an older classification system and JIA being more recently introduced. Whereas under the JRA classification system three subtypes were identified (systemic, pauciarticular, and polyarticular), under the newer JIA classification system seven subtypes are identified. As a result, the term JIA is now preferred, both to help distinguish the condition as different from adult RA and because the newer classification system provides for more accurate delineation of and less confusion between subtypes or forms. This newer terminology has been adopted by the clinical community and also by the Agency. Therefore, JIA is used in this review even though the currently approved MTX labels use the older JRA terminology.

Subtypes of JIA include [Petty 2001; Beukelman 2011]:

- systemic (sJIA). This form, formerly called systemic JRA (sJRA), is characterized by fever, arthritis, salmon pink rash, lymph node involvement, and internal organ involvement.
- oligoarticular JIA (oJIA). Formerly called pauciarticular-course JRA, this form was renamed to distinguish it from the polyarticular form. It affects 4 or fewer joints in the first 6 months.
- polyarticular JIA (pJIA). This form, formerly called polyarticular-course JRA, affects 5 or more joints in the first 6 months. It is subdivided into rheumatoid factor (RF) positive and RF negative subtypes.
- enthesitis-related arthritis. Enthesitis is the point at which a ligament, tendon, or joint capsule attaches to the bone. This form includes juvenile ankylosing spondylitis and arthritis associated with inflammatory bowel disease.

- psoriatic arthritis, i.e., arthritis associated with psoriasis.
- undifferentiated arthritis.

JIA is an autoimmune disease, in which the body's immune system mistakenly attacks some of its own healthy cells and tissues resulting in inflammation of joints that can lead to joint damage. The most common symptom is persistent joint swelling, pain, and stiffness that is typically worse in the morning or after a nap. The knees, hands and feet are commonly affected. Patients with systemic disease often have fever and skin rash that may wax and wane, swollen lymph nodes, and internal organ involvement, including the lining of the hears. Eye involvement (uveitis) is common, particularly in children with oligoarthritis type.

As noted previously in this review, the prevalence of JIA has been estimated to be between 57 and 220 per 100,000 children younger than 16 years of age, with pJIA affecting approximately 2 to 17% of children with JIA. pJIA is similar to adult RA with articular manifestations being predominant. It is therefore considered the childhood equivalent of RA. However, RA and pJIA are considered different diseases even though the same armamentarium of drugs used to treat RA are generally used (with a few exceptions) for many of the childhood forms as well. While sJIA may occur in children younger than 2 years of age, most authorities consider that pJIA rarely occurs before 2 years of age; therefore, the Agency has generally used a cutoff of 2 years of age as the lower age bound for this condition.

First line treatment of JIA typically involves use of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and naproxen sodium [aspirin is an NSAID, but typically is not used for this condition]. If NSAIDS do not relieve the symptoms, so-called disease-modifying anti-rheumatic drugs (DMARDs) are used. MTX is considered to be a DMARD, along with corticosteroids and biologic agents. However, MTX is currently approved only for the treatment of "polyarticular-course JRA who have an insufficient therapeutic response to NSAIDS" without regard to whether the patient is RF positive or negative. While clinical guidelines for treatment of JIA do include MTX as part of the treatment regimen for other forms of JIA when arthritis is active (e.g., systemic JIA with active arthritis) or when disease activity is high (e.g., oligoarticular JIA with high disease activity) [Beukelman 2011], and while it is clear from the literature that MTX is used in this fashion in the clinical setting, the applicant has not requested expansion beyond pJIA to other JIA subtypes. Specifically, the applicant submitted literature intended to support SC use of MTX rather than to support use of MTX for other forms of JIA. Therefore, the scope of this review is restricted to pJIA, and the literature review in the next section summarizes the key articles that support such use.

6.2.2.2 Literature Review

The applicant reviewed the current literature for use of IM and SC forms of MTX in JRA/JIA. They identified 5 studies that evaluated a total of 551 patients ranging in age from <2 to 28 years who were treated with dosages between 5 to 40 mg once weekly for

6-12 months, with one study evaluating patients out to 138 months. The results of these studies are briefly summarized below.

Alsufyani et al, 2004

This was a retrospective analysis of patients with JIA who were treated with SC MTX after failing oral MTX because of lack of efficacy or intolerable adverse events. The study cohort consisted of patients with JIA treated at the University of British Columbia, Vancouver, BC, Canada between 1988-2001. A total of 61 (43 females, 18 males; mean age of 11.9 years, range 3-20 years) who had disease duration ≥6 months and 3 or more active joints prior to initiation of treatment with methotrexate were included in the analysis. Disease subtypes included: 8 systemic, 25 polyarticular (12 RA positive), 14 oligoarticular, 5 enthesitis-related, and 4 unclassified. All patients had received oral methotrexate for ≥3 months at a weekly dosage of at least 10 mg/m^2 (if tolerated) and received oral folic acid (1-2 mg daily). The average disease duration was 10.9 months (range 2-99 months) and the average age at time of treatment with oral methotrexate was 11.9 years (range 3-20).

Forty patients (66%) fulfilled the criteria for improvement after oral MTX, and 31 patients were switched from oral to SC MTX: 13 with no improvement, and 18 who had improved but had insufficient clinical improvement (n = 7) or nausea (n = 11). After 3 months on SC MTX at a mean dose of 15.4 mg/m^2 (range 5-20), 23 of 30 patients (77%) showed statistically significant improvement ($p < 0.05$) in a variety of outcome measures compared to pre-SC values on oral MTX.

A total of 15 patients were reported to have “toxicity” related to oral MTX (11 with nausea and 4 with raised serum liver enzyme levels). Nine of the 11 patients with nausea experienced a complete resolution of symptoms after switching to SC MTX; the other 2 patients had less severe nausea that was tolerable on SC MTX. All 4 children with raised liver enzymes were able to remain on oral MTX as the abnormalities resolved after temporary discontinuation of oral MTX.

Four children experienced transient toxicity related to SC MTX (liver enzyme abnormalities, or mild lymphopenia); 2 required temporary discontinuation of treatment, after which treatment was reinstituted without recurrence.

The authors concluded that for patients who fail oral MTX either because of inefficacy or toxicity, the use of SC MTX has a high likelihood of success, with more than 70% of patients achieving clinically significant improvement without clinically significant toxicity.

Ravelli et al, 1998

This was a prospective, open label, multi-center study to compare the efficacy of MTX after oral and IM administration in children with juvenile chronic arthritis (JCA). The study was conduced at 11 centers in Italy, enrolling children with a diagnosis of JCA according to the criteria set by the European League Against Rheumatism (EULAR) including children with a disease duration of at least 6 months with at least 3 joints with active arthritis that was not adequately controlled in NSAIDS or DMARDS.

A total of 257 patients (89 with polyarticular, 72 with pauciarticular, 95 with systemic) with a mean age 9.35 years (range 1.7-28 years) were treated with oral (n=127) or IM (n=129) MTX at a dose of 10 mg/m^2/week over a 6 month period. Response was defined as a ≥50% reduction in number of joints with active arthritis and/or the articular severity score. After 6 months the response rate was 58% in the oral cohort and 61% in the IM cohort. Higher response rates were observed in the pauci-polyarticular (60% in oral, 71% in IM) when compared to the systemic subtype patients (53% in oral, 45% in IM). The frequency of adverse reactions (Table 13) was generally similar between treatment groups, and no patients were discontinued due to an adverse reaction.

The authors concluded that MTX at the conventional dose regimen is equally effective in children with JCA when administered orally or by intramuscular injections.

Table 13. Ravelli 1998. Frequency of adverse reactions by route of administration

Adverse Reaction	Oral (n=125)	IM (n=126)
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Source: Ravelli 1998, Table 2, page 182

Ruperto et al, 2004

This was a randomized, multi-center trial conducted in Europe, Brazil, Israel, Korea, Mexico, Turkey, and the United States. The trial evaluated the efficacy and safety of parenteral methotrexate at intermediate (15 mg/m^2/week) and higher (30 mg/m^2/week) dosages in patients with polyarticular-course JIA who failed to improve after 6 months of oral, SC, or IM MTX at standard doses (8-12.5 mg/m^2/week). In the screening phase, 595 patients with JIA (325 with polyarthritis, 183 with extended oligoarthritis, and 87 with systemic-onset arthritis) were treated for a mean (±SD) of 5.6 ±1.5 months. MTX was administered orally in 463 children (78%), SC in 101 children (17%), and IM in 31 children (5%) at a mean ±SD dose of 10.0 ±2.3 mg/m^2/week. Of these, 430 (72%) improved in ACR 30, 133 (23%) did not improve, and 32 (5%) were lost to follow-up. Eighty eligible non-responders (mean age 8.2 ±6 years) were then randomized to receive either intermediate (n=40) or higher (n=40) dose MTX SC or IM once weekly for an additional 6 months.

After 6 months, there were no significant differences in response rates between the intermediate dose and higher doses for ACR30 (62.5%, 95% CI 46%-77% vs. 57.5%, 95% CI 41%-73%, p = 0.65), ACR 50 (57.5%, 95% CI 41-73% vs. 55%, 95% CI 38-71%, p = 0.82), or ACR70 (45%, 95% CI 29-61% vs. 47.5, 95% CI 32-64%, p = 0.82), respectively. However, nine patients (5 in the intermediate dose group and 4 in the high dose group) met the definition of complete disease control.

In the screening phase, 25 patients interrupted their MTX treatment temporarily or completely: 10 due to laboratory abnormalities (8 elevated transaminase, 2 leukopenia), 9 due to gastrointestinal symptoms (3 nausea, 4 vomiting, 1 mouth sores, 1 loss of appetite), 5 due to infections (2 upper respiratory tract infection, 2 urinary tract infection, 1 pneumonitis), and 1 due to focal seizures.

In the treatment phase, the number of patients who dropped out of the study due to MTX-related toxicity was similar between the intermediate- and the higher-dose group and did not differ from the dropout rate observed in the screening phase. Of the 40 patients who were randomized to receive the intermediate dose of MTX, 34 (85%) completed the trial and 6 (15%) dropped out: 3 due to a disease flare that required treatment with steroids (1 also required treatment with intravenous immunoglobulin and cyclosporine), 2 due to adverse events (1 with severe alopecia and 1 with seizures that were not related to MTX), and 1 due to withdrawal of parental consent. Of the 40 patients randomized to receive the higher dose of MTX, 29 completed the trial (72.5%) and 11 (27.5%) dropped out: 5 due to an adverse event (2 with nausea, loss of appetite, and general malaise, 1 with documented acute familial pancreatitis, 1 with dizziness, syncope, and unconsciousness, and 1 with papilloedema from a large arterovenous malformation), 3 due to an insufficient therapeutic effect requiring treatments (1 received sulfasalazine, 1 received etanercept, and 1 received prednisone), 2 due to withdrawal of parental consent, and 1 lost to follow-up.

Comparing the intermediate- with the higher-dose MTX group, there were no differences in the frequency of moderate or severe adverse events that were attributed as possibly or definitely related to MTX (although a trend toward more frequent toxicity was observed in the higher-dose group) and there were no differences in the frequency of patients with laboratory abnormalities. The most common adverse events (combined treatment groups) were nausea (n=17, 21%), vomiting (n=9, 11%), mouth sores (n=8, 10%), loss of appetite (n=6, 7.5%), hair loss (n=4, 5%), and malaise (n=4, 5%). No patient experienced diarrhea, pneumonitis, rash, or hepatomegaly. All other adverse events were mild and were considered to be unrelated to the MTX treatment. The most common laboratory abnormalities (combined group) were levels of AST and/or ALT greater than twice the ULN on at least 1 determination (n=4, 5%) and leucopenia $\leq 4{,}000/mm^3$ on at least 1 determination (n=4, 5%).

The authors concluded that a trial of parenteral administration of an intermediate dose (15 mg/m^2/week) of MTX is warranted in JRA patients who do not respond to standard doses of 10 mg/m^2/week, whereas a higher dose (30 mg/m^2/week) provides no additional therapeutic benefit.

Tukova et al, 2010

This was a dose-escalation comparative PK study in responders and non-responders, to investigate whether methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms and erythrocyte concentration of methotrexate (EMTX) could serve as predictors of methotrexate efficacy and toxicity in patients with JIA. The study was performed at the University of Prague between 2005 and 2008.

Patients with JIA and disease activity requiring MTX for at least 3 months were recruited for the study. Only patients within the extreme ends of the response spectrum were enrolled, i.e., patients who were full responders to MTX treatment and patients who non-responders. Criteria for inactive disease included: no active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate (ESR) or CRP; and physician's global assessment of disease activity indicating clinical disease quiescence. [Wallace 2004] To be considered a non-responder the patient must have been treated with a minimum weekly dosage of 15 mg/m^2 SC for at least 3 months and at least 3 of any 6 JIA core set variables could not have improved by a minimum of 30% and no more than 1 of the remaining variables could have improved by >30%. Prior to study entry, patients were treated with a dose escalation protocol with initial weekly doses of 7.5-10 mg/m^2 orally, with titration up to 15 mg/m^2 (maximum 20-25 mg). Patients requiring more than 10 mg/m^2 were switched to SC dosing, although SC dosing was also used as the primary route of MTX administration in children under 4 years of age and patients with high disease activity. Most patients received folic acid supplementation (5-10 mg/week), and all were allowed one NSIAD, usually ibuprofen.

The ACR30 was used to define improvement. Efficacy was assessed monthly during dose escalation, and every 3 months once patients were on a stable dose. Outcome measures included number of joints with active arthritis, joints with limited range of motion, physician's global assessment of disease activity, parent's global assessment of the child's overall wellbeing, disability index of the Childhood Health Assessment Questionnaire (CHAQ), and erythrocyte sedimentation rate (ESR).

Genetic analyses and EMTX and folate assessment were performed in 69 patients (30 males, 39 females) with mean age 9 years (range 2.5 -19.6 years), of whom 51 (74%) were classified as complete responders and 18 (26%) as non-responders. In the non-responders, disease activity persisted despite 37% higher subcutaneous dosages of methotrexate than in responders who received the drug orally (n = 24) or subcutaneously (n = 27) ($p < 0.0001$). No significant relationship was found between EMTX and treatment efficacy. Analysis of MTHFR allele and genotype frequencies in relation to response failed to detect any significant association.

The study report does not state whether there were any differences in AEs based on route of MTX administration. Mild to moderate MTX toxicity was noted in a total of 21 patients (30.4%), with GI complaints (mucosal, nausea, vomiting, abdominal pain) in 16, hepatopathy in 3, and alopecia in 2 patients. Other adverse effects (bone marrow suppression, behavioral changes, nodulosis) were not seen. The frequency of overall adverse effects was 29.4% in responders (15/51) and 33.3% in non-responders (6/18) ($p = 0.77$).

Wallace et al, 2012

This was a randomized, partial double-blind, placebo-controlled trial conducted at 15 sites in the United States between May 2007 and October 2010. The trial was funded by NIH but received support from Amgen, the manufacturer of etanercept. The objective of the trial is stated to have been to evaluate whether aggressive therapy early

in the course of RA positive and RA negative pJIA can induce clinical inactive disease within 6 months. However, all patients received open-label SC MTX, with the differences between the treatment arms being the addition of blinded etanercept and prednisolone or their corresponding placebos. As a result, it primarily focused on whether the addition of these medications would change the outcomes in these children when added to SC MTX as a baseline treatment.

Patients were randomized to receive either: (Arm 1, n = 42) open-label MTX (0.5 mg/kg/week, maximum 40 mg) SC, blinded etanercept (0.8 mg/kg/week, maximum 50 mg), and blinded prednisolone (0.5 mg/kg/day, maximum 60 mg, tapered to 0 by 17 weeks, or (Arm 2, n = 43) open-label MTX (same dosage), etanercept placebo, and prednisolone placebo. All patients also received 1 mg/day of folic acid and were allowed to receive NSAIDs as concomitant therapy.

The study design was somewhat complex; a diagram of the study phases is shown in Figure 10. The primary outcome measure was clinical inactive disease at 6 months, defined as no joints with active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; ESR in the normal range; and a physician's global assessment of disease activity score of 0. An exploratory phase lasted up to 12 months after enrollment to determine the rate of clinical remission on medication (i.e., 6 months of continuous clinical inactive disease) at 12 months. Patients who did not achieve an improvement in their ACR Pediatric 70 after 4 months of blinded treatment were considered treatment failures, placed in the exploratory phase of the trial, and treated with open-label medications similar to Arm 1 and placed in the exploratory phase of the trial.

Figure 10. Wallace et al, 2012. Diagram of the study phases.

The trial included 85 children (22 males, 63 females) ages 2-16 years who had disease duration <12 months. The mean age at baseline was 10.5 ± 4.3 years and the mean disease duration was 5.1 ± 0.6 months; 73 (85.9%) patients were white, 5 (5.9%) were black, and 7 (8.2%) were classified as other.

The study did not meet its primary endpoint, i.e., SC MTX plus etanercept and prednisolone was not significantly better than SC MTX alone. After 4 months 30 of 42

patients in Arm 1 and 19 of 43 patients in Arm 2 had achieved at least an ACR Pediatric 70 and continued in the double-blind study. By 6 months, clinical inactive disease had been achieved in 17/42 (40%) in Arm 1 and 10/43 (23%) in Arm 2 (x^2 = 2.91, p = 0.088). After 12 months, clinical remission was achieved in 9 patients in Arm 1 and 3 patients in Arm 2 (p = 0.053).

Three patients experienced SAEs: pneumonia, a psychotic event that resolved with tapering of prednisolone, and septic hip joint. In addition, the following AEs were reported: 4 elevated transaminase levels resulting in study withdrawal; 1 low white blood cell count; 1 peritonsillar abscess; 1 worsening of a pre-existing, recurrent herpes simplex virus infection; and 1 pneumonia. Infection rates were as follows: 18 infections occurred during 247 months of MTX monotherapy (0.87/year); 16 occurred during 297 months of MTX and etanercept therapy (0.65/year), and 17 occurred during 360 months of MTX, etanercept, and prednisolone therapy (0.57/year).

The authors concluded that early treatment with SC MTX with or without additional therapy in children with recent-onset polyarticular JIA can result in clinical inactive disease by 6 months and clinical remission on medication within 12 months of treatment in a substantial proportion of patients.

6.2.2.3 Discussion

As requested by the Agency, the applicant has submitted bioequivalence data and published pediatric literature to support the SC route of administration in patients with pJIA. My review of the data presented supports the proposed dosing administered by the SC route for pJIA. Further, my review of these data does not reveal any specific safety concerns with this route of administration in children beyond those already labeled. Study-10-001 showed bioequivalence between IM and SC administration of MTX, and Study MTX-11-003 showed higher bioavailability with IM and SC dosing than with oral doses above 15 mg. These data are consistent with clinical results of published studies suggesting equal or greater efficacy with SC dosing and no increase in safety concerns. [Arthur 2001; Ravelli 1998; Ruperto 2004; Tukova 2010; Wallace 2012]

Parenterally administered MTX is also recommended for the treatment of pJIA in essentially all published treatment guidelines, including those from the American College of Rheumatology (ACR) [Beukelman 2011], the Working Groups for Children and Adolescents with Rheumatic Diseases in Germany [Niehues 2005], and Pediatric Rheumatology Austria [Niehues & Lankisch 2006]. Further, a survey on the use of MTX by pediatric rheumatologists in Canada showed that most (78.6%) used oral MTX initially, but for more severe cases or when dose escalation was necessary, SC administration was the preferred route. [Chedeville 2007] Therefore, based on the information presented by the applicant, the proposed SC route for administration of MTX in children is acceptable.

My review revealed that, just as for adults, children with pJIA do not require weekly visits for supervision of care and laboratory tests to monitor MTX therapy. Therefore, the condition is appropriate to home treatment using an auto-injector device.

The currently approved recommended dosing regimen for the treatment of pJIA is based on body surface area (BSA), with doses adjusted incrementally every 2 to 4 weeks to achieve an optimal response. The recommended starting dose is 10 mg/m^2 administered once weekly, with dose escalation to 15-30 mg/m^2/week, if needed. The dosing regimen allows for administration of MTX orally, IM, or SC. These doses are supported by doses recommended in clinical guidelines and by my review of the pediatric literature.

Antares has revised the proposed Dosage and Administration section to dose children with pJIA starting with 10 mg and allow dosing increases in 5 mg increments to match the applicant's lowest proposed dose of 10 mg, with availability of higher doses in 5 mg increments up to 25 mg. They state that "patients requiring doses less than 10 mg/week may not be suitable for treatment" with Otrexup, and therefore, doses lower than 10 mg are not proposed. Consistent with this approach, Antares has requested a waiver of pediatric studies below 6 years of age because they state that their proposed product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight and the product is not likely to be used in a substantial number of patients in this age group.

Since dosing of MTX for the treatment of pJIA is based on BSA, the recommended starting dose should be based on BSA and not based on body weight or a standardized dose, as proposed by the applicant.

It should be noted that MTX doses for patients with pJIA are often lower than the lowest proposed dose of 10 mg weekly, which corresponds (based on a dose of 10 mg/m^2) to a BSA of 1.0 and a weight of about 28 kg (62 lb) (Figure 12). Assuming average height for weight, the 10 mg dose corresponds to 50th percentile for boys around 8 years of age and 50th percentile for girls around 8.5 years of age (Figure 11). Since pJIA is considered to begin around 2 years of age, the lowest starting dose of 10 mg for this product will therefore not be sufficient to allow for use in all pediatric patients. Based on the CDC growth charts (Figure 11), the lowest weight would likely be about 10 kg, which corresponds to a BSA (Figure 12) of 0.47 m^2, and a dose of 5 mg. Intermediate doses of 7.5 mg and 12.5 mg would allow dosing for most age and weight groups. Corresponding weights for standardized doses of 5, 7.5, 10, and 12.5 mg in children are shown in Table 14, using a dose of 10 mg/m^2 and assuming an average height for weight. However, since PREA (triggered by the new route for RA) is satisfied by the fact that MTX is already labeled as safe and effective in children 2 years of age and older with pJIA when administered by the SC route, no additional doses are required under PREA. Nevertheless, the Division will ask the sponsor to consider development of 5 and 7.5 mg doses to fill this gap.

Antares has requested a waiver of PK studies in children of all ages, and a waiver of PK studies in children is appropriate from an ethical perspective because the information is available from data in adults. Antares has also requested a waiver of pediatric studies

for RA/pJIA below 6 years of age because they state that their proposed product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight and the product is not likely to be used in a substantial number of patients in this age group. However, this is not appropriate. Rather, the pediatric assessment will be considered to be complete for 2 years of age and older, and a waiver will be granted from birth to 2 years of age because the disease does not exist in this age range.

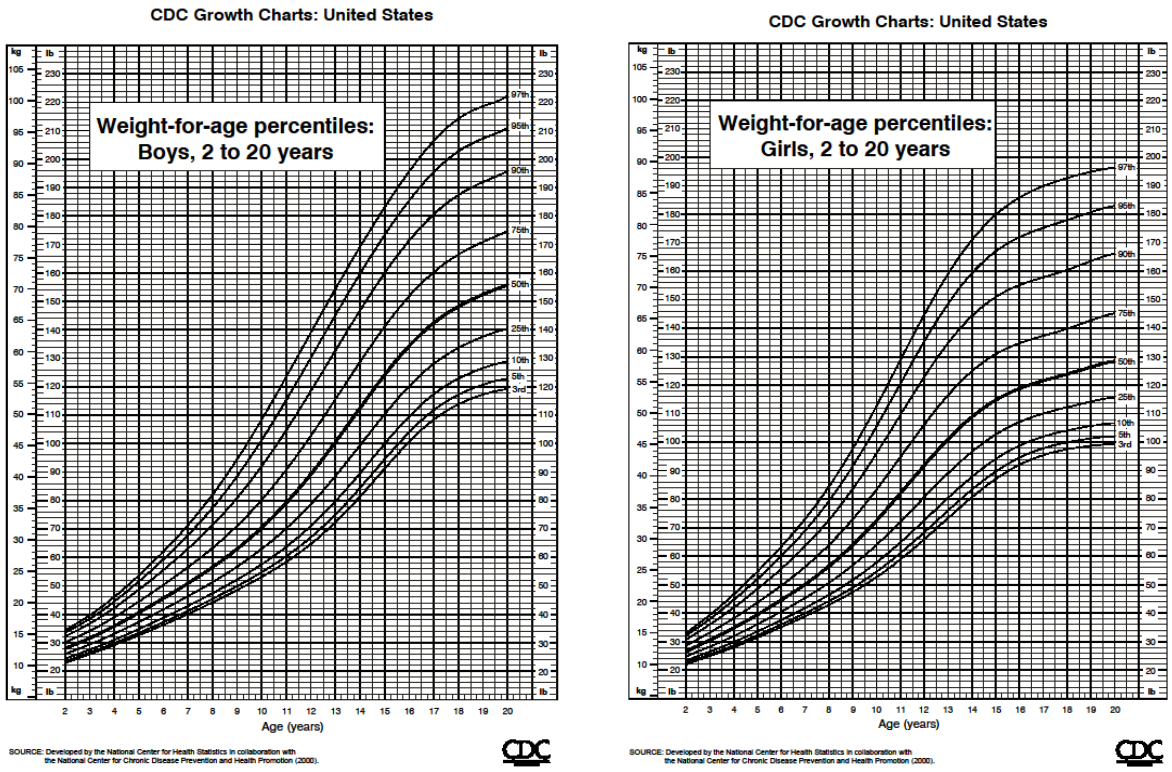

Figure 11. CDC growth charts for boys and girls 2-20 years of age

Source: http://www.cdc.gov/growthcharts/clinical_charts.htm, Accessed 5/1/2013.

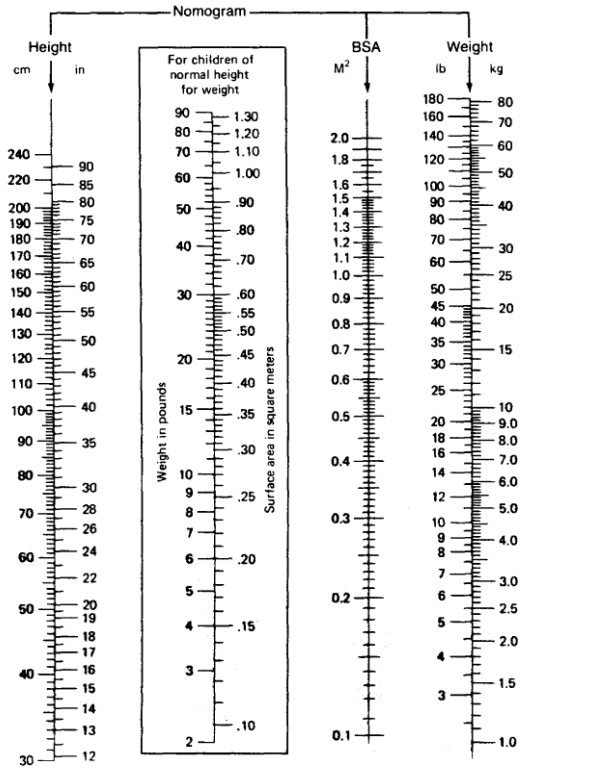

Figure 3–1. West Nomogram (for Estimation of BSA). The BSA is indicated where a straight line connecting the height and weight intersects the BSA column or, if the patient is roughly of normal proportion, from the weight alone (enclosed area). (Nomogram modified from data of E. Boyd by C. D. West; from Vaughan, V. C., and R. J. McKay, eds., *Nelson Textbook of Pediatrics*, 12th ed., Philadelphia: Saunders, 1983.)

Figure 12. Nomogram for estimation of body surface area (BSA)

Source: See notation within the figure.

Table 14. Corresponding weights for standardized 10 mg/m^2 doses in children

Dose mg	BSA	Weight*	
		kg	lb
5	0.5	11.5	25
7.5	0.75	18	40
10	1.0	28	62
12.5	1.25	38	84
*Assumes an average height for weight			

7 Review of Safety

Safety Summary

Two BA/BE studies are submitted, and one actual use study in patients and were reviewed for safety. All were single dose studies, and no unexpected findings were noted.

Review of the literature does not reveal any specific safety concerns beyond those already labeled for oral use in patients with RA, and oral, IM, and SC use in patients with pJIA. Since no clinical trials were submitted and the literature does not add any new safety data for use via the subcutaneous route of administration, the rest of the safety section in this review is blank.

Adult RA care guidelines recommend monitoring with periodic blood counts, creatinine, and liver functions, and these are generally followed in children as well. The recommendations also call for use of folate supplementation while on MTX, although the current labeling for the MTX products state the opposite.

The guidelines also propose that Varicella vaccination should be administered to children who are candidates for MTX because children taking MTX may be immunocompromised and, therefore, may have a more severe clinical course if infected with varicella. [Chedeville 2007] That said, varicella is also a significant risk in adults. With varicella vaccine now a part of the routine childhood vaccination program in the United States, this is less of an issue for children, but many are still not immunized and many adolescents and adults have either not been immunized or have not had the disease. Therefore, this recommendation is suggestive that a Precaution be added to evaluate whether the patient is immune to Varicella and to consider the use of Varicella vaccine before initiating therapy with MTX.

7.1 Methods

NA

7.2 Adequacy of Safety Assessments

NA

7.3 Major Safety Results

NA

7.4 Supportive Safety Results

NA

7.5 Other Safety Explorations

NA

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information is submitted with this NDA. Methotrexate is already labeled as causing chromosomal damage, although the risk of neoplasia in humans is unknown.

7.6.2 Human Reproduction and Pregnancy Data

No new information is submitted with this NDA. Methotrexate is already labeled as Pregnancy Category X, with a contraindication for use in pregnancy and in breastfeeding mothers.

7.6.3 Assessment of Effects on Growth

No new information is submitted with this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information is submitted with this NDA. Methotrexate is already labeled for much higher doses when used for treatment of neoplastic diseases, and for use of leucovorin to diminish the toxicity and counteract the effects in overdosage.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

The applicant has submitted published literature to support the use of the proposed product by the SC route. Since no specific safety concerns were noted, the reviewer teams did not request an evaluation of postmarketing safety reports to see if additional safety concerns have been reported.

9 Appendices

9.1 Literature Review References

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9.2 Labeling Recommendations

9.2.1 Device, Trainer Device, and Instruction Set

This section summarizes the evaluation of the trainer, the actual device, and the instruction set in the proposed IFU, TIFU and on the devices labeling that was performed by the clinical review team as well as reviewers in ONDQA and CDRH. Note that this section is specific to labeling of the instructions for use, and not to other aspects of the labeling.

Examples of the trainer and live devices were requested and evaluated by members of the review teams, including DPARP, DDDP, ONDQA, OSE, and CDRH. All proposed labeling and labeling instructions were reviewed.

9.2.1.1 Proposed Device and Trainer

A placebo live device (i.e. with a needle) was reviewed alongside a trainer device. It was noted that the proposed live device looks very similar to the trainer device. Both have clear plastic body and gray cap (marked as 1) and safety clip (marked as 2). As a result, the actual product is not sufficiently distinguished from the trainer that the two might not be confused. In fact, this reviewer almost made that mistake while looking at the two proposed devices. To address this, the applicant will need to change the color of the two caps to distinguish the live device from the trainer. However, this may not be sufficient. Since the plastic bodies on the trainer and live devices are clear and see-through, the main differences will be the color of the caps and the labeling. Therefore, it

is recommended that the plastic body of the trainer also be changed in such a way as to distinguish it as well.

Additionally, the proposed trainer labeling is not clearly marked that the device a trainer device. The TIFU and trainer labeling uses the terminology [redacted](b) (4), and not the terminology of 'trainer', and it does not it state 'for practice only'. It does say that it contains no needle and no medicine, but the print is too small to clearly identify it as a trainer. The applicant will need to address these issues.

9.2.1.2 Proposed IFU

Upon review, it was noted that the proposed IFU includes pictures (labeled as Figures C and D) showing the device being gripped in a manner opposite to that in which it would be used, and therefore in a manner that could lead to accidental needle sticks. The applicant will be asked to replace these pictures with pictures showing the product being gripped correctly.

It was also noted that the preparations for use do not include washing hands or instructions for preparing the skin for an injection.

9.2.2 PI and PPI

Labeling revisions are ongoing at the time of completion of this document. Therefore, this section only provides a brief summary of the main issues found during initial review of the PI and PPI, and is not intended as a complete review of the labeling.

As is appropriate, the proposed PI is in PLR format, whereas the reference products are not. Changes to PLR format involve significant reorganization of sections of the labeling and revision of certain aspects of the labeling language. That said, the expectation is that this product would not differ substantially from the current reference products based on such a reorganization. In fact, an effort will be made not to update the labeling for this product to today's science, which might make the labeling for this product differ substantively from those of the reference products. [redacted](b) (4) Wording will therefore be kept the same as much as possible, although it may appear in different sections because of the PLR format differences.

However, because the product is an auto-injector intended only for SC administration and is available only in limited dosage strengths, the Indications and Dosage and Administration sections will necessarily differ substantively from the current labeling, with Limitations of Use added for other routes of administration and for doses that cannot be achieved by the proposed product. For example, the current dosing recommendation for treatment of pJIA is based on body surface area (BSA). Since many of the doses that may be required in younger children will not be available or cannot be achieved with use of this product, the D&A recommendations will need to be significantly revised.

In a number of instances, the applicant has taken the opportunity to make revisions to the labeling that are not necessarily appropriate, and the PI will be revised to correct these oversteps.

The PI for the reference products use the older terminology of pJRA, and the applicant as continued to use that approach for the labeling of this product. The terminology will be changed to match that currently being used by the Agency [and the professional community]; therefore, pJIA will be used instead.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not held during the review of this product.

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

/s/

PETER R STARKE
08/19/2013

THERESA M MICHELE
08/20/2013

CLINICAL FILING CHECKLIST

NDA:	**204-824**
Drug Name:	**Methotrexate Auto-injector**
Applicant:	**Antares Pharma, Inc.**
Type:	**NDA**
Stamp Date:	**December 14, 2012**
PDUFA Date:	**October 11, 2013**
Review Date:	**February 8, 2013**

This is a 505(b)(2) new drug application submitted by Antares Pharma, Inc. for a drug/device combination of Methotrexate (MTX) Injection in an auto-injector, referencing Methotrexate Sodium Injection EQ 50 mg base/2mL (NDA 11-719). MTX is a folate analog metabolic inhibitor currently indicated for the treatment of malignancies, severe psoriasis, and rheumatoid arthritis (RA) including polyarticular-course juvenile rheumatoid arthritis (JRA). The proposed product is a single-use, single-dose, pre-filled, auto-injector (called a Medi-Jet) containing 10, 15, 20, or 25 mg of MTX as a sterile preservative-free solution for subcutaneous injection. The product includes a single-dose syringe with a 27-gauge, ½ inch needle that delivers a fixed volume 0.4 mL per injection. The needle is protected before use by a needle safety guard and safety cap, and after use by a soft needle shield.

The proposed indications for this product include RA, JRA, moderate to severe psoriasis[1], but not treatment of malignancies. The applicant has requested a proposed Trade Name of Otrexup™. Because the applicant has requested an extension of the psoriasis indication, discussion is underway with regard to whether the application will be administratively split by indication, with Original 1 for RA and JRA to be reviewed in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), and Original 2 for moderate to severe psoriasis to be reviewed in the Division of Dermatology and Dental Products (DDDP). However, in the interim, DDDP has provided DPARP with the following comment to forward to the applicant:

> We note that you have proposed labeling for moderate psoriasis. As a 505(b)(2) application, the indication for your product should match that for the listed product, as appropriate, given the limitations of an auto-injector product intended for home administration. Provide revised labeling that matches the labeled indication for psoriasis for the reference product.

The clinical program included 4 clinical studies, and was discussed over multiple interactions with the Agency. Clinical pharmacology was assessed in 2 open-label, randomized, 3-way crossover bioavailability studies (MTX-10-001 and MTX-11-003) designed to compare systemic exposure when dosed subcutaneously (SC) via the Medi-Jet with SC and IM dosing via a needle and syringe (MTX-10-001) and to compare SC administration with the Medi-Jet dosed in the abdomen and thigh with oral administration (MTX-11-003), device handling and safety was assessed in 1 multicenter, open-label, single-dose study (MTX-11-002), and usability of the device was assessed in 1 summative device usability study using a dummy device (MTX-11-004). Additionally, the application includes a literature review summarizing the efficacy and

[1] The reference product does not include an indication for treatment of moderate psoriasis.

safety of the new route of SC administration because SC administration is not currently in the label for treatment of either RA/JRA or psoriasis[2].

The application will trigger PREA because as a new drug-device combination it will have a new dosing regimen, and because of the new route of administration. The applicant has requested a waiver of pediatric PK studies in all ages, and specifically for pediatric studies in children less than 6 years of age because the product cannot be varied in small dosing increments that would be required for dosing in pediatric patients according to BSA or weight and the product is not likely to be used in a substantial number of patients in this age group.

The application is all-electronic in eCTD format. There are no missing data elements, and the application is fileable from a clinical perspective. There is one 74-day comment for the application.

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic in eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Clinical overview and clinical summaries
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Clinical overview and clinical summaries
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Approved Product. Risk-benefit submitted in the clinical overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) referencing Methotrexate Sodium Injection EQ 50 mg base/2mL (NDA 011719)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to			X	Approved drug product.

[2] The reference product includes oral, IM, IV, and intrathecal routes of administration, but not SC dosing.

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				Dose already established.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[3]) been exposed at the dose (or dose range) believed to be efficacious?			X	Approved drug product.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			X	

[3] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[4] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 13.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant has submitted a request for a waiver for patients less than 6 years of age because the dosage cannot be varied for this age group and the product is not likely to be used in a substantial number of patients in this age group.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			For PK studies
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			For PK studies
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No efficacy studies
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No efficacy studies
CASE REPORT FORMS					

[4] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We note that you have proposed labeling for moderate psoriasis. As a 505(b)(2) application, the indication for your product should match that for the listed product, as appropriate, given the limitations of an auto-injector product intended for home administration. Provide revised labeling that matches the labeled indication for psoriasis for the reference product.

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

/s/

PETER R STARKE
02/08/2013

THERESA M MICHELE
02/08/2013