1. はじめに

この臨床試験は，マラビロックの投与を考慮した患者さまを対象にケモカイン受容体指向性（トロピズム）検査を実施し，CCR5 指向性 HIV のみが検出された患者さまにマラビロックの投与を開始する，という手順が必要な試験になっています。ここでは指向性検査実施のための登録と検体の採取，送付等の手順についてご説明します。

2. ケモカイン受容体指向性（トロピズム）検査を実施するための登録

まずは，検査しようとする患者さまが以下の指向性検査の選択基準に適合していることをご確認下さい。

ケモカイン受容体指向性検査の選択基準

- **現在 HAART 療法を施行中，もしくは以前施行していたが何らかの理由で休薬中であり，CCR5 指向性と判明した場合はマラビロックによる治療を開始できる患者**
- **直近の血漿中ウィルス RNA 量が 1,000 コピー/mL 以上であること**

適合していることを確認されたら，指向性検査実施患者登録票（別紙様式１）に必要事項を記入して，代表研究責任者あてに FAX で送付してください。代表研究責任者からは折り返し，検体受領日を指向性検査実施受付票（別紙様式２）により FAX でお知らせします。検体受領日を指定させていただくのは，検査を米国の検査会社で実施するため，検体を可能な限り一括で空輸するためです。指定された検体受領日から遡って１週間以内に患者さまが来院できないなどの事情がある場合には，お知らせ下さい。

3. ケモカイン受容体指向性（トロピズム）検査の実施

採血日が決まったら，患者さまに来院頂き，採血をお願いします。全血８mL を EDTA 管に採取して採血後は速やかに（遅くとも２時間以内に），1,000～1,200g で遠心して血漿３mL を分離し，速やかに-20 ℃に凍結保存してください。**検体には各施設の研究責任者がプロトコールに定められた方法で作成した登録番号のみを明記してください。**検体受領日には，担当者がご指定の検体受領場所に伺います。検体を東京医科大学に集めてから一括して米国の検査会社に送付します。

4. ケモカイン受容体指向性（トロピズム）検査の結果報告

検査の結果が出るまでに４週間程度かかります。検査結果は米国の検査会社から，代表研究責任者のところに一括して送られます。登録された患者さまの検査結果は，代表研究責任者を介して各施設の研究代表者に検査結果報告票（別紙様式３）により通知されます。

5. マラビロックを投与するための登録

指向性検査の結果，CCR5 指向性ウィルスのみが検出された場合には，マラビロックを投与するための手続きに進んでください。登録はエイズ治療薬研究班により定められた方法に従ってください。

(http://www.iijnet.or.jp/aidsdrugmhw/text/1aids/c/c_nyushu.htm)

6. ケモカイン受容体指向性（トロピズム）再検査の申し込み方法

以下に示す治療失敗の基準に該当した場合は，マラビロックの投与を中止しますが，中止する前に可能な限りウィルスの指向性を確認していただくことになっています。

治療失敗の基準

a)治療開始時のウィルス量が 5,000 コピー/ mL 以上であった症例では，治療開始４週目以降に行われた採血で，治療開始前の３倍以上に増加している場合

b)治療開始時のウィルス量が 5,000 コピー/ mL 未満であった症例では，治療開始４週目以降に行われた採血で，ウィルス量の絶対値が 15,000 コピー/ mL 以上に増加している場合

c)血漿中ウィルス量が 400 コピー/ mL 以下に達したことがありながら，
４週間の間隔をおいた２度の測定で 5,000 コピー/ mL 以上に達した場合

指向性検査を申し込むには，指向性検査再申込票（別紙様式４）に必要事項を記入して代表研究責任者にＦＡＸしてください。折り返し検体受領日をお知らせします。指向性検査用の検体採取後すぐにマラビロックを中止するか，約４週間後に送られてくる指向性検査の結果報告を待ってから中止するかは各施設の研究責任者の総合的な判断によるものとします。

FAX 03-3340-5448 厚生労働省エイズ治療薬研究班　研究代表者へ送付してください。

指向性検査実施患者登録票（様式１）

年　月　日

厚生労働省エイズ治療薬研究班　研究代表者　福武勝幸殿

下記の患者の治療において，日本での既承認薬のみによる治療は困難なため，本邦では未承認の CCR5 阻害薬マラビロックによる治療を考慮しています。そのため，ウィルスの指向性検査を実施したく患者を登録し，検査を申し込みます。

なお私は指向性検査の結果，CCR5 指向性ウィルスのみが検出された場合にはマラビロックによる治療が開始できるが，重複・混合指向性または CXCR4 指向性ウィルスが検出された場合にはマラビロックによる治療は出来ないことを理解しています。患者にもその旨十分な説明をして了解を得ています。また検査の費用は研究班の予算から支出されるため，患者が費用を負担する必要はないことを理解し，また患者にも説明して了承を得ています。

申込医師名		病院名・住所	
診療科名			
職名			
電話番号	（　　）	FAX 番号	（　　）
E-mail			

登録番号 プロトコール９頁に記載の方法で作成のこと			
最近の CD4 数 年　月　日	/μL	最近の HIV-RNA 量 年　月　日	copies/mL
次回外来受診日（入院患者では記入不要）		月　日	
上記以外で採血のため来院可能な日 （検体受領日の調整のため，出来るだけ記入して下さい）			

研究事務局使用欄（記入しないで下さい）

指向性検査実施受付票（様式２）

[　　]　病院
[　　]　先生

以下の患者さまの指向性検査実施を受付しましたのでお知らせします。

登　録　番　号	

検体は，以下の日時に担当者が受領に伺います。受領日からさかのぼって１週間以内に採血したEDTA血漿３mLを-20 ℃に凍結保存しておいてください。**検体には登録番号のみを明記してください。**受領場所と当日どなたを訪ねればよいかは，後日担当者から電話またはメールで確認しますので，ご指示をお願いします。

検　体　受　領　日　時	月　　日　　時ごろ

何らかの事情で，上記の日時に検体が準備できなくなった場合には，速やかに研究代表者までご連絡下さい。改めて日時を調整します。

厚生労働省エイズ治療薬研究班　研究代表者　福武勝幸
Tel 03-3342-6111（内線 5086）
Fax 03-3340-5448

指向性検査結果報告票（様式３）

[　　] 病院
[　　] 先生

以下の患者さまの指向性検査の結果が報告されましたのでお知らせします。

登　録　番　号	

検　査　結　果	□　CCR5 指向性ウィルスのみを検出しました。 □　重複または混合指向性ウィルスを検出しました。 □　CXCR4 指向性ウィルスのみを検出しました。 □　指向性検査をおこなうことができませんでした。

チェックのついているものが，該当する検査結果です。

厚生労働省エイズ治療薬研究班　研究代表者　福武勝幸
Tel 03-3342-6111（内線 5086）
Fax 03-3340-5448

FAX 03-3340-5448 厚生労働省エイズ治療薬研究班　研究代表者へ送付してください。

指向性検査再申込票（様式４）

年　月　日

厚生労働省エイズ治療薬研究班　研究代表者　福武勝幸殿

下記の患者においてマラビロックによる治療を実施していますが，治療無効と判断されるため，ウィルスの指向性を確認したく検査を申し込みます。

申込医師名		病院名・住所
診療科名		
職名		

患　者　登　録　番　号	

最近の CD4 数 年　月　日	/μL	最近の HIV-RNA 量 年　月　日	copies/mL
次回外来受診日（入院患者では記入不要）		月　日	
上記以外で採血のため来院可能な日 （検体受領日の調整のため，出来るだけ記入して下さい）			

治療開始後の経過と治療無効と判断した理由をご記入下さい。

エイズ治療薬研究班　多施設共同臨床研究

治療歴のあるHIV-1感染者におけるケモカイン受容体指向性

（トロピズム）の検討とマラビロックの有効性と安全性に関する臨床研究

血中濃度測定実施要領

この文書は標記の臨床試験で行われる血中濃度測定の実施方法などについて，試験参加施設の担当の先生を対象に説明しています。ご不明の点がありましたら，下記あてにお尋ね下さい。

共同臨床研究代表研究責任者
東京医科大学　臨床検査医学講座主任教授
厚生労働省　エイズ治療薬研究班研究代表者

福武 勝幸

〒160-0023 東京都新宿区西新宿 6-7-1
Tel 03-3342-6111（内線 5086）
Fax 03-3340-5448

共同臨床研究分担研究者
国立病院機構名古屋医療センター　薬剤科　試験検査室

高橋 昌明

〒460-0001 愛知県名古屋市中区三の丸4-1-1
Tel 052-951-1111（内線 3280）
masaakit@nnh.hosp.go.jp

1. はじめに

この臨床試験では，マラビロックを投与中の患者さまで薬物血中濃度測定を行うことになっています。ここでは血中濃度測定の申し込み方法と検体の採取，送付等の手順についてご説明します。

2. 血中濃度測定の申し込み方法

まずは，検査しようとする患者さまが以下の条件に適合していることをご確認下さい。

血中濃度測定の条件

以下の１または２のいずれかを満たすこと

１．薬物動態解析のための濃度測定

- **採血日がマラビロックの投与を開始して７日目以降であること。**
- **採血日は，朝の服薬をしない状態で来院し。採血した後で服薬できること。さらに服薬の２～４時間後に２度目の採血を行えること。**

２．有害事象等への対応のための濃度測定

- **有害事象の出現などで，１とは別に血中濃度を確認する必要があると担当医が判断していること。**

適合していることを確認されてから，採血を実施してください。

3. 採血の実施と検体の送付

１）薬物動態解析のための濃度測定

マラビロックとその他の併用薬全てについて**朝のくすりを服薬しない状態で患者さまに来院いただいて**，採血をお願いします（トラフ用採血）。採血の時刻を記録してその直後にマラビロックを含む朝のくすり全てを服用してください。その 2～4 時間後に再度採血を行い，時刻を記録してください（Cmax 用採血）。

２）有害事象等への対応のための濃度測定

採血のタイミング（トラフ，Cmax 付近など）は担当の先生が血中濃度を知りたい時点としてください。服薬後の時間の制限はありませんが，最終服薬時刻と採血時刻は記録してください。

３）採血と検体送付

採血は１回あたり全血４mL をヘパリン管に採取して採血後は速やかに（遅くとも２時間以内に），1,000～1,200g で遠心して血漿 1～2 mL を分離し，速やかに-20 ℃で凍結保存してください。**検体にはプロトコールに定められた方法で作成した登録番号と採血日時を明記してください。**血中濃度測定申込票（別紙様式）とともに，濃度測定を担当する国立病院機構名古屋医療センター薬剤科に送付してください。測定施設への検体到着が平日になるようご配慮ください（**土曜，日曜，祝日は検体受付ができません**）。

4. 薬物血中濃度の結果報告

検査の結果は検体受領後１日程度で出ます。検査結果は名古屋医療センターから，依頼医師と代表研究責任者のところに電子メールで送られます（検査結果送付先の申込票に必ず電子メールアドレスを記入してください)。結果を各施設から研究班に報告する必要はありません。

5. 血中濃度測定の結果に基づく休薬と用量変更

血中濃度測定の結果，休薬や用量変更が必要と判断された場合には，共同研究代表研究責任者と合議の上で，休薬や投与量の変更を行うことが出来ます。

この用紙を記入後，検体（凍結ヘパリン血漿　1～2mL）とともに名古屋医療センターに送付してください。

マラビロック血中濃度測定申込票

国立病院機構名古屋医療センター　薬剤科　高橋昌明殿

下記の患者のマラビロック血中濃度測定を申し込みます。なお，検査の費用は研究班の予算から支出されるため，患者が費用を負担する必要はないことを理解し，また患者にも説明して了承を得ています。

申込医師名		**病院名・住所**	
診療科名			
職名			
電話番号	（　　）	**FAX番号**	（　　）
E-mail			

患者登録番号・年齢・性別		（　　歳）M・F	
最近のCD4数 年　月　日	/μL	最近のHIV-RNA量 年　月　日	copies/mL

測定の目的 該当するものを○で囲む	薬物動態トラフ　・　薬物動態Cmax　・　有害事象		
採血日	年　月　日	**採血時刻**	時　分（AM・PM）
最後の服薬は？ 必ず記入してください	年　月　日　時　分（AM・PM）		

測定の目的 該当するものを○で囲む	薬物動態トラフ　・　薬物動態Cmax　・　有害事象		
採血日	年　月　日	**採血時刻**	時　分（AM・PM）
最後の服薬は？ 必ず記入してください	年　月　日　時　分（AM・PM）		

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SELZENTRY safely and effectively. See full prescribing information.

SELZENTRY (maraviroc) tablets
Initial U.S. Approval: 2007

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning
Hepatotoxicity has been reported which may be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE).
Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. (5.1)

----------INDICATIONS AND USAGE----------
SELZENTRY is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents (1).

Tropism testing is required for the appropriate use of SELZENTRY (1).

----------DOSAGE AND ADMINISTRATION----------

When given with potent CYP3A inhibitors (with or without potent CYP3A inducers) including PIs (except tipranavir/ritonavir), delavirdine (2, 7.1)	150 mg twice daily
With NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not potent CYP3A inhibitors or CYP3A inducers (2, 7.1)	300 mg twice daily
With potent CYP3A inducers including efavirenz (without a potent CYP3A inhibitor) (2, 7.1)	600 mg twice daily

A more complete list of coadministered drugs is listed in *Dosage and Administration (2)*

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 150 mg and 300 mg (3).

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Use caution when administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C (5.1)
- More cardiovascular events including myocardial ischemia and/or infarction were observed in patients who received SELZENTRY. Use with caution in patients at increased risk of cardiovascular events (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>8% incidence) which occurred at a higher frequency compared to placebo are upper respiratory tract infections, cough, pyrexia, rash, and dizziness (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Coadministration with CYP3A inhibitors, including protease inhibitors (except tipranavir/ritonavir) and delavirdine, will increase the concentration of SELZENTRY (7.1)
- Coadministration with CYP3A inducers, including efavirenz may decrease the concentration of SELZENTRY (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- SELZENTRY should only be used in pregnant women if the potential benefit justifies the potential risk to the fetus (8.1)
- There are no data available in pediatric patients; therefore SELZENTRY should not be used in patients <16 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised 6/2009

FULL PRESCRIBING INFORMATION*

*Sections or subsections omitted from the Full Prescribing Information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

Hepatotoxicity has been reported with SELZENTRY use. Evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE) prior to the development of hepatotoxicity may occur. Patients with signs or symptoms of hepatitis or allergic reaction following use of SELZENTRY should be evaluated immediately [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

SELZENTRY, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of SELZENTRY of 48 weeks duration. Both studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI, or enfuvirtide) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with SELZENTRY:

- Tropism testing is required for the appropriate use of SELZENTRY.
- Use of SELZENTRY is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a phase 2 study of this patient group.
- The safety and efficacy of SELZENTRY have not been established in treatment-naïve adult patients or pediatric patients.

2 DOSAGE AND ADMINISTRATION

The recommended dose of SELZENTRY differs based on concomitant medications due to drug interactions (see Table 1). SELZENTRY can be taken with or without food. SELZENTRY must be given in combination with other antiretroviral medications.

Table 1 gives the recommended dose adjustments [*see Drug Interactions (7.1)*].

Table 1 Recommended Dosing Regimen

Concomitant Medications	SELZENTRY Dose
Potent CYP3A inhibitors (with or without a CYP3A inducer) including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin • other potent CYP3A inhibitors (e.g., nefazodone, telithromycin)	150 mg twice daily
Other concomitant medications, including tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: • efavirenz • rifampin • carbamazepine, phenobarbital, and phenytoin	600 mg twice daily

3 DOSAGE FORMS AND STRENGTHS

- 150 mg blue, oval film-coated tablets debossed with "Pfizer" on one side and "MVC 150" on the other
- 300 mg blue, oval film-coated tablets debossed with "Pfizer" on one side and "MVC 300" on the other

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

A case of possible SELZENTRY-induced hepatotoxicity with allergic features has been reported in a study of healthy volunteers. In addition, an increase in hepatic adverse events with SELZENTRY was observed during studies of treatment-experienced subjects with HIV infection, although there was no overall increase in ACTG Grade 3/4 liver function test abnormalities [*see Adverse Reactions (6)*]. Discontinuation of SELZENTRY should be considered in any patient with signs or symptoms of hepatitis, or with increased liver transaminases combined with rash or other systemic symptoms.

The safety and efficacy of SELZENTRY have not been specifically studied in patients with significant underlying liver disorders. In studies of treatment-experienced HIV-infected subjects, approximately 6% of subjects were co-infected with hepatitis B and approximately 6% were co-infected with hepatitis C. Due to the small number of co-infected subjects studied, no conclusions can be drawn regarding whether they are at an increased risk for hepatic adverse events with SELZENTRY administration. However, caution should be used when administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C.

5.2 Cardiovascular Events

Use with caution in patients at increased risk for cardiovascular events. Eleven subjects (1.3%) who received SELZENTRY had cardiovascular events including myocardial ischemia and/or infarction during the Phase 3 studies [total exposure 609 patient-years (300 on once daily + 309 on twice daily SELZENTRY)], while no subjects who received placebo had such events (total exposure 111 patient-years). These subjects generally had cardiac disease or cardiac risk factors prior to SELZENTRY use, and the relative contribution of SELZENTRY to these events is not known.

When SELZENTRY was administered to healthy volunteers at doses higher than the recommended dose, symptomatic postural hypotension was seen at a greater frequency than in placebo. However, when SELZENTRY was given at the recommended dose in HIV subjects in Phase 3 studies, postural hypotension was seen at a rate similar to placebo (approximately 0.5%). Caution should be used when administering SELZENTRY in patients with a history of postural hypotension or on concomitant medication known to lower blood pressure.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including maraviroc. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as infection with *Mycobacterium* avium, cytomegalovirus, *Pneumocystis* jirovecii, *Mycobacterium* tuberculosis, or reactivation of *Herpes* simplex and *Herpes* zoster), which may necessitate further evaluation and treatment.

5.4 Potential Risk of Infection

SELZENTRY antagonizes the CCR5 co-receptor located on some immune cells, and therefore could potentially increase the risk of developing infections. The overall incidence and severity of infection, as well as AIDS-defining category C infections, was comparable in the treatment groups during the Phase 3 studies of SELZENTRY. While there was a higher rate of certain upper respiratory tract infections reported in the SELZENTRY arm compared to placebo (23% versus 13%), there was a lower rate of pneumonia (2% vs 5%) reported in patients receiving SELZENTRY. A higher incidence of Herpes virus infections (11 per 100 patient-years) was also reported in the SELZENTRY arm when adjusted for exposure compared to placebo (8 per 100 patient-years). Patients should be monitored closely for evidence of infections while receiving SELZENTRY.

5.5 Potential Risk of Malignancy

While no increase in malignancy has been observed with SELZENTRY, due to this drug's mechanism of action it could affect immune surveillance and lead to an increased risk of malignancy. Long-term follow-up is needed to more fully assess this risk.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hepatotoxicity *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Cardiovascular events *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of SELZENTRY is primarily based on 840 HIV-infected subjects who received at least one dose of SELZENTRY during two Phase 3 trials. A total of 426 of these subjects received the indicated twice daily dosing regimen.

Assessment of treatment-emergent adverse events is based on the pooled data from two studies in subjects with CCR5-tropic HIV-1 (A4001027 and A4001028). The median duration of maraviroc therapy for subjects in these studies was 48 weeks, with the total exposure on SELZENTRY twice daily at 309 patient-years versus 111 patient-years on placebo + OBT. The population was 89% male and 84% white, with mean age of 46 years (range 17-75 years). Subjects received dose equivalents of 300 mg maraviroc once or twice daily.

The most common adverse events reported with SELZENTRY twice daily therapy with frequency rates higher than placebo, regardless of causality, were upper respiratory tract infections, cough, pyrexia, rash, and dizziness. Additional adverse events that occurred with once daily dosing at a higher rate than both placebo and twice daily dosing were diarrhea, edema, influenza, esophageal candidiasis, sleep disorders, rhinitis, parasomnias, and urinary abnormalities. In these two studies, the rate of discontinuation due to adverse events was 5% for subjects who received SELZENTRY twice daily + optimized background therapy (OBT) as well as those who received placebo + OBT. Most of the adverse events reported were judged to be mild to moderate in severity. The data described below occurred with SELZENTRY twice daily dosing.

The total number of subjects reporting infections were 233 (55%) and 84 (40%) in the SELZENTRY twice daily and placebo groups, respectively. Correcting for the longer duration of exposure on SELZENTRY compared to placebo, the exposure-adjusted frequency (rate per 100 subject-years) of these events was 133 for both SELZENTRY twice daily and placebo.

Dizziness or postural dizziness occurred in 8% of subjects on either SELZENTRY and placebo, with 2 subjects (0.5%) on SELZENTRY permanently discontinuing therapy (1 due to syncope, 1 due to orthostatic hypotension) versus 1 subject on placebo (0.5%) permanently discontinuing therapy due to dizziness.

Treatment-emergent adverse events, regardless of causality, from A4001027 and A4001028 are summarized in Table 2. Selected events occurring at ≥2% of subjects and at a numerically higher rate in subjects treated with SELZENTRY are included; events that occurred at the same or higher rate on placebo are not displayed.

Table 2
Percentage of Subjects with Selected Treatment-Emergent Adverse Events (All Causality)
(≥2% on SELZENTRY and at a higher rate compared to placebo)

Studies A4001027 and A4001028 (Pooled Analysis, 48 Weeks)

	SELZENTRY Twice Daily*	Exposure-adjusted rate (per 100 pt-yrs) PYE=309**	Placebo	Exposure-adjusted rate (per 100 pt-yrs) PYE=111**
	N=426 (%)		N=209 (%)	
EYE DISORDERS				
Conjunctivitis	2	3	1	3
Ocular infections, inflammations and associated manifestations	2	3	1	2
GASTROINTESTINAL DISORDERS				
Constipation	6	9	3	6
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Pyrexia	13	20	9	17
Pain and discomfort	4	5	3	5
INFECTIONS AND INFESTATIONS				
Upper respiratory tract infection	23	37	13	27
Herpes Infection	8	11	4	8
Sinusitis	7	10	3	6
Bronchitis	7	9	5	9
Folliculitis	4	5	2	4
Pneumonia	2	3	5	10
Anogenital warts	2	3	1	3
Influenza	2	3	0.5	1
Otitis media	2	3	0.5	1
METABOLISM AND NUTRITION DISORDERS				
Appetite disorders	8	11	7	13
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Joint related signs and symptoms	7	10	3	5
Muscle pains	3	4	0.5	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED				
Skin neoplasms benign	3	4	1	3
NERVOUS SYSTEM DISORDERS				
Dizziness/postural dizziness	9	13	8	17
Paresthesias and dysesthesias	5	7	3	6
Sensory abnormalities	4	6	1	3
Disturbances in consciousness	4	5	3	6
Peripheral neuropathies	4	5	3	6

	SELZENTRY Twice Daily*	Exposure-adjusted rate (per 100 pt-yrs) PYE=309**	Placebo	Exposure-adjusted rate (per 100 pt-yrs) PYE=111**
PSYCHIATRIC DISORDERS				
Disturbances in initiating and maintaining sleep	8	11	5	10
Depressive disorders	4	6	3	5
Anxiety symptoms	4	5	3	7
RENAL AND URINARY DISORDERS				
Bladder and urethral symptoms	5	7	1	3
Urinary tract signs and symptoms	3	4	1	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Coughing and associated symptoms	14	21	5	10
Upper respiratory tract signs and symptoms	6	9	3	6
Nasal congestion and inflammations	4	6	3	5
Breathing abnormalities	4	5	2	5
Paranasal sinus disorders	3	4	0.5	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	11	16	5	11
Apocrine and eccrine gland disorders	5	7	4	7.5
Pruritus	4	5	2	4
Lipodystrophies	3	5	0.5	1
Erythemas	2	3	1	2
VASCULAR DISORDERS				
Vascular hypertensive disorders	3	4	2	4

* 300 mg dose equivalent
** PYE = patient years of exposure

Less Common Adverse Events
The following adverse events occurred in <2% of SELZENTRY-treated patients. These events have been included because of their seriousness and either increased frequency on SELZENTRY or are potential risks due to the mechanism of action. Events attributed to the patient's underlying HIV infection are not listed.

Blood and Lymphatic System: Marrow depression and hypoplastic anemia

Cardiac Disorders: unstable angina, acute cardiac failure, coronary artery disease, coronary artery occlusion, myocardial infarction, myocardial ischemia

Hepatobiliary Disorders: hepatic cirrhosis, hepatic failure, cholestatic jaundice, portal vein thrombosis

Infections and Infestations: endocarditis, infective myositis, viral meningitis, pneumonia, treponema infections, septic shock

Musculoskeletal and Connective Tissue Disorders: myositis, osteonecrosis, rhabdomyolysis, blood CK increased

Neoplasms benign, malignant and Unspecified (incl Cysts and Polyps): anal cancer, anaplastic large cell lymphomas T- and null-cell types, bile duct neoplasms malignant, endocrine neoplasms malignant and unspecified, basal cell carcinoma, lymphoma, metastases to liver, esophageal carcinoma, squamous cell carcinoma, tongue neoplasm (malignant stage unspecified)

Nervous System Disorders: cerebrovascular accident, convulsions and epilepsy, tremor (excluding congenital)

Laboratory Abnormalities

Table 3 shows the treatment-emergent Grade 3-4 laboratory abnormalities that occurred in >2% of patients receiving SELZENTRY.

Table 3
Maximum Shift in Laboratory Test Values (Without Regard to Baseline)
Incidence ≥2% of Grade 3-4 Abnormalities (ACTG Criteria)

Studies A4001027 and A4001028 (Pooled Analysis, 48 Weeks)

Laboratory Parameter Preferred Term, %	Limit	SELZENTRY Twice daily + OBT N =421* %	Placebo + OBT N =207* %
Aspartate aminotransferase	>5.0x ULN	4.8	2.9
Alanine aminotransferase	>5.0x ULN	2.6	3.4
Total bilirubin	>5.0x ULN	5.5	5.3
Amylase	>2.0x ULN	5.7	5.8
Lipase	>2.0x ULN	4.9	6.3
Absolute neutrophil count	<750/mm^3	4.3	2.4

* Percentages based on total patients evaluated for each laboratory parameter

7 DRUG INTERACTIONS

7.1 Effect of Concomitant Drugs on the Pharmacokinetics of Maraviroc

Maraviroc is a substrate of CYP3A and Pgp and hence its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes/transporters. Therefore, a dose adjustment may be required when maraviroc is coadministered with those drugs [see *Dosage and Administration (2)*].

Concomitant use of maraviroc and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of maraviroc with St. John's wort is expected to substantially decrease maraviroc concentrations and may result in suboptimal levels of maraviroc and lead to loss of virologic response and possible resistance to maraviroc.

For additional drug interaction information see *Clinical Pharmacology (12.3)*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with maraviroc in rats at exposures (AUC) approximately 20-fold higher and in rabbits at approximately 5-fold higher than human exposures at the recommended daily dose (up to 1000 mg/kg/day in rats and 75 mg/kg/day in rabbits). During the pre- and post-natal development studies in the offspring, development of the offspring, including fertility and reproductive performance, was not affected by the maternal administration of maraviroc.

However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SELZENTRY should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to SELZENTRY and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. It is not known whether maraviroc is secreted into human milk. Because of the potential for both HIV transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving SELZENTRY.

8.4 Pediatric Use

The pharmacokinetics, safety and efficacy of maraviroc in patients <16 years of age have not been established. Therefore, maraviroc should not be used in this patient population.

8.5 Geriatric Use

There were insufficient numbers of subjects aged 65 and over in the clinical studies to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering SELZENTRY in elderly patients, also reflecting the greater frequency of decreased hepatic and renal function, of concomitant disease and other drug therapy.

8.6 Renal Impairment

The safety and efficacy of maraviroc have not been specifically studied in patients with renal impairment, therefore maraviroc should be used with caution in this population. In the absence of metabolic inhibitors, renal clearance accounts for approximately 23% of total clearance of maraviroc. Maraviroc concentrations may be increased in patients with renal impairment, especially when CYP3A inhibitors are coadministered. Patients with a creatinine clearance of less than 50 mL/min who receive maraviroc and a CYP3A inhibitor may be at an increased risk of adverse effects related to increased maraviroc concentrations, such as dizziness and postural hypotension. Thus, patients with a creatinine clearance of less than 50 mL/min should receive maraviroc and a CYP3A inhibitor only if the potential benefit is felt to outweigh the risk, and they should be monitored for adverse effects.

8.7 Hepatic Impairment

Maraviroc is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because maraviroc concentrations may be increased. Maraviroc has not been studied in subjects with severe hepatic impairment. [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

8.8 Gender

Population pharmacokinetic analysis of pooled Phase 1/2a data indicated gender (female: n=96, 23.2% of the total population) does not affect maraviroc concentrations. Dosage adjustment based on gender is not necessary.

8.9 Race

Population pharmacokinetic analysis of pooled Phase 1/2a data indicated exposure was 26.5% higher in Asians (N=95) as compared to non-Asians (n=318). However, a study designed to evaluate pharmacokinetic differences between Caucasians (n=12) and Singaporeans (n=12) showed no difference between these two populations. Only 14 Black subjects were included in the population pharmacokinetic analysis. No dosage adjustment based on race is needed.

10 OVERDOSAGE

The highest dose administered in clinical studies was 1200 mg. The dose-limiting adverse event was postural hypotension, which was observed at 600 mg. While the recommended dose for SELZENTRY in patients receiving a CYP3A inducer without a CYP3A inhibitor is 600 mg twice daily, this dose is appropriate due to enhanced metabolism.

Prolongation of the QT interval was seen in dogs and monkeys at plasma concentrations 6 and 12 times, respectively, those expected in humans at the intended exposure of 300 mg equivalents twice daily. However, no significant QT prolongation was seen in the studies in treatment-experienced patients with HIV using the recommended doses of maraviroc or in a specific pharmacokinetic study to evaluate the potential of maraviroc to prolong the QT interval [*see Clinical Pharmacology (12.3)]*.

There is no specific antidote for overdose with maraviroc. Treatment of overdose should consist of general supportive measures including keeping the patient in a supine position, careful assessment of patient vital signs, blood pressure and ECG.

If indicated, elimination of unabsorbed active maraviroc should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since maraviroc is moderately protein-bound, dialysis may be beneficial in removal of this medicine.

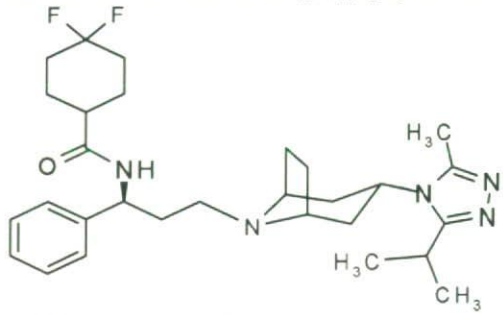
11 DESCRIPTION

SELZENTRY (maraviroc) is a selective, slowly reversible, small molecule antagonist of the interaction between human CCR5 and HIV-1 gp120. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells.

SELZENTRY is available as film-coated tablets for oral administration containing either 150 or 300 mg of maraviroc and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate (anhydrous), sodium starch glycolate, and magnesium stearate. The film coat [Opadry® II Blue (85G20583)] contains FD&C blue #2 aluminum lake, soya lecithin, polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc and titanium dioxide.

Maraviroc is chemically described as 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide.

The molecular formula is $C_{29}H_{41}F_2N_5O$ and the structural formula is:



Maraviroc is a white to pale colored powder with a molecular weight of 513.67. It is highly soluble across the physiological pH range (pH 1.0 to 7.5).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Maraviroc is an antiviral drug [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Exposure Response Relationship

The relationship between maraviroc mean predicted plasma trough concentration (C_{min}) (1-9 samples per patient taken on up to 7 visits) and virologic response was evaluated in 973 treatment-experienced HIV-1-infected subjects in studies A4001027 and A4001028. The C_{min}, baseline viral load, baseline $CD4^+$ cell count and overall sensitivity score (OSS) were found to be important predictors of virologic success (defined as viral load < 400 copies/mL at 24 weeks). Table 4 illustrates the proportion of patients with virologic success (%) within each C_{min} quartile for 150 mg twice daily and 300 mg twice daily groups.

Table 4 Patients with Virologic Success by C_{min} Quartile

	150 mg BID (with CYP3A inhibitors)			300 mg BID (without CYP3A inhibitors)		
	n	Median C_{min}	% patients with virologic success	n	Median C_{min}	% patients with virologic success
Placebo	160	-	30.6	35	-	28.6
Q1	78	33	52.6	22	13	50.0
Q2	77	87	63.6	22	29	68.2
Q3	78	166	78.2	22	46	63.6
Q4	78	279	74.4	22	97	68.2

Effects on Electrocardiogram

A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female volunteers was conducted with three single oral doses of maraviroc and moxifloxacin. The placebo-adjusted mean maximum (upper 1-sided 95% CI) increases in QTc from baseline after 100, 300 and 900 mg of maraviroc were –2 (0), -1 (1), and 1 (3) msec, respectively, and 13 (15) msec for moxifloxacin 400 mg. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec.

12.3 Pharmacokinetics

Table 5 Mean Maraviroc Pharmacokinetic Parameters

	Maraviroc dose	N	AUC_{12} (ng.h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Healthy volunteers (phase 1)	300 mg twice daily	64	2908	888	43.1
Asymptomatic HIV patients (phase 2a)	300 mg twice daily	8	2550	618	33.6
Treatment-experienced HIV patients (phase 3)*	300 mg twice daily	94	1513	266	37.2
	150 mg twice daily (+ CYP3A inhibitor)	375	2463	332	101

* The estimated exposure is lower compared to other studies possibly due to food effect, compliance and concomitant medications.

Absorption

Peak maraviroc plasma concentrations are attained 0.5-4h following single oral doses of 1-1200 mg administered to uninfected volunteers. The pharmacokinetics of oral maraviroc are not dose-proportional over the dose range.

The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg. Maraviroc is a substrate for the efflux transporter P-glycoprotein.