CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-187

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY TEAM LEADER MEMO

NDA: 22-187
DRUG: Intelence (Etravirine)
FORMULATION: 100 mg tablets
APPLICANT: Tibotec, Inc.

TEAM LEADER: Kellie Schoolar Reynolds, Pharm.D.
SUBMISSION DATE: July 18, 2007

Etravirine is an HIV non-nucleoside reverse transcriptase inhibitor (NNRTI). Etravirine 200 mg twice daily is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents.

The clinical pharmacology information reviewed in support of this application describes etravirine pharmacokinetics, the effect of food on etravirine exposure, mass balance, in vitro metabolism, drug-drug interactions, the effect of hepatic impairment, and the effect of gender and race. I concur with the conclusions of Dr. Vikram Arya's Clinical Pharmacology Review. He concludes the applicant provided adequate clinical pharmacology and biopharmaceutics information in this NDA, with one notable exception, described below.

Concern arose because all subjects in the Phase 3 trials (C206 and C216) received the HIV protease inhibitor darunavir/ritonavir as part of their optimized background regimen. The Phase 3 trials provide the majority of the safety and efficacy data for etravirine. A phase 1 drug interaction study indicated administration of darunavir/ritonavir with etravirine decreases etravirine plasma AUC (area under the plasma concentration vs time curve), on average, by 37%. Thus, the safety and efficacy data were collected from patients with reduced etravirine exposure. Because of the successful efficacy outcome of the studies, the reduced plasma exposure does not pose an efficacy concern. However, the applicant's initial NDA submission did not address the potential safety concerns for patients who take etravirine without darunavir/ritonavir. On average, etravirine exposure in patients who take etravirine without darunavir/ritonavir and without other drugs that alter etravirine exposure will be approximately 60% higher than exposure in subjects in the Phase 3 studies. If patients take etravirine without darunavir/ritonavir, but with drugs that increase etravirine exposure, etravirine exposure may be more than 60% higher than exposure in subjects in the Phase 3 studies. More details on the potential for higher etravirine concentrations are included below. *In addition, see the memo entitled "Additional exposure-safety analyses covering high exposure patients" by Pravin Jadhav, Ph.D., Pharmacometric Reviewer.*

Phase 1 drug interaction data indicate the protease inhibitors atazanavir/ritonavir and lopinavir/ritonavir increase etravirine exposure, so coadministration with either of these protease inhibitors may lead to etravirine exposure more than 60% higher than exposure in subjects in the Phase 3 studies.

Atazanavir/Ritonavir

The phase 1 drug interaction data indicate atazanavir/ritonavir 300/100 mg once daily increases mean etravirine AUC by 30%. Thus, the mean AUC of etravirine after co-administration of etravirine with atazanavir/ritonavir is anticipated to be approximately 100 % higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. The full impact of the mean 100% increase in etravirine exposure was not evaluated by the review team because the effect of etravirine on atazanavir concentrations does not allow co-administration of these drugs. Administration of etravirine with atazanavir/ritonavir 300/100 once daily decreases mean atazanavir Cmin by 38%. This decrease in C_{min} of atazanavir in the presence of etravirine is greater than the decrease in the mean C_{min} of atazanavir in the presence of tenofovir. Because the mean C_{min} of atazanavir (when given with low dose ritonavir) in the presence of tenofovir represents the lowest mean C_{min} for which efficacy data are available, co-administration of

atazanavir/ritonavir with etravirine may lead to sub-therapeutic exposures of atazanavir. The addition of 100 mg atazanavir, to provide a total dose of atazanavir/ritonavir 400/100mg, is not acceptable because etravirine concentrations may be increased by a greater extent than with atazanavir/ritonavir 300/100 mg.

Because for the above concerns, the following language is proposed in the Drug Interaction section of the label:
Concomitant use of INTELENCE™ with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with atazanavir/ritonavir is anticipated to be approximately 100 % higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. Therefore, INTELENCE™ and atazanavir/ritonavir should not be co-administered.

Lopinavir/ritonavir
The phase 1 drug interaction data indicate lopinavir/ritonavir 400/100 mg bid increases mean etravirine AUC by 17%. Thus, the mean AUC of etravirine after co-administration of etravirine with lopinavir/ritonavir is anticipated to be approximately 85 % higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. Etravirine does not alter lopinavir concentrations.

The review team evaluated the following information to determine whether the coadministration of etravirine with lopinavir/ritonavir is acceptable:

1. Safety and exposure data are available for subjects in Phase 2b studies who received etravirine with lopinavir/ritonavir. However, the Phase 2b studies used formulation 035, rather than formulation 060 (Phase 3 and to-be-marketed formulation). Formulation 035 has lower bioavailability than formulation 060 and etravirine plasma concentrations for subjects who received etravirine and lopinavir/ritonavir in Phase 2b are not higher than the exposures observed in Phase 3 (etravirine plus darunavir/ritonavir).

2. Anticipated distribution of etravirine exposure across a population that receives etravirine (formulation 060, 200 mg bid) with lopinavir/ritonavir, as compared to the distribution of exposure observed in phase 3. This analysis was achieved by multiplying the highest etravirine AUC value observed for each subject with pharmacokinetic data in Phase 3 by a factor of 1.85. Results are summarized below.

	Observation from Phase 3 data N= 582	Multiply each AUC by 1.85, to account for administration of lopinavir/ritonavir rather than darunavir/ritonavir.
AUC_{12} (ng*hr/mL) range	145 - 69997	268 – 129,495
% subjects with AUC > 70,000	0	0.51%
% subjects with AUC between 50,000 to 70,000	0.34%	0.51%
% subjects with AUC between 30,000 to 50,000	0.69%	4.47%
% subjects with AUC between 10,000 to 30,000	16.67%	48.97%

As noted in the table above, AUC greater than 30,000 is rare when etravirine is administered with darunavir/ritonavir or with lopinavir/ritonavir. However, almost 50% of patients who receive etravirine with lopinavir/ritonavir may have etravirine AUC between 10,000 to 30,000, while AUCs in this range were observed for 17% of subjects in phase 3. The safety database for etravirine

exposures that may be observed in approximately 50% of patients who receive etravirine with lopinavir/ritonavir is limited. However, due to variability in etravirine pharmacokinetics, the etravirine exposure in most patients who receive etravirine with lopinavir/ritonavir will be not higher than that observed in at least a small percentage of subjects in Phase 3.

The review team decided to allow co-administration of etravirine with lopinavir/ritonavir because there are no obvious safety concerns and it is important to provide health care providers flexibility in the selection of antiretroviral regimens for individual patients.

The label will include the following recommendation regarding the interaction between etravirine and lopinavir/ritonavir:

The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be approximately 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. therefore, INTELENCE™ and lopinavir/ritonavir may be co-administered with caution.

Administration of etravirine in antiretroviral regimens that do not increase or decrease etravirine plasma exposure

If etravirine is administered as part of an antiretroviral regimen that does not include drugs which increase or decrease etravirine concentrations (for example, a regimen that includes raltegravir), the etravirine exposure may be approximately 60% higher than exposure in subjects in the Phase 3 studies. The exercise conducted for etravirine plus lopinavir/ritonavir supports these regimens.

The label includes language in the Drug Interaction section to indicate the lower exposure observed in the phase 3 studies:

The mean systemic exposure (AUC) of etravirine was reduced by approximately 37% when INTELENCE™ was co-administered with darunavir/ritonavir. Because all subjects in the Phase 3 trials received darunavir/ritonavir as part of the background regimen and etravirine exposures from these trials were determined to be safe and effective, INTELENCE™ and darunavir/ritonavir can be co-administered without any dose adjustments.

Post marketing commitments

The clinical review team drafted the following post marketing commitment to collect additional safety data in subjects who receive etravirine as part of a regimen that does not include darunavir/ritonavir. The commitment was accepted by the applicant, following negotiations.

Conduct a 48-week clinical study of treatment-experienced patients enrolling at least 200 subjects to evaluate safety and pharmacokinetics of etravirine when given with drug combinations that do not contain darunavir/rtv. Submit an interim report including analyses of 12-week safety data and supportive efficacy data with the Safety Update submission for the traditional approval supplemental new drug application for etravirine.

Protocol submission: July 2008
Final study report submission: July 2011

In addition to post marketing commitments from the clinical review team, the clinical pharmacology reviewers drafted the following four commitments for drug interaction studies. Following discussion with the applicant, the first two were finalized and the other two were deleted.

1. Conduct an *in vivo* drug-drug interaction study between etravirine and fluconazole (accepted as PMC)

2. Conduct an *in vivo* drug-drug interaction study between etravirine and buprenorphine/naloxone. (accepted as PMC)

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/s/

Kellie Reynolds
1/17/2008 12:54:26 PM
BIOPHARMACEUTICS

John Lazor
1/17/2008 04:58:39 PM
BIOPHARMACEUTICS

PHARMACOMETRICS MEMO

NDA Number:	22187
Generic Name:	Etravirine (TMC125)
Proposed Indication:	Treatment experienced subjects infected with HIV-1
Sponsor:	Tibotec
Type of Submission:	NME
Pharmacometrics (PM) Reviewer:	Pravin Jadhav Ph.D.
Clinical Pharmacology Team Leader:	Kellie S. Reynolds Pharm.D.
PM Team Leader:	Jogarao Gobburu Ph.D.
Proposed Dosage and Administration:	200 mg BID

Additional exposure-safety analyses focusing on high etravirine exposure subjects

This document serves as an addendum to the Clinical Pharmacology/Pharmacometrics review dated January 16, 2008.

Executive summary

1. The highest quartile of etravirine exposure in DUET (C206 and C216) trials covers expected exposure if etravirine is coadministered with drugs that increase etravirine exposure, for example, lopinavir/ritonavir.
2. The comparison of adverse event profiles was made between subjects in the highest exposure quartile and subjects in other 3 exposure quartiles. There were differences in hypersensitivity (1.4% vs 0%), hypetriglyceridemia (4.1% vs 2.8%), peripheral neuropathy (5.5% vs 2.6%), anxiety (4.8% vs 1.9%), rash (11.7% vs 7.9%), grade 3 serum creatinine elevation (5% vs 0.9%). See Dr. Charu Mullick's review for clinical implications of these findings. In conclusion, there were no major safety concerns in subjects with high exposure. Thus, although limited, some safety experience was available at high exposure if etravirine is coadministered with drugs that increase etravirine exposure, for example, lopinavir/ritonavir. According to Dr. Mullick, drugs that increase etravirine exposure should be co-administered with etravirine with caution. Prescribers and users are alerted to this information in the Highlights section of the package insert, with additional details about specific drug interactions in the Full Prescribing Information in the package insert.

Etravirine exposure

Concern arose because all subjects in the Phase 3 trials (C206 and C216) received the HIV protease inhibitor darunavir/ritonavir as part of their optimized background regimen. A phase 1 drug interaction study indicated administration of darunavir/ritonavir with etravirine decreases etravirine plasma AUC (area under the plasma concentration vs time curve), on average, by 37%. If subjects take etravirine without darunavir/ritonavir, but with drugs that increase etravirine exposure, etravirine exposure may be higher than observed in DUET studies (for example, potentially 85% higher with lopinavir/ritonavir in the background regimen). See Dr. Kellie Reynold's team leader memo (dated January 17, 2008) covering these aspects of drug-drug interaction data.

The question of interest was:

"Are exposure achieved in DUET trials cover expected exposure if etravirine is coadministered with drugs that increase etravirine exposure, for example, lopinavir/ritonavir?"

Table 1 summarizes etravirine exposure in two phase IIb trials (C203 and C223) when etravirine was combined with lopinavir/ritonavir (formulation TF035) and exposure in the DUET trials. The data are divided based on exposure quartiles to differentiate high exposure group from low exposure groups.

Table 1: Comparison of etravirine exposure (Geometric mean AUC, hr•ng/mL) in two phase IIb trials (C203 and C223) when etravirine was combined with lopinavir/ritonavir (LPV) irrespective of atazanavir (ATZ) use and exposure in DUET trials

		Mean±SD	Median	IQR	Range
DUET trials	Etravirine Highest Exposure Quartile	10474.8±4988.4	8882.4	7417.7-12187.6	6530.9-64164.9
	Etravirine Other 3 Exposure Quartile	3776.3±1474.1	3826.4	2717.4-4853.4	145.3-6528.2
Phase IIb trials	Etravirine +LPV+/-ATZ	5816.6±5587	3811.6	2210.9-6828.2	707.7-32673

When etravirine was combined with lopinavir/ritonavir in phase IIb trials, the exposure were lower (median: 3811.6 vs 8882.4 in the highest exposure quartile) than exposure observed in DUET trials. However, the formulation (TF035) used in the phase IIb trial had lower bioavailability than the formulation (F060) used in DUET trials.

Thus, DUET trials offer safety and effectiveness data at exposure higher than exposure seen in etravirine other trials. If drugs such as, lopinavir/ritonavir and/or absence of darunavir/ritonavir are expected to increase etravirine exposure beyond DUET trial experience, no such data are available. However, expected exposure for above scenarios can be derived based on exposure in DUET trials. Also, the safety and effectiveness data from the highest exposure quartiles could be used to support administration of such drugs, if expected and highest quartile exposure are comparable.

The analysis was done to derive expected distribution of etravirine exposure across a population that might receive etravirine (formulation 060, 200 mg bid) with lopinavir/ritonavir, as compared to the distribution of exposure observed in phase 3. This analysis was achieved by multiplying the highest etravirine AUC value observed for each subject with pharmacokinetic data in Phase 3 by a factor of 1.85 (See Dr. Kellie Reynold's team leader memo (dated January 17, 2008) as shown in Figure 1. As expected, the distribution was shifted to right with more subjects appearing in the high concentration group. Table 2 illustrates comparison of observed and expected etravirine exposure by different AUC cut-off. In the observed data, AUC greater than 30,000 was rare when etravirine is administered with darunavir/ritonavir or with lopinavir/ritonavir. However, almost 50% of subjects who receive etravirine with lopinavir/ritonavir may have etravirine AUC between 10,000 to 30,000, while AUCs in this range were observed for 17% of subjects in phase 3. Important to note, this analyses assumed exposure increase in all subjects, however, only a certain fraction of the population will receive lopinavir/ritonavir. Therefore, numbers presented here are the worst case estimates and it is likely to observe exposures between 10,000-30,000 in 17-50% of the subjects to be treated with etravirine. The next analyses will cover review of safety data in the highest quartile group (AUC range: 6530.9-64164.9 hr•ng/mL) and comparison with other etravirine treated patients.

Figure 1: Expected etravirine exposure in a population that might receive etravirine (formulation 060, 200 mg bid) with lopinavir/ritonavir (AUC>6000 hr•ng/mL are shown for clarity, as the concerns are around high exposure groups)

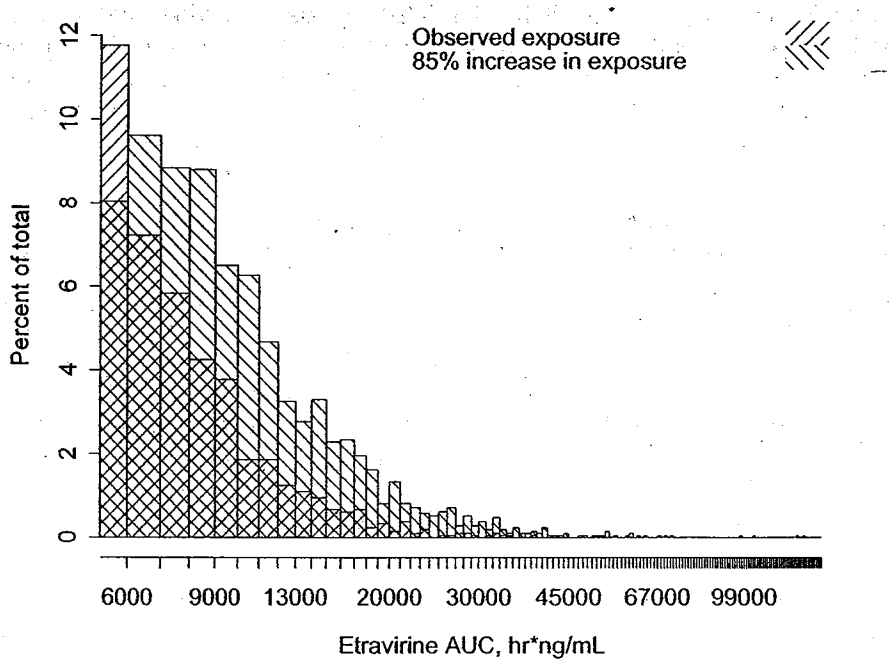

Table 2: Comparison of expected travirine exposure in a population that might receive etravirine (formulation 060, 200 mg bid) with lopinavir/ritonavir and exposure observed in DUET trials

	Observation* from Phase 3 data N= 577	Multiply each AUC by 1.85, to account for administration of lopinavir/ritonavir rather than darunavir/ritonavir†
AUC_{12} (ng*hr/mL) range	145 – 69997	268 – 129,495
% subjects with AUC > 70,000	0	0.52%
% subjects with AUC between 50,000 to 70,000	0.35%	0.69%
% subjects with AUC between 30,000 to 50,000	0.69%	4.51%
% subjects with AUC between 10,000 to 30,000	16.81%	49.39%

In conclusion, the highest quartile of etravirine exposure in DUET (C206 and C216) trials covers expected exposure if etravirine is coadministered with drugs that increase etravirine exposure, for example, lopinavir/ritonavir.

* If multiple PK measurement were available, highest individual predicted AUC (model run 75) was considered to be the exposure for a given subject.
† assumes 1.85 fold increase in exposure in all subjects receiving etravirine. The % subjects who will actually receive drugs that increase etravirine exposure need to be accounted for.

Exposure-safety analyses

Subjects receiving etravirine in DUET trials were categorized into quartiles of etravirine exposure. Pharmacokinetic data were available for 576[‡] of 599 etravirine-treated subjects. Adverse events and laboratory results were compared between 145 subjects in the highest quartile and 431 subjects in the lower three quartiles (lower quartiles). Additional comparisons with placebo-treated subjects in the Phase 3 trials (604 subjects), subjects receiving etravirine with LPV/rtv in Phase IIb trials (147 subjects) and all subjects treated with etravirine in Phase IIb trials (196 subjects) were performed.

Safety analyses of subjects in the highest quartile of etravirine exposures consist of comparisons of common adverse events and evaluation of select laboratory abnormalities.

Appendix I lists comparison of adverse events among the highest quartile, lower 3 quartiles of etravirine exposure and placebo treated subjects in DUET trials. Also included are etravirine+LPV and all etravirine treated subjects in phase IIb trials[§] See Dr. Muliick's review for common adverse events observed in 3 or more subjects in the highest quartile. Rash was the most frequent AE reported in the highest quartile group and a modest increase in rash (any type) in subjects in the highest quartile (21.4%) was noted as compared to subjects in lower quartiles (15.8%) and the placebo arm (13.5%). Additionally, there were differences in hypersensitivity (1.4% vs 0%), hypetriglyceridemia (4.1% vs 2.8%), peripheral neuropathy (5.5% vs 2.6%), anxiety (4.8% vs 1.9%).

Appendix II lists comparison of treatment-emergent abnormalities of select laboratory tests among the highest quartile, lower 3 quartiles of etravirine exposure and placebo treated subjects in DUET trials. The events of interest (grade 3 and 4) are highlighted. There proportion of patients with grade 3 serum creatinine elevation was more in the highest quartile compared to lower 3 quartiles (5% vs 0.9%).

See Dr. Charu Mullick's review for clinical implications of these findings. The review also includes analyses of number of deaths and permanent discontinuations with respect to exposure quartiles. In conclusion, there were no major safety concerns in subjects with high exposure. Thus, although limited, some safety experience was available at expected exposure if etravirine is coadministered with drugs that increase etravirine exposure, for example, lopinavir/ritonavir.

According to Dr. Mullick, drugs that increase etravirine exposure should be co-administered with etravirine with caution. Prescribers and users are alerted to this information in the Highlights section of the package insert, with additional details about specific drug interactions in the Full Prescribing Information in the package insert.

[‡] PK data were available for 577 subjects, however, one of the subjects (C216-0815) was not considered for as a part of ITT database used for safety and effectiveness analyses.

[§] For phase IIb trials, the 400mg BID (TF035) data were excluded from the analyses as the dose is lower than to be marketed dose of 200mg BID (F060).

Appendices

Appendix I

Comparison of adverse events among the highest quartile, lower 3 quartiles of etravirine exposure and placebo treated subjects in DUET trials. Also included are etravirine+LPV and all etravirine treated subjects in phase IIb trials.[**]

Body system or organ class	Dictionary derived AE term	Highest Quartile (DUET) N=145 (%)	Lower Quartiles (DUET) N=431 (%)	Placebo Subjects (DUET) N=604 (%)	Etravirine and LPV (Phase IIb) N=147 (%)	Etravirine (Phase IIb) N=196 (%)
	ANAEMIA	5.5	3.9	4.5	0.7	1
	ANAEMIA NOS				0.7	0.5
	EOSINOPHILIA	0.7	0	0		
	FEBRILE NEUTROPENIA	0	0.2	0		
	GRANULOCYTOPENIA	0	0	0.2		
	GRANULOCYTOSIS	0	0	0.2		
	HAEMOLYTIC ANAEMIA	0.7	0	0		
	IRON DEFICIENCY ANAEMIA	0	0	0.2	0.7	0.5
BLOOD AND LYMPHATIC SYSTEM DISORDERS	LEUKOCYTOSIS	0	0.5	0.2		
	LEUKOPENIA	0	0	1.5		
	LYMPH NODE PAIN	0	0.2	0		
	LYMPHADENOPATHY	4.1	3.9	4.8	10.9	10.2
	LYMPHOPENIA	0	0	0.2		
	NEUTROPENIA	2.8	1.9	4.1	1.4	1
	PANCYTOPENIA	0.7	0	0.2	0.7	0.5
	POLYCYTHAEMIA				0.7	0.5
	SPLENOMEGALY	0	0.2	0.2		
	THROMBOCYTOPENIA	0.7	1.6	1.3	1.4	1
	THROMBOTIC MICROANGIOPATHY	0	0	0.2		
CARDIAC DISORDERS	ACUTE CORONARY SYNDROME	0	0.2	0		
	ACUTE MYOCARDIAL INFARCTION	0.7	0.5	0		
	ANGINA PECTORIS	0	0.5	0.2		
	ANGINA PECTORIS AGGRAVATED				0.7	0.5
	ANGINA UNSTABLE	0.7	0	0		
	AORTIC VALVE DISEASE	0	0.2	0		
	AORTIC VALVE STENOSIS	0	0.2	0		
	ARRHYTHMIA	0	0.2	0		

[**] Data source for DUET trials- aead.xpt, cmad.xpt, dmad.xpt and run75 NONMEM POPPK analyses; for phase IIb trials- aead.xpt, cmad.xpt and ppad.xpt. ITT population was used in the analyses. The blank cells mean the AE term did not appear in the database. Data from "TREATMENT" phase were included.

	ATRIAL FIBRILLATION	0	0.2	0		
	ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	0	0.2		
	BRADYCARDIA	0	0.2	0.3		
	BRADYCARDIA NOS				0.7	0.5
	BUNDLE BRANCH BLOCK NOS				0.7	0.5
	BUNDLE BRANCH BLOCK RIGHT	0	0.2	0	0.7	1
	CARDIAC ARREST	0	0	0.3		
	CARDIAC FAILURE CONGESTIVE	0	0.2	0		
	CARDIAC VALVE DISEASE				0.7	0.5
	CARDIOGENIC SHOCK	0	0.2	0		
	CARDIOMYOPATHY	0	0	0.2		
	CARDIOVASCULAR DISORDER NOS				0.7	0.5
	CORONARY ARTERY DISEASE	0	0	0.2		
	CORONARY ARTERY DISEASE NOS				0.7	0.5
	CORONARY ARTERY INSUFFICIENCY	0	0	0.2		
	CORONARY ARTERY OCCLUSION				0.7	0.5
	CORONARY ARTERY STENOSIS	0	0	0.2		
	DIASTOLIC DYSFUNCTION	0.7	0	0		
	EXTRASYSTOLES	0	0.2	0		
	HYPERTENSIVE HEART DISEASE	0	0.2	0		
	MYOCARDIAL INFARCTION	0	0.7	0.2		
	MYOCARDIAL ISCHAEMIA	0	0	0.7		
	PALPITATIONS	0.7	0	0.5	1.4	1.5
	RIGHT VENTRICULAR FAILURE	0	0.2	0		
	SINUS BRADYCARDIA	0	0	0.3		
	SINUS TACHYCARDIA	0	0.2	0.2	0.7	0.5
	SUPRAVENTRICULAR EXTRASYSTOLES	0	0.2	0		
	TACHYCARDIA	0	0.5	0.5	1.4	1.5
	TACHYCARDIA NOS				0	0.5
	VENTRICULAR EXTRASYSTOLES				0.7	0.5
	VENTRICULAR TACHYCARDIA	0	0	0.2		
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	PIGMENTED NAEVUS				0.7	0.5
	PORPHYRIA NON-ACUTE	0	0	0.2		
EAR AND LABYRINTH DISORDERS	CERUMEN IMPACTION	2.1	0.5	0.8	0.7	0.5
	DEAFNESS NOS				0.7	0.5
	DEAFNESS UNILATERAL	0	0.2	0		
	EAR CONGESTION				0.7	0.5
	EAR INFECTION NOS				0	1
	EAR PAIN	0.7	0.9	0.3	0.7	1
	HYPOACUSIS	0	0	0.3		

	OTITIS MEDIA SEROUS ACUTE NOS				0	0.5
	SENSATION OF BLOCK IN EAR				0.7	0.5
	SUDDEN HEARING LOSS	0	0	0.2		
	TINNITUS	0.7	0.7	0.7	0.7	0.5
	VERTIGO	0	0.5	1	0.7	0.5
	VERTIGO POSITIONAL	0	0.2	0.3		
	ADRENAL INSUFFICIENCY	0	0	0.2		
	HYPERPARATHYROIDISM PRIMARY	0	0	0.2		
	HYPOGONADISM	0	0.5	0		
ENDOCRINE DISORDERS	HYPOTHYROIDISM	0	0.2	0.3		
	INSULIN-REQUIRING TYPE II DIABETES MELLITUS				0.7	0.5
	SECONDARY HYPERTHYROIDISM	0.7	0	0		
	THYROID NODULE				0.7	0.5
	THYROIDITIS SUBACUTE	0.7	0	0		
EYE DISORDERS	ABNORMAL SENSATION IN EYE				0.7	0.5
	ASTIGMATISM	0	0	0.2		
	BLEPHARITIS	0	0.5	0		
	BLEPHAROSPASM	0	0	0.2		
	BLINDNESS	0	0.2	0	0.7	0.5
	CATARACT	0	0.2	0.2	0.7	0.5
	CHALAZION	0.7	0	0	0.7	0.5
	CONJUNCTIVAL HAEMORRHAGE	0.7	0	0		
	CONJUNCTIVAL HYPERAEMIA	0.7	0.2	0.5		
	CONJUNCTIVITIS	1.4	1.2	1.2	2	3.1
	CONJUNCTIVITIS ALLERGIC	0	0	0.2		
	CORNEAL LESION	0.7	0	0		
	DIPLOPIA	0.7	0	0		
	DRY EYE	1.4	0	0.3		
	DRY EYE NOS				0.7	0.5
	DUANE'S SYNDROME				0.7	0.5
	EYE DISORDER	0	0	0.2		
	EYE INFECTION NOS				0.7	0.5
	EYE INFLAMMATION	0.7	0	0		
	EYE IRRITATION	0.7	0	0	0.7	1
	EYE PAIN	0	0.2	0.5	1.4	1
	EYE PRURITUS	0.7	0.2	0.2	0.7	0.5
	EYE SWELLING	0.7	0.2	0.2	0.7	0.5
	EYELID OEDEMA	0	0	0.5	0.7	1
	EYELIDS PRURITUS	0	0	0.2		
	HORDEOLUM				1.4	1
	IRIDOCYCLITIS	0	0	0.2		
	IRITIS	0	0.2	0		

	KERATITIS	0	0	0.2	0	0.5
	KERATOCONJUNCTIVITIS SICCA				0	0.5
	LACRIMATION INCREASED	0	0.2	0.2		
	MACULAR DEGENERATION	0	0	0.2		
	OCULAR HYPERAEMIA	0	0.2	0		
	OCULAR ICTERUS				0.7	0.5
	OPTIC NEUROPATHY	0	0.2	0		
	PHOSPHENES				0	0.5
	PHOTOPHOBIA	0.7	0.2	0	0.7	1
	PHOTOPSIA	0	0	0.2		
	PUPIL FIXED	0	0	0.2		
	RETINAL DETACHMENT	0	0.2	0.2		
	RETINAL EXUDATES	0	0	0.2		
	RETINAL HAEMORRHAGE	0	0	0.2		
	SCLERAL HYPERAEMIA	0	0	0.2		
	STRABISMUS	0	0	0.2		
	VISION BLURRED	2.1	0.5	0.5	4.1	3.6
	VISUAL ACUITY REDUCED	1.4	0.5	0.5	0.7	1
	VISUAL DISTURBANCE	0	0.5	0		
	VITREOUS FLOATERS				0.7	0.5
GASTROINTESTINAL DISORDERS	ABDOMINAL DISCOMFORT	0.7	0.7	0.3	2.7	2
	ABDOMINAL DISTENSION	2.1	2.3	2.3	5.4	5.1
	ABDOMINAL HAEMATOMA	0.7	0	0		
	ABDOMINAL HERNIA	0.7	0	0	1.4	1
	ABDOMINAL PAIN	2.1	4.4	3.1	2	2
	ABDOMINAL PAIN LOWER	0	1.2	0.2		
	ABDOMINAL PAIN NOS				14.3	13.8
	ABDOMINAL PAIN UPPER	4.1	2.8	2.3	1.4	1.5
	ABDOMINAL TENDERNESS	0	0.2	0.3	2	1.5
	ABNORMAL FAECES				1.4	1
	ABSCESS ORAL				0.7	0.5
	ANAL DISCOMFORT	0	0.2	0.5	0.7	0.5
	ANAL FISSURE	0.7	0.5	0		
	ANAL FISTULA	0	0	0.2		
	ANAL HAEMORRHAGE	0.7	0.7	0.2		
	ANAL INFECTION NOS				0.7	0.5
	ANAL INJURY				0.7	0.5
	ANAL SKIN TAGS	0.7	0	0	0.7	0.5
	ANAL ULCER	0.7	0	0.3		
	ANOGENITAL DYSPLASIA	0	0.2	0.2		
	ANORECTAL DISORDER	0	0	0.3		
	APHTHOUS STOMATITIS	0.7	1.2	0.8	3.4	3.6

APPENDIX DISORDER	0	0	0.2		
APTYALISM	0	0.2	0		
ASCITES	0	0	0.2	0.7	0.5
BOWEL MOVEMENT IRREGULARITY	0	0	0.2		
BREATH ODOUR	0	0	0.2		
CHAPPED LIPS				0.7	0.5
CHEILITIS	1.4	0.7	0.8	0.7	0.5
CHEILOSIS	0	0	0.2		
COLITIS	0	0.5	0.3		
COLONIC POLYP				0.7	0.5
CONSTIPATION	2.1	1.6	2.2	5.4	5.1
DENTAL CARIES	0	0	0.5	0.7	0.5
DIARRHOEA	15.2	15.5	20.4	8.2	8.7
DIARRHOEA AGGRAVATED				1.4	1
DIARRHOEA HAEMORRHAGIC				0	0.5
DIARRHOEA NOS				19	16.8
DRY MOUTH	1.4	0.9	0.3	3.4	4.6
DYSPEPSIA	1.4	1.6	3.6	3.4	3.1
DYSPEPSIA AGGRAVATED				0	0.5
DYSPHAGIA	0	0.9	0.3	4.1	4.6
DYSPHAGIA AGGRAVATED				0.7	0.5
ENTERITIS	0	0	0.3		
ENTEROCOLITIS				0.7	0.5
EPIGASTRIC DISCOMFORT	0.7	0	0		
FAECAL INCONTINENCE	0	0	0.2		
FAECAL VOLUME INCREASED	0	0	0.2		
FAECALOMA	0	0.2	0		
FAECES DISCOLOURED				0.7	0.5
FAECES PALE				1.4	1
FLATULENCE	2.8	3.7	3.5	10.2	9.2
FOOD POISONING	0.7	0.2	0.2	1.4	1
FOOD POISONING NOS				0	0.5
FREQUENT BOWEL MOVEMENTS	0	0.2	0	0.7	0.5
GASTRIC DISORDER	0	0.2	0		
GASTRIC ULCER	0.7	0.2	0		
GASTRITIS	2.1	1.9	0.8		
GASTROENTERITIS NOS				3.4	3.1
GASTROENTERITIS VIRAL NOS				0.7	0.5
GASTROINTESTINAL DISORDER	0	0.2	0.2		
GASTROINTESTINAL HAEMORRHAGE	0	0	0.3		
GASTROINTESTINAL INFECTION NOS				0.7	0.5
GASTROINTESTINAL MOTILITY	0	0	0.2		

DISORDER					
GASTROOESOPHAGEAL REFLUX DISEASE	2.1	1.6	1.8	3.4	3.6
GINGIVAL BLEEDING				0.7	0.5
GINGIVAL HYPERPLASIA	0	0.2	0		
GINGIVAL PAIN				0.7	0.5
GINGIVAL RECESSION	0	0.2	0		
GINGIVITIS	1.4	0.7	0.5	2	1.5
GLOSSITIS	0	0.2	0		
GLOSSODYNIA	0.7	0	0		
HAEMATEMESIS	0.7	0.2	0		
HAEMATOCHEZIA	0	0	0.3		
HAEMORRHOIDS	2.1	2.1	1	2.7	2
HIATUS HERNIA	0	0.5	0	0.7	0.5
HYPERACIDITY				0	0.5
HYPOAESTHESIA ORAL	0	0	0.3	0.7	0.5
ILEUS	0	0	0.3		
INGUINAL HERNIA	0.7	0.2	0		
INGUINAL HERNIA NOS				0.7	0.5
INTESTINAL PERFORATION	0	0	0.2		
IRRITABLE BOWEL SYNDROME	0	0.2	0.2		
LEUKOPLAKIA ORAL	0.7	0.2	0		
LEUKOPLAKIA ORAL NOS				1.4	1
LIP PAIN				0.7	0.5
LIP ULCERATION	0	0	0.2		
LOOSE STOOLS				2.7	2.6
MALABSORPTION	0	0.2	0		
MELAENA	0.7	0	0	0.7	0.5
MOUTH ULCERATION	1.4	0.5	0.7	0.7	1.5
NAUSEA	11.7	13.2	11.1	21.1	20.4
ODYNOPHAGIA	0.7	0	0.5	1.4	1.5
OESOPHAGEAL OBSTRUCTION	0	0	0.2		
OESOPHAGEAL VARICES HAEMORRHAGE	0	0	0.2		
OESOPHAGITIS	0	0	1		
OESOPHAGITIS NOS				0.7	0.5
ORAL LICHEN PLANUS	0	0	0.2		
ORAL PAIN	0	0.2	0		
ORAL SOFT TISSUE DISORDER	0	0	0.2		
ORAL SOFT TISSUE DISORDER NOS				0	0.5
PALATAL DISORDER	0	0.5	0		
PANCREATIC DISORDER NOS				0	0.5
PANCREATIC INSUFFICIENCY	0	0	0.2		

PANCREATIC MASS	0	0.2	0		
PANCREATIC PSEUDOCYST	0	0	0.2		
PANCREATITIS	0	0.7	0.3	0.7	0.5
PANCREATITIS DUE TO BILIARY OBSTRUCTION				0.7	0.5
PANCREATITIS NOS				1.4	1.5
PANCREATITIS RELAPSING				0	0.5
PAROTID DUCT CYST	0	0	0.2		
PAROTID GLAND ENLARGEMENT	0	0	0.5		
PERIANAL ERYTHEMA	0	0	0.2		
PERIPROCTAL SWELLING				0.7	0.5
PERLECHE				0.7	0.5
PROCTALGIA	0.7	0.2	0.3	0.7	0.5
PROCTITIS	0	0	0.5		
PROCTITIS HERPES				0.7	0.5
PROCTITIS NOS				0.7	0.5
PRURITUS ANI				0.7	0.5
RECTAL DISCHARGE	0.7	0.2	0		
RECTAL HAEMORRHAGE	0.7	0.5	0.7		
RECTAL ULCER	0	0	0.2	0.7	0.5
REFLUX GASTRITIS	0	0.2	0		
REFLUX OESOPHAGITIS				0.7	0.5
RETCHING	0	0.2	0		
SALIVARY GLAND CALCULUS	0	0.2	0		
SALIVARY GLAND CYST	0	0.2	0		
STEATORRHOEA	0.7	0	0	0	0.5
STOMACH DISCOMFORT	0	0.2	0.3	1.4	1
STOMATITIS	1.4	0.9	0.2		
SUBMAXILLARY GLAND ENLARGEMENT	0	0	0.2		
SWOLLEN TONGUE	0.7	0	0		
TONGUE BLACK HAIRY				0.7	0.5
TONGUE COATED	0	0	0.2		
TONGUE CYST	0.7	0	0		
TONGUE DISCOLOURATION				0.7	0.5
TONGUE ULCERATION	0	0.2	0	0.7	0.5
TOOTH DISORDER	0	0.2	0	0.7	0.5
TOOTH IMPACTED	0	0.2	0		
TOOTHACHE	0	0.2	0.8	0.7	1
UMBILICAL HERNIA	0	0	0.2	1.4	1
VARICES OESOPHAGEAL	0.7	0	0.2		
VOMITING	4.8	6.3	5.5	2.7	4.1
VOMITING NOS				10.2	8.2
VOMITING OF MEDICATION				0.7	0.5

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ADVERSE DRUG REACTION NOS				0.7	0.5
	ASTHENIA	2.1	3.9	4.5	8.8	8.2
	AXILLARY PAIN	0	0.2	0.3		
	CATHETER SITE PAIN	0	0	0.3		
	CHEST DISCOMFORT	0.7	0	0.3	0	0.5
	CHEST PAIN	0.7	0.2	0.2	2	2
	CHILLS	0	0.9	0.8		
	CYST	0	0	0.3		
	DISCOMFORT				0	0.5
	DISCOMFORT NOS				0.7	0.5
	DRUG INEFFECTIVE				0.7	0.5
	DRUG INTOLERANCE	0	0	0.3		
	DRUG WITHDRAWAL SYNDROME	0	0.2	0		
	DYSPLASIA	0.7	0	0		
	FACE OEDEMA	0	0.2	0.3	1.4	1
	FATIGUE	5.5	7.7	8.4	18.4	17.3
	FATIGUE AGGRAVATED				0.7	0.5
	FEELING ABNORMAL	0	0	0.2		
	FEELING HOT	1.4	0.2	0	0	1
	FEELING OF BODY TEMPERATURE CHANGE	0	0	0.2		
	GENERAL PHYSICAL HEALTH DETERIORATION	0	0	0.2		
	GENERALISED OEDEMA	0	0.2	0		
	GRANULOMA	0	0	0.2		
	HERNIA	0	0	0.2	0.7	0.5
	INFLAMMATION	0	0	0.2		
	INFLUENZA LIKE ILLNESS	0	0.5	0.3	8.2	7.1
	INJECTION SITE BRUISING	0	0	0.2		
	INJECTION SITE DERMATITIS				0.7	0.5
	INJECTION SITE DISCOLOURATION	0	0	0.2		
	INJECTION SITE DISCOMFORT	0	0.2	0		
	INJECTION SITE ERYTHEMA	1.4	0.9	0.5	0	1
	INJECTION SITE HAEMATOMA	0.7	0	0.2		
	INJECTION SITE HYPERSENSITIVITY				0	0.5
	INJECTION SITE INDURATION	0.7	1.6	0.7	0.7	2
	INJECTION SITE INFLAMMATION	0	0.2	0.3	0.7	0.5
	INJECTION SITE IRRITATION	0	0	0.2		
	INJECTION SITE MASS	0	0.2	0.5		
	INJECTION SITE NODULE	10.3	6	6.6	8.2	6.6
	INJECTION SITE OEDEMA	0	0.2	0		
	INJECTION SITE PAIN	2.8	2.8	1.7	1.4	2
	INJECTION SITE PARAESTHESIA	0	0	0.2		

	INJECTION SITE PIGMENTATION CHANGES				0	0.5
	INJECTION SITE PRURITUS	0.7	0.2	0.3	0.7	0.5
	INJECTION SITE REACTION	11	9.5	10.9	8.2	8.2
	INJECTION SITE REACTION NOS				6.8	7.1
	INJECTION SITE SWELLING	0.7	0	0.2		
	INTERMITTENT PYREXIA				0.7	0.5
	IRRITABILITY	0	0.5	0	0	0.5
	LOCAL SWELLING	0	0	0.2		
	LOWER EXTREMITY MASS	0	0.2	0		
	MALAISE	0	0.2	0.3	2.7	2
	MASS	0	0	0.3		
	MUCOSAL DRYNESS	0	0.2	0		
	MULTI-ORGAN FAILURE	0	0	0.2		
	NODULE	0	0	0.2	0.7	0.5
	NON-CARDIAC CHEST PAIN	1.4	1.2	0.3	0.7	1
	OEDEMA	0	0.2	0.2		
	OEDEMA PERIPHERAL	3.4	2.8	2.6	3.4	4.1
	PAIN	0	0.9	0.7	3.4	3.1
	PAIN NOS				0.7	0.5
	PAPILLITIS	0	0	0.5		
	PITTING OEDEMA	0	0	0.2	1.4	1
	PYREXIA	7.6	4.9	8.9	19	16.8
	RIGORS				2	2.6
	SLUGGISHNESS	0	0.2	0		
	SUDDEN DEATH	0	0.2	0		
	SWELLING	0	0.5	0		
	TEMPERATURE INTOLERANCE	0	0.2	0		
	TENDERNESS				0.7	0.5
	THIRST				0	0.5
	ULCER	0.7	0	0		
	XEROSIS	0	0.2	0		
HEPATOBILIARY DISORDERS	CHOLANGITIS	0	0	0.3		
	CHOLECYSTITIS	0	0.2	0.3		
	CHOLECYSTITIS NOS				0.7	0.5
	CHOLELITHIASIS	0	0	0.5	1.4	1
	CYTOLYTIC HEPATITIS	0.7	0.2	0		
	HEPATIC CIRRHOSIS	0.7	0	0.2		
	HEPATIC CYST	0.7	0	0		
	HEPATIC FUNCTION ABNORMAL NOS				0.7	0.5
	HEPATIC STEATOSIS	0.7	0	0	0.7	0.5
	HEPATITIS	0	0.2	0.3		
	HEPATOMEGALY	0	0.7	0.8	1.4	1

	HEPATOSPLENOMEGALY	0	0.2	0.3	0.7	0.5
	HEPATOSPLENOMEGALY NOS				0.7	0.5
	HYPERBILIRUBINAEMIA	0	0	0.2		
	JAUNDICE	0.7	0.2	0.3	0.7	0.5
	JAUNDICE NOS				0.7	0.5
	LIVER FATTY				0	0.5
	ALLERGY TO ARTHROPOD BITE	0	0	0.3		
	ALLERGY TO ARTHROPOD STING	0	0	0.2		
	ALLERGY TO CHEMICALS	0.7	0	0		
	ALLERGY TO METALS	0.7	0	0		
	ANAPHYLACTIC SHOCK				0	0.5
IMMUNE SYSTEM DISORDERS	DRUG HYPERSENSITIVITY	1.4	0	0.7	0.7	0.5
	HYPERSENSITIVITY	2.8	0.2	0.2	0.7	0.5
	HYPERSENSITIVITY NOS				0.7	0.5
	IMMUNE RECONSTITUTION SYNDROME	0	0.2	0.2		
	MULTIPLE ALLERGIES	0	0	0.3		
	SEASONAL ALLERGY	0	0.2	0.5	4.1	3.6
INFECTIONS AND INFESTATIONS	ABDOMINAL ABSCESS	0	0	0.2		
	ABSCESS	0	0	0.2		
	ABSCESS LIMB	0	0	0.2	0.7	0.5
	ABSCESS NECK				0.7	0.5
	ACARODERMATITIS	0.7	0.9	0.5		
	ACQUIRED IMMUNODEFICIENCY SYNDROME	0	0	0.2		
	ACUTE SINUSITIS	0.7	0.5	0.3		
	ACUTE TONSILLITIS	0	0.5	0		
	AMOEBIASIS	0	0.2	0		
	ANAL ABSCESS	0	0	0.3		
	ANOGENITAL WARTS	1.4	3.2	3		
	APPENDICITIS	0	0	0.2		
	ARTHRITIS BACTERIAL	0	0	0.2		
	BACTERIAL SEPSIS	0	0	0.2		
	BALANTIDIASIS	0	0.2	0		
	BODY TINEA	1.4	0.5	0.3		
	BRONCHIECTASIS	0	0	0.3		
	BRONCHITIS	6.2	6	4.5	2	2.6
	BRONCHITIS ACUTE	1.4	0.9	0.7	1.4	1
	BRONCHITIS BACTERIAL	0	0.2	0		
	BRONCHITIS VIRAL	0	0.2	0	0	0.5
	BRONCHOPNEUMONIA	0	0	0.3		
	BRONCHOPULMONARY ASPERGILLOSIS	0.7	0	0		

BURN INFECTION	0	0	0.2		
CAMPYLOBACTER INFECTION	0	0.2	0.2	0	0.5
CAMPYLOBACTER INTESTINAL INFECTION	0	0	0.2		
CANDIDIASIS	0.7	0.7	1.5	0.7	2
CARBUNCLE	0	0	0.2		
CATHETER RELATED INFECTION	0	0.5	0		
CELLULITIS	0.7	0.7	1.3	3.4	2.6
CELLULITIS ORBITAL	0.7	0	0		
CENTRAL LINE INFECTION	0.7	0	0		
CERVICITIS	0	0.2	0.2		
CHLAMYDIAL INFECTION	0	0.2	0.2		
CHRONIC SINUSITIS	0.7	0	0	0.7	0.5
CLOSTRIDIUM DIFFICILE COLITIS	0.7	0.2	0.7		
COCCIDIOIDOMYCOSIS	0	0	0.2		
CONDYLOMA ACUMINATUM				2.7	2.6
CONJUNCTIVITIS BACTERIAL	0	0	0.2		
CONJUNCTIVITIS INFECTIVE	0.7	0.2	0		
CONJUNCTIVITIS VIRAL	0.7	0	0.3		
CYSTITIS	0.7	0.7	0.5	0	0.5
CYTOMEGALOVIRUS CHORIORETINITIS	0.7	0.2	1.3		
CYTOMEGALOVIRUS INFECTION	0	0.2	0.2		
CYTOMEGALOVIRUS OESOPHAGITIS	0	0	0.2		
CYTOMEGALOVIRUS VIRAEMIA	0	0.5	0		
DERMATOPHYTOSIS	0	0.2	0		
DIARRHOEA INFECTIOUS	0	0.2	0		
DISSEMINATED CRYPTOCOCCOSIS	0	0	0.2		
DIVERTICULITIS	0	0	0.2		
EAR INFECTION	1.4	0.5	0.3	0.7	0.5
EAR INFECTION STAPHYLOCOCCAL	0	0.2	0		
ENCEPHALITIS CYTOMEGALOVIRUS	0	0	0.2		
ERYSIPELAS	0	0.2	0.2		
EYE ABSCESS	0	0.2	0		
EYE INFECTION	0	0.2	0	0.7	0.5
EYE INFECTION FUNGAL	0	0	0.2		
FOLLICULITIS	1.4	1.9	3.3	3.4	3.6
FOOT INFECTION FUNGAL NOS				0.7	0.5
FUNGAL INFECTION	0	0	0.2		
FUNGAL INFECTION NOS				2	1.5
FUNGAL SKIN INFECTION	1.4	1.2	0.3		
FURUNCLE	0.7	0.2	0.2	2.7	2

GASTRITIS VIRAL	0	0.2	0		
GASTROENTERITIS	1.4	1.4	1.3		
GASTROENTERITIS CRYPTOSPORIDIAL	0	0	0.7		
GASTROENTERITIS VIRAL	0	0.9	0.3		
GASTROINTESTINAL CANDIDIASIS	0.7	0	0		
GASTROINTESTINAL INFECTION	0	0	0.2		
GENITAL CANDIDIASIS	0	0.5	0.2		
GENITAL INFECTION FUNGAL	0.7	0	0		
GIARDIASIS	0	0.2	0.7	0	1
GINGIVAL INFECTION	0	0.5	0.2	1.4	1
GONORRHOEA				0	0.5
HELICOBACTER INFECTION	0	0.2	0	0.7	0.5
HEPATITIS B	0.7	0	0		
HERPES OESOPHAGITIS	0	0	0.2		
HERPES SIMPLEX	8.3	7.7	6.6	6.8	5.6
HERPES SIMPLEX OPHTHALMIC				0.7	0.5
HERPES VIRAL INFECTION NOS				0.7	1
HERPES ZOSTER	2.1	3.5	2.2	4.8	4.1
HERPES ZOSTER DISSEMINATED	0	0.2	0		
HERPES ZOSTER INFECTION NEUROLOGICAL	0	0.2	0		
HERPES ZOSTER MULTI-DERMATOMAL	0.7	0	0		
HERPETIC STOMATITIS	0	0	0.2		
HIV WASTING SYNDROME	0	0.2	0.7		
HUMAN POLYOMAVIRUS INFECTION	0	0.2	0		
IMPETIGO	0.7	0	0		
INFECTED SEBACEOUS CYST	0	0	0.2		
INFECTION				0.7	0.5
INFECTION PARASITIC	0	0	0.2		
INFLUENZA	6.2	3	2.6	4.8	4.1
INJECTION SITE CELLULITIS	0	0.5	0.2		
INJECTION SITE INFECTION				0	0.5
INTERTRIGO CANDIDA				0	0.5
KERATITIS HERPETIC	0	0	0.2		
LABYRINTHITIS	0	0	0.3		
LARYNGITIS	0	0.5	0.2		
LARYNGITIS VIRAL	0	0	0.2		
LICE INFESTATION	0	0	0.2	0.7	0.5
LOCALISED INFECTION	0.7	0	0.3	0.7	0.5
LOWER RESPIRATORY TRACT INFECTION	0	0.2	0.7		
LUNG INFECTION	0	0.2	0		

LUNG INFECTION PSEUDOMONAL	0.7	0	0		
LYMPH NODE TUBERCULOSIS	0	0	0.2		
LYMPHOGRANULOMA VENEREUM				0.7	0.5
MASTITIS	0	0.2	0		
MENINGITIS	0	0	0.2		
MENINGITIS CRYPTOCOCCAL	0	0.2	0.3		
MENINGITIS LISTERIA	0.7	0	0		
MOLLUSCUM CONTAGIOSUM	1.4	1.6	1.2	0.7	0.5
MYCOBACTERIAL INFECTION				0.7	0.5
MYCOBACTERIUM AVIUM COMPLEX INFECTION	0	0	1		
NAIL FUNGAL INFECTION NOS				0	1
NAIL INFECTION	0	0.2	0		
NASOPHARYNGITIS	5.5	9.3	7.5	12.2	14.8
OESOPHAGEAL CANDIDIASIS	0	0.7	1.5	1.4	2
ONYCHOMYCOSIS	1.4	3	2.2	0.7	0.5
ORAL CANDIDIASIS	7.6	5.6	5	8.2	8.2
ORAL FUNGAL INFECTION	0	0	0.2		
ORAL HAIRY LEUKOPLAKIA	1.4	1.2	1.2	4.8	4.6
ORCHITIS	0	0.2	0		
OROPHARYNGEAL CANDIDIASIS	0	0.5	0.5	0	0.5
OSTEOMYELITIS	0.7	0.2	0.2		
OTITIS EXTERNA	0	0.2	0.3	2.7	2
OTITIS MEDIA	0	0.7	0.3	0.7	1
OTITIS MEDIA ACUTE	0	0.2	0		
PAPILLOMA VIRAL INFECTION	0.7	0.2	0.3		
PARASITIC INFECTION INTESTINAL	0	0.5	0	0.7	0.5
PARONYCHIA	0	0.5	0		
PAROTITIS	0	0	0.3		
PARVOVIRUS INFECTION	0	0.2	0		
PERIANAL ABSCESS	0	0.7	0		
PERIANAL FUNGAL INFECTION	0	0	0.2		
PERIORBITAL CELLULITIS	0.7	0	0		
PHARYNGEAL CANDIDIASIS	0	0.2	0		
PHARYNGITIS	3.4	1.4	1.8	7.5	8.2
PHARYNGITIS BACTERIAL	0	0	0.2		
PHARYNGITIS STREPTOCOCCAL	0	0.2	0		
PHARYNGOTONSILLITIS	0	0	0.3		
PNEUMOCYSTIS JIROVECI PNEUMONIA	0.7	0.5	1		
PNEUMONIA	1.4	1.2	2.6	1.4	2
PNEUMONIA BACTERIAL	0	0.7	0.7		
PNEUMONIA FUNGAL	0	0.2	0		

PNEUMONIA KLEBSIELLA				0.7	0.5
PNEUMONIA LEGIONELLA	0	0	0.2		
PNEUMONIA PNEUMOCOCCAL	0	0	0.2		
PNEUMONIA STREPTOCOCCAL	0	0	0.2		
POSTOPERATIVE WOUND INFECTION	0	0.2	0		
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY	0	0.2	0.2		
PROTEUS INFECTION NOS				0.7	0.5
PSEUDOMEMBRANOUS COLITIS	0	0.2	0		
PSEUDOMONAS INFECTION	0	0	0.2		
PSOAS ABSCESS				0.7	0.5
PYELONEPHRITIS	0	0.2	0		
PYELONEPHRITIS ACUTE	0	0	0.2		
PYOMYOSITIS	0	0	0.2		
RASH PUSTULAR	0	0	0.3		
RESPIRATORY TRACT INFECTION	0.7	0.5	0.8		
RESPIRATORY TRACT INFECTION VIRAL	0	0.7	0.8		
RHINITIS	1.4	0.7	1.8		
SCABIES INFESTATION				0.7	0.5
SCROTAL ABSCESS	0	0.2	0		
SCROTAL INFECTION	0	0.2	0		
SECONDARY SYPHILIS	0	0	0.2	1.4	1
SEPSIS	0	0.5	0.8		
SIALOADENITIS	0	0.2	0		
SINUSITIS	4.1	2.8	5	5.4	4.6
SINUSITIS BACTERIAL	0	0.2	0		
SKIN BACTERIAL INFECTION	0	0.2	0		
SKIN FUNGAL INFECTION NOS				0.7	0.5
SKIN INFECTION	0	0	0.2		
STAPHYLOCOCCAL ABSCESS				0	0.5
STAPHYLOCOCCAL BACTERAEMIA				0.7	0.5
STAPHYLOCOCCAL INFECTION	0.7	0.2	0.3	0	0.5
STAPHYLOCOCCAL SEPSIS				0.7	0.5
STAPHYLOCOCCAL SKIN INFECTION	0	0	0.2		
SUBCUTANEOUS ABSCESS	0	0.5	1		
SUPERINFECTION	0	0	0.2		
SUPERINFECTION LUNG	0	0.5	0		
SYPHILIS	0.7	0.2	0.7	0.7	0.5
SYPHILIS NOS				1.4	1
TINEA CRURIS	0.7	0.2	0.5		
TINEA INFECTION	0	0.2	0.2		

	TINEA PEDIS	1.4	0.5	1.3	0	1
	TINEA VERSICOLOUR	0.7	0.2	0.2	1.4	1
	TONSILLITIS	0	0.2	0.7		
	TOOTH ABSCESS	0.7	0.5	1	1.4	1.5
	TOOTH INFECTION	0	0.7	0.3	2.7	2
	TRACHEITIS	0	0.5	0.3		
	TRACHEOBRONCHITIS	0	0	0.3	0	0.5
	TRICHOPHYTON INFECTION	0	0	0.2		
	TUBERCULOSIS	0	0	0.2		
	UPPER RESPIRATORY TRACT INFECTION	6.9	3.7	6.6	2.7	2.6
	URETHRITIS	0	1.2	0.2	0.7	1
	URETHRITIS GONOCOCCAL	0	0	0.2		
	URINARY TRACT INFECTION	2.8	1.9	2.3	2	2.6
	URINARY TRACT INFECTION STAPHYLOCOCCAL				0.7	0.5
	VAGINAL CANDIDIASIS	0.7	0.7	0.7		
	VARICELLA	0	0.2	0		
	VIRAL INFECTION	0.7	0.5	0.3	0	0.5
	VIRAL INFECTION NOS				1.4	1
	VIRAL SINUSITIS	0	0.2	0		
	VIRAL UPPER RESPIRATORY TRACT INFECTION	0	0.5	0.3		
	VULVITIS	0	0	0.2		
	VULVOVAGINITIS	0.7	0	0		
	WOUND INFECTION	0	0	0.2	0.7	0.5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ABRASION NOS				1.4	1
	ACCIDENTAL OVERDOSE				0	0.5
	ANIMAL BITE				0.7	0.5
	ANIMAL SCRATCH				0.7	0.5
	ANKLE FRACTURE	0	0	0.2	1.4	1
	ARTHROPOD BITE	0.7	0	0.7	0.7	0.5
	ARTHROPOD STING	0	0.2	0.2	0	0.5
	BACK INJURY	0	0.2	0.2		
	BACK INJURY NOS				0.7	0.5
	BURNS SECOND DEGREE	0	0	0.2		
	CLAVICLE FRACTURE	0	0	0.2	0.7	0.5
	CONTUSION	0.7	0.2	0.2	2.7	2.6
	DISLOCATION OF JOINT PROSTHESIS				0.7	0.5
	DRUG TOXICITY	0.7	0	0		
	EPICONDYLITIS	1.4	0	0.2		
	EXCORIATION	1.4	0.2	0.3		
	FACE INJURY	0	0	0.2		
	FACIAL BONES FRACTURE	0	0	0.2		

FALL	0	0.5	0.3		
FEEDING TUBE COMPLICATION	0	0.2	0		
FOOT FRACTURE	0	0	0.2	0	0.5
FOREIGN BODY IN EYE	0	0	0.2		
FRACTURE OF PENIS				0.7	0.5
HAND FRACTURE	0	0	0.2		
HEAD INJURY	0	0	0.2		
HEAT STROKE	0	0.2	0		
JOINT DISLOCATION	0	0	0.3	0	0.5
JOINT INJURY	0	0.2	0.3		
JOINT SPRAIN	1.4	0	0.3	1.4	1
LACERATION				0.7	0.5
LIGAMENT RUPTURE	0	0.5	0		
LIMB INJURY	0	0	0.3		
LIMB INJURY NOS				0	0.5
LOWER LIMB FRACTURE	0	0.2	0		
MENISCUS LESION	0	0.2	0.3		
MUSCLE STRAIN	0	0.5	0.3		
POST PROCEDURAL OEDEMA	0	0	0.2		
POST PROCEDURAL PAIN				0.7	0.5
POST-TRAUMATIC PAIN	0	0	0.2		
POSTOPERATIVE FEVER				0.7	0.5
PROCEDURAL PAIN	0.7	0.5	0.8		
RADIATION SKIN INJURY	0	0	0.2		
RADIUS FRACTURE	0	0	0.2		
RIB FRACTURE	0	0.2	0	0.7	0.5
SCRATCH	0	0.2	0.2	1.4	1
SKELETAL INJURY	0	0	0.2		
SKIN INJURY	0	0.2	0.2		
SKIN LACERATION	0	0.2	0.3		
STRESS FRACTURE				0.7	0.5
SUBDURAL HAEMATOMA	0	0.2	0		
SUNBURN	0.7	0	0.2	0.7	0.5
THERMAL BURN	0.7	0.2	0.3		
TIBIA FRACTURE	0	0	0.2		
TONGUE INJURY	0	0.2	0		
TOOTH AVULSION	0	0.2	0		
TOOTH FRACTURE	0	0.7	0.2		
TRAUMATIC HAEMATOMA	0.7	0	0		
UPPER LIMB FRACTURE	0	0.2	0.2		
UPPER LIMB FRACTURE NOS				0	0.5
VACCINATION COMPLICATION				0.7	0.5

	WRIST FRACTURE	0	0	0.2		
	ALANINE AMINOTRANSFERASE INCREASED	4.1	1.6	1.5	4.1	4.6
INVESTIGATIONS	ANGIOGRAM NOS				0.7	0.5
	ASPARTATE AMINOTRANSFERASE INCREASED	2.1	1.4	1.3	3.4	4.1
	BILIRUBIN CONJUGATED INCREASED	0.7	0	0		
	BIOPSY KIDNEY	0	0	0.3		
	BLEEDING TIME PROLONGED	0	0	0.2		
	BLOOD ALBUMIN DECREASED	0	0	0.2		
	BLOOD ALKALINE PHOSPHATASE INCREASED	0.7	0.2	1		
	BLOOD ALKALINE PHOSPHATASE NOS INCREASED				0.7	1
	BLOOD AMYLASE INCREASED	1.4	2.8	2.6	2	2
	BLOOD BILIRUBIN INCREASED	0.7	0.2	0.2	2	1.5
	BLOOD CHOLESTEROL INCREASED	2.8	0.5	1.2	2.7	2
	BLOOD CREATINE PHOSPHOKINASE INCREASED	0	0.5	0.3	2.7	3.1
	BLOOD CREATININE INCREASED	3.4	0.9	1.8	1.4	1
	BLOOD GLUCOSE DECREASED	0	0	0.2		
	BLOOD GLUCOSE INCREASED	1.4	0.5	0.3	0.7	0.5
	BLOOD INSULIN INCREASED	0	0	0.5		
	BLOOD LACTATE DEHYDROGENASE INCREASED	1.4	0.5	0.2	0.7	0.5
	BLOOD POTASSIUM DECREASED	0	0	0.8		
	BLOOD PRESSURE DECREASED	0	0	0.3		
	BLOOD PRESSURE DIASTOLIC INCREASED	0	0.2	0.2		
	BLOOD PRESSURE INCREASED	0	0.7	0.3	0.7	0.5
	BLOOD PRESSURE SYSTOLIC INCREASED	0	0.2	0.2		
	BLOOD PROLACTIN INCREASED	0	0.2	0		
	BLOOD SODIUM DECREASED	0	0	0.2		
	BLOOD SODIUM INCREASED	0	0	0.2		
	BLOOD TESTOSTERONE DECREASED	0	0.2	0	1.4	1
	BLOOD THYROID STIMULATING HORMONE INCREASED	1.4	0	0.3		
	BLOOD TRIGLYCERIDES INCREASED	5.5	1.4	1.7	3.4	3.1
	BLOOD UREA INCREASED				0.7	0.5
	BLOOD URIC ACID INCREASED	1.4	0.7	0.5	1.4	1
	BONE DENSITY DECREASED	0	0	0.2		
	C-REACTIVE PROTEIN INCREASED	0	0	0.2	1.4	1
	CARDIAC ENZYMES INCREASED				0.7	0.5

CARDIAC MURMUR	0	0.7	0.2	2	1.5
CARDIAC MURMUR NOS				0.7	0.5
CAROTID BRUIT	0	0.2	0		
CHEST X-RAY ABNORMAL	0	0	0.2		
CREATININE RENAL CLEARANCE DECREASED	0	0.2	0.3		
ECG SIGNS OF VENTRICULAR HYPERTROPHY	0	0.2	0		
ELECTROCARDIOGRAM ABNORMAL	0	0.5	0.5	0	0.5
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED	0	0.5	0.5		
ELECTROCARDIOGRAM QT PROLONGED	0	0.2	0.3		
ELECTROCARDIOGRAM ST-T CHANGE	0.7	0	0		
ELECTROCARDIOGRAM T WAVE ABNORMAL	1.4	0.5	0.5		
ELECTROMYOGRAM	0.7	0	0		
ENDOSCOPY UPPER GASTROINTESTINAL TRACT				0.7	0.5
EOSINOPHIL COUNT INCREASED	0	0.2	0		
FULL BLOOD COUNT ABNORMAL				0.7	0.5
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0	0	0.2	3.4	3.1
GASTRIC PH DECREASED	0	0	0.3		
GRIP STRENGTH DECREASED	0	0	0.2		
HAEMATOCRIT DECREASED	0.7	0.2	0	0.7	0.5
HAEMOGLOBIN DECREASED	1.4	0.7	0.8	0.7	0.5
HEART RATE DECREASED	0	0	0.2		
HEART RATE INCREASED				0	0.5
HEPATIC ENZYME INCREASED	0	0.2	0	0.7	0.5
HIGH DENSITY LIPOPROTEIN DECREASED	0.7	0	0.2		
INVESTIGATION				0.7	0.5
LIPASE INCREASED	1.4	1.6	2.2	1.4	1
LIPIDS INCREASED	0	0.5	0		
LIVER FUNCTION TEST ABNORMAL	0	0	0.3	0.7	0.5
LIVER PALPABLE SUBCOSTAL				2	1.5
LOW DENSITY LIPOPROTEIN INCREASED	0	1.6	0.3	0.7	0.5
LYMPHOCYTE MORPHOLOGY ABNORMAL	0	0.2	0		
NEUTROPHIL COUNT DECREASED	0	0.2	1	0.7	0.5
NEUTROPHIL COUNT INCREASED	0	0.5	0.2	0.7	0.5
PANCREATIC ENZYMES INCREASED				0.7	1
PLATELET COUNT DECREASED	0	0.2	0.2		

	POSITIVE ROMBERGISM	0	0	0.2		
	PROTEIN URINE PRESENT	0	0.2	0.3		
	PULSE ABNORMAL	0	0	0.2		
	RED BLOOD CELL COUNT DECREASED	0	0.2	0		
	RED BLOOD CELL NUCLEATED MORPHOLOGY PRESENT	0	0.2	0		
	RED BLOOD CELLS URINE POSITIVE	0	0	0.2	0.7	0.5
	RESPIRATORY RATE INCREASED	0	0	0.2		
	SCAN MYOCARDIAL PERFUSION				0.7	0.5
	SMEAR CERVIX ABNORMAL				0	0.5
	SYPHILIS TEST POSITIVE				0.7	0.5
	TRANSAMINASES INCREASED	0	0.5	0	0.7	0.5
	TRI-IODOTHYRONINE DECREASED	0	0	0.2		
	TRI-IODOTHYRONINE INCREASED	0	0	0.2		
	URINARY CASTS	0	0	0.2		
	URINE ANALYSIS ABNORMAL	0	0	0.3		
	URINE BILIRUBIN INCREASED	0.7	0.5	0.2		
	URINE CYTOLOGY ABNORMAL	0	0	0.2		
	URINE CYTOMEGALOVIRUS POSITIVE	0	0.2	0		
	URINE GLUCOSE FALSE POSITIVE				0.7	0.5
	URINE KETONE BODY PRESENT	0	0	0.2		
	VIBRATION TEST ABNORMAL	0	0.7	1	0.7	0.5
	WEIGHT DECREASED	0.7	0.9	3	6.1	6.6
	WEIGHT INCREASED	0	0.7	0.3	0.7	0.5
	WHITE BLOOD CELL COUNT DECREASED	0.7	0.2	0.5	0	0.5
	WHITE BLOOD CELL COUNT INCREASED	0	0.2	0.2		
	WHITE BLOOD CELLS URINE POSITIVE	0	0.5	0.2	0.7	0.5
METABOLISM AND NUTRITION DISORDERS	ANOREXIA	0.7	1.6	1.7	4.8	4.6
	APPETITE DECREASED NOS				1.4	1.5
	CACHEXIA	0	0	0.3	1.4	1
	DECREASED APPETITE	0.7	0.5	1	1.4	2.6
	DEHYDRATION	0.7	0.7	1.3	2	1.5
	DIABETES MELLITUS	2.1	0.7	0.3		
	DIABETES MELLITUS INADEQUATE CONTROL	1.4	0	0		
	DIABETES MELLITUS NON-INSULIN-DEPENDENT	0	0	0.5		
	DYSLIPIDAEMIA	2.1	0.7	0.8		
	FACIAL WASTING	0.7	0.9	1.5		
	FAILURE TO THRIVE				0.7	0.5

	FAT REDISTRIBUTION				2	1.5
	FLUID RETENTION	0	0	0.2		
	FOLATE DEFICIENCY	0	0.2	0.3		
	GLUCOSE TOLERANCE IMPAIRED	0	0.2	0		
	GOUT	0.7	0.7	0.8	0	0.5
	HYPERCHOLESTEROLAEMIA	3.4	2.1	0.7	2	2
	HYPERCREATININAEMIA	0.7	0.2	0		
	HYPERGLYCAEMIA	0	0.7	0.2	0.7	0.5
	HYPERGLYCAEMIA NOS				0.7	0.5
	HYPERHOMOCYSTEINAEMIA	0	0.2	0		
	HYPERINSULINAEMIA	0	0.2	0.5		
	HYPERKALAEMIA	0	0	0.3		
	HYPERLIPIDAEMIA	1.4	1.2	0.7	0.7	0.5
	HYPERTRIGLYCERIDAEMIA	4.1	2.8	1.7	4.8	4.1
	HYPERURICAEMIA	0	0	0.5	2	1.5
	HYPERVOLAEMIA	0	0	0.2		
	HYPOALBUMINAEMIA	0.7	0	0		
	HYPOCALCAEMIA	0.7	0.2	0	0.7	0.5
	HYPOCHOLESTEROLAEMIA	0	0.2	0		
	HYPOGLYCAEMIA	0	0.2	0.3		
	HYPOKALAEMIA	0	1.6	0.7		
	HYPONATRAEMIA	0	0.2	0.2		
	HYPOPHOSPHATAEMIA	0	0	0.3		
	HYPOVITAMINOSIS	0	0	0.2		
	HYPOVOLAEMIA	0	0	0.2	0	0.5
	INCREASED APPETITE	2.1	0.7	0.2		
	INSULIN RESISTANCE	0	0	0.2		
	KETOACIDOSIS	0	0	0.2		
	MALNUTRITION				0.7	0.5
	METABOLIC ACIDOSIS	0	0.2	0		
	OBESITY				0	1
	VITAMIN B12 DEFICIENCY				0.7	0.5
	VITAMIN B6 DEFICIENCY	0	0.2	0		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	AMYOTROPHY	0	0.2	0		
	ARTHRALGIA	0.7	4.2	5.3	10.9	9.7
	ARTHRITIS	0	0.5	0.3	0.7	0.5
	ARTHRITIS NOS				0.7	0.5
	ARTHROPATHY	0	0.5	0	0.7	0.5
	AXILLARY MASS				0.7	0.5
	BACK PAIN	4.8	2.8	4.3	8.8	8.2
	BONE DISORDER	0	0.2	0		
	BONE PAIN	0	0	0.2	0.7	0.5

BURSITIS	0	0.5	0	0.7	1
CHEST WALL PAIN				1.4	1
CLUBBING	0	0	0.2		
COMPRESSION FRACTURE				0.7	0.5
COSTOCHONDRITIS	0.7	0	0.2	0.7	1
EXOSTOSIS	0	0	0.2		
FACIAL PAIN				0	0.5
FLANK PAIN	0.7	0.5	0.2	0.7	1
GOUTY ARTHRITIS	0	0.5	0.3		
GROIN PAIN	0	0.2	0.3	0.7	0.5
HAEMARTHROSIS	0	0.2	0		
INTERVERTEBRAL DISC DISORDER				0	0.5
INTERVERTEBRAL DISC PROTRUSION	0.7	0.2	0.2		
JAW DISORDER				0.7	0.5
JOINT STIFFNESS	0.7	0.2	0.7		
JOINT SWELLING	0.7	0.7	0.2	2	1.5
LIGAMENT SPRAIN				0.7	0.5
LIMB DISCOMFORT	0	0.2	0	0.7	0.5
METATARSALGIA				0.7	0.5
MUSCLE ATROPHY	0	0.2	0.2		
MUSCLE CONTRACTURE	0	0	0.2		
MUSCLE CRAMP				4.8	4.6
MUSCLE FATIGUE				0	0.5
MUSCLE MASS	0	0.2	0		
MUSCLE SPASMS	2.1	2.1	2	0.7	0.5
MUSCLE SPASTICITY				0.7	0.5
MUSCULAR WEAKNESS	0	0.7	0.3		
MUSCULOSKELETAL CHEST PAIN	0.7	0.7	0.7	1.4	2
MUSCULOSKELETAL DISCOMFORT	0.7	0.5	0		
MUSCULOSKELETAL PAIN	1.4	1.4	1.2		
MUSCULOSKELETAL STIFFNESS	0	0.2	0.3		
MYALGIA	3.4	1.9	3.8	3.4	3.1
MYOPATHY				0.7	0.5
MYOSCLEROSIS	0	0.2	0		
NECK MASS				0	0.5
NECK PAIN	0.7	1.2	0.7	0.7	0.5
NODULE ON EXTREMITY				0	0.5
OSTEOARTHRITIS	1.4	0.2	0.5	0.7	0.5
OSTEONECROSIS	0	0.2	0.2	0.7	0.5
OSTEOPENIA	0	0	0.3		
OSTEOPOROSIS	0	0.5	0.2		
PAIN IN EXTREMITY	2.8	3.7	3.1	2.7	3.6

	PAIN IN FOOT				1.4	1
	PAIN IN JAW	0	0.2	0		
	PAIN IN LIMB				2.7	2
	PATELLOFEMORAL PAIN SYNDROME	0.7	0	0		
	PATHOLOGICAL FRACTURE	0	0	0.2		
	PLANTAR FASCIITIS				2	1.5
	POLYARTHRITIS				0.7	0.5
	RHABDOMYOLYSIS	0	0.2	0.2		
	SACRAL PAIN	0	0	0.2		
	SCLERODERMA	0	0.2	0		
	SENSATION OF HEAVINESS				0.7	0.5
	SPINAL OSTEOARTHRITIS	0.7	0	0		
	SPONDYLITIS	0	0.2	0		
	SYNOVIAL CYST	0	0.5	0		
	SYNOVITIS	0	0.2	0		
	TENDON PAIN	0	0	0.2		
	TENDONITIS	0	0.7	0.7	2	1.5
	TENOSYNOVITIS	0	0.2	0		
	TORTICOLLIS	0	0.2	0.2	0.7	0.5
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	ACUTE MYELOID LEUKAEMIA	0	0.2	0		
	ANAL CANAL CANCER NOS				0.7	0.5
	ANAL CANCER	0	0	0.5		
	ANAL CANCER STAGE 0	1.4	0	0.2		
	B-CELL LYMPHOMA	0	0	0.2		
	BASAL CELL CARCINOMA	0	0.5	0.3	0.7	0.5
	BOWEN'S DISEASE				0.7	0.5
	BUCCAL CAVITY PAPILLOMA	0	0	0.3		
	BURKITT'S LYMPHOMA	0.7	0	0	0.7	0.5
	BUSCHKE-LOWENSTEIN'S TUMOUR	0	0.2	0		
	CENTRAL NERVOUS SYSTEM LYMPHOMA	0	0	0.2		
	DIFFUSE LARGE B-CELL LYMPHOMA	0.7	0	0		
	FIBROMA NOS				0.7	0.5
	HAEMANGIOMA ACQUIRED				0.7	0.5
	HEPATIC NEOPLASM	0	0.2	0		
	HODGKIN'S DISEASE	0	0.2	0	0.7	0.5
	KAPOSI'S SARCOMA	0	0.5	0.5		
	LEIOMYOMA	0	0.2	0		
	LIPOMA	0.7	0.2	0.2		
	LYMPHOMA	0	0.2	0		
	MALIGNANT NEOPLASM PROGRESSION	0	0	0.2		

	MENINGIOMA	0	0.2	0		
	NON-HODGKIN'S LYMPHOMA	0	0	0.2		
	ORAL FIBROMA	0	0	0.2		
	PLASMABLASTIC LYMPHOMA	0	0	0.2		
	PROSTATIC ADENOMA	0.7	0	0		
	PYOGENIC GRANULOMA	0	0	0.2		
	RECTAL CANCER RECURRENT	0	0	0.2		
	SKIN PAPILLOMA	2.8	4.6	2.5	6.1	5.1
	SQUAMOUS CELL CARCINOMA	1.4	0.2	0.3	1.4	1.5
	SQUAMOUS CELL CARCINOMA OF SKIN	0	0.2	0		
	THYROID NEOPLASM	0	0.2	0		
	TONGUE NEOPLASM	0	0.2	0		
NERVOUS SYSTEM DISORDERS	AGEUSIA	0.7	0.2	0		
	AMNESIA	0	0.9	0.5	0.7	0.5
	APHONIA	0	0	0.2	0.7	0.5
	AREFLEXIA	0	0	0.2		
	BALANCE IMPAIRED NOS				0.7	0.5
	BRAIN MASS	0	0	0.2		
	BURNING SENSATION	0	0.2	0		
	BURNING SENSATION NOS				0.7	0.5
	CARPAL TUNNEL SYNDROME	0	0.2	0.3		
	CEREBROVASCULAR DISORDER	0	0.2	0		
	CERVICOBRACHIAL SYNDROME	0	0.5	0		
	COMPLEX PARTIAL SEIZURES	0	0	0.2		
	CONVULSION	0	0.2	0.5		
	DEPRESSED LEVEL OF CONSCIOUSNESS	0	0	0.2		
	DISTURBANCE IN ATTENTION	0.7	0	1		
	DIZZINESS	2.1	2.8	4.1	10.2	9.7
	DIZZINESS POSTURAL	0.7	0	0		
	DYSAESTHESIA	0	0	0.2	0.7	0.5
	DYSARTHRIA	0	0	0.2		
	DYSGEUSIA	1.4	0.2	0.8	0.7	0.5
	DYSKINESIA	0	0.2	0		
	DYSPHASIA	0	0.2	0.2		
	FACIAL NERVE DISORDER	0.7	0	0		
	FORMICATION	0	0.5	0		
	HEADACHE	6.2	10.7	12.3	21.1	17.9
	HEMIPARESIS	0	0	0.2		
	HEMIPLEGIA	0	0.5	0		
	HEPATIC ENCEPHALOPATHY	0.7	0	0		
	HYPERAESTHESIA	0	0.2	0		

HYPERSOMNIA	0	0.2	0.3	0.7	0.5
HYPOAESTHESIA	0	1.2	1	4.8	4.6
HYPOGEUSIA	0	0	0.3		
HYPOREFLEXIA	0	0.2	0	2	2
ISCHAEMIC STROKE	0	0	0.3		
LETHARGY	0	0	0.3		
MEMORY IMPAIRMENT	0	0.9	0.5	1.4	1
MENTAL IMPAIRMENT	0	0.2	0		
MIGRAINE	0	0.2	0.5		
MUSCLE CONTRACTIONS INVOLUNTARY				0.7	0.5
NEURALGIA	0.7	0.2	0.5		
NEURITIS CRANIAL				0	0.5
NEUROLOGICAL SYMPTOM	0	0	0.2		
NEUROMYOPATHY	0	0	0.2		
NEUROPATHY	2.8	1.4	1.8	1.4	1
NEUROPATHY NOS				0	0.5
NEUROPATHY PERIPHERAL	5.5	2.6	1.5	2.7	2
PARAESTHESIA	2.8	2.1	2.6	2	3.1
PARAESTHESIA EAR				0	0.5
PARTIAL SEIZURES	0	0.2	0		
PERIPHERAL NEUROPATHY NOS				0	1
PERIPHERAL PARALYSIS				0	0.5
PETIT MAL EPILEPSY	0	0	0.2		
POLYNEUROPATHY	0	0	0.2		
POOR QUALITY SLEEP	0	0.2	0		
POST HERPETIC NEURALGIA	0.7	0.2	0		
POST-TRAUMATIC HEADACHE				0	0.5
RADICULAR PAIN	0	0	0.2		
RESTLESS LEGS SYNDROME	0	0.2	0.3		
RESTLESSNESS				0	1
SCIATICA	0	0.2	0.5	0.7	0.5
SEIZURE ANOXIC	0	0.2	0		
SENSORY DISTURBANCE	0	0	0.2		
SINUS HEADACHE	0	0.2	0.3	0	0.5
SLEEP PHASE RHYTHM DISTURBANCE	0	0.2	0.2		
SOMNOLENCE	2.1	1.4	2	2	1.5
SPINAL CORD COMPRESSION	0	0.2	0.2		
SYNCOPE	0.7	0.5	0.5	0.7	1
SYNCOPE VASOVAGAL	0.7	0	0	0.7	0.5
TENSION HEADACHES				1.4	1
TRANSIENT ISCHAEMIC ATTACK	0	0	0.2		
TREMOR	2.1	0.5	0.7	0.7	1.5

	VASOVAGAL ATTACK				0.7	0.5
NONE	NONE	6.9	7.9	7.5	2.7	2.6
	ABNORMAL DREAMS	0.7	0.5	0.7	2	1.5
	ADJUSTMENT DISORDER NOS				0.7	0.5
	AGITATION	0	0	0.2		
	ANGER	0	0	0.2		
	ANHEDONIA	0	0	0.2		
	ANXIETY	4.8	1.9	3	2	2
	BIPOLAR I DISORDER				0.7	0.5
	CLAUSTROPHOBIA	0	0.2	0		
	CONFUSIONAL STATE	0	0	0.2	0.7	0.5
	DECREASED ACTIVITY				0.7	0.5
	DEPRESSED MOOD	0	0.2	0.2	0	0.5
	DEPRESSION	2.8	3.2	5	5.4	4.6
	DEPRESSION AGGRAVATED				1.4	1
	DISORIENTATION	0	0	0.3	0.7	0.5
	DISTRACTIBILITY	0	0.2	0		
	DYSTHYMIC DISORDER	0	0	0.2		
	HALLUCINATION, AUDITORY				0.7	0.5
	INITIAL INSOMNIA	0	0	0.2		
	INSOMNIA	10.3	3.9	6.6	10.9	12.2
PSYCHIATRIC DISORDERS	LIBIDO DECREASED	0.7	0.2	0.5	1.4	1
	LIBIDO DISORDER	0	0	0.2		
	LOSS OF LIBIDO	0	0	0.2	1.4	1
	MAJOR DEPRESSION	0	0.2	0		
	MENTAL DISORDER	0	0	0.2		
	MENTAL STATUS CHANGES	0	0	0.3	0.7	0.5
	MIDDLE INSOMNIA				0.7	0.5
	MOOD ALTERED	0	0	0.2		
	MOOD SWINGS	0.7	0	0.2	1.4	1
	NERVOUSNESS	0	0.2	0.2		
	NIGHTMARE	0	0.5	0.2		
	PANIC ATTACK	0.7	0.2	0		
	PANIC DISORDER	0	0	0.2		
	PARANOIA				0.7	0.5
	SEASONAL AFFECTIVE DISORDER				0.7	0.5
	SLEEP DISORDER	0.7	1.4	0.7		
	SLEEP DISORDER NOS				2	1.5
	STRESS	0	0.2	0		
	STRESS SYMPTOMS				1.4	1
	SUICIDAL IDEATION	0	0	0.2		
	SUICIDE ATTEMPT	0	0	0.2		

RENAL AND URINARY DISORDERS	AZOTAEMIA	0	0.2	0		
	BILIRUBINURIA	0	0	0.2		
	BLADDER DISORDER	0	0.2	0		
	BLADDER FIBROSIS	0	0.2	0		
	CALCULUS URETERIC				0	0.5
	CHROMATURIA				0.7	0.5
	COSTOVERTEBRAL ANGLE TENDERNESS	0	0.5	0		
	DYSURIA	0.7	0.9	0.8	0.7	1
	GLOMERULONEPHRITIS MEMBRANOUS	0	0.2	0		
	GLYCOSURIA	0	0	0.2		
	HAEMATURIA	0.7	0.5	1.3	2	1.5
	INCONTINENCE	0	0.2	0.2		
	LEUKOCYTURIA	0	0	0.2		
	MICTURITION URGENCY	0	0.2	0.3	0.7	0.5
	NEPHROLITHIASIS	0.7	0.7	0.8	2	1.5
	NOCTURIA	0	0.2	0.3	2	3.1
	NOCTURIA AGGRAVATED				0.7	0.5
	POLLAKIURIA	0	0.9	1		
	POLYURIA				2	2.6
	PROTEINURIA	0	1.2	1.3	1.4	2
	RENAL COLIC	0	0.2	0.3	0.7	1
	RENAL CYST	0	0	0.2		
	RENAL CYST NOS				0.7	0.5
	RENAL DISORDER	0	0	0.2		
	RENAL FAILURE	2.1	1.9	1		
	RENAL FAILURE ACUTE	0.7	0.2	1		
	RENAL FAILURE CHRONIC	0	0	0.3		
	RENAL IMPAIRMENT	0.7	0	0.5		
	RENAL INSUFFICIENCY				2.7	2.6
	RENAL PAIN				1.4	1
	RENAL TUBULAR DISORDER	0.7	0.2	0		
	URETHRAL DISCHARGE	0	0	0.2		
	URETHRAL MEATUS STENOSIS	0	0	0.2		
	URINARY FREQUENCY				2	1.5
	URINARY FREQUENCY AGGRAVATED				0.7	0.5
	URINARY HESITATION	0	0.2	0		
	URINARY INCONTINENCE	0	0.5	0		
	URINARY RETENTION	0	0	0.3		
	URINARY TRACT INFECTION NOS				4.8	3.6
	URINARY TRACT INFECTION PSEUDOMONAL				0.7	0.5
	URINE ABNORMAL NOS				0.7	0.5

	URINE ODOUR ABNORMAL	0	0	0.2		
	BALANITIS	0.7	0	0.2		
	BALANITIS NOS				0.7	0.5
	BENIGN PROSTATIC HYPERPLASIA	0.7	0.2	0.2	0.7	0.5
	BREAST MASS	0	0.2	0		
	BREAST MASS NOS				0.7	0.5
	BREAST PAIN	0	0.2	0.2		
	CERVICAL DYSPLASIA	0	0	0.2		
	DYSMENORRHOEA	0	0	0.2		
	EJACULATION DISORDER	0	0.2	0		
	EPIDIDYMITIS	0	0	0.2		
	ERECTILE DYSFUNCTION	1.4	0.5	0.8	0.7	1
	ERECTILE DYSFUNCTION NOS				3.4	3.1
	FIBROCYSTIC BREAST DISEASE	0	0	0.2		
	GENITAL LESION	0.7	0.2	0.2		
	GENITAL PRURITUS FEMALE	0.7	0	0		
	GYNAECOMASTIA	0.7	0.5	0		
	HAEMATOSPERMIA	0.7	0	0	0.7	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	HYPERTROPHY BREAST				0.7	0.5
	MENORRHAGIA	0	0	0.2		
	NIPPLE EXUDATE BLOODY				0.7	0.5
	NIPPLE OEDEMA				0.7	0.5
	PENILE DISCHARGE				0.7	0.5
	PENILE SWELLING	0	0.2	0		
	PENIS DISORDER	0	0	0.2		
	PEYRONIE'S DISEASE				0.7	0.5
	PROSTATIC HYPERTROPHY				0.7	0.5
	PROSTATITIS	0.7	0.2	0		
	SEXUAL DYSFUNCTION	0	0.2	0		
	TESTICULAR PAIN	0	0.2	0		
	TESTICULAR SWELLING	0	0.2	0		
	VAGINAL DISCHARGE	0	0.2	0		
	VAGINAL DYSPLASIA	0	0.2	0		
	VAGINAL HAEMORRHAGE				0.7	0.5
	VAGINAL LESION	0	0	0.2		
	VARICOCELE	0	0.2	0		
	VULVOVAGINAL DISCOMFORT				0.7	0.5
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ACUTE EXACERBATION OF CHRONIC BRONCHITIS NOS				0.7	0.5
	ACUTE PULMONARY OEDEMA	0	0.2	0.2		
	ALLERGIC RESPIRATORY DISEASE	0	0	0.2		
	ALLERGIC SINUSITIS	0	0.2	0		
	ASTHMA	0.7	0.9	0	0.7	1

ASTHMA NOS				1.4	1
ASTHMATIC CRISIS	0	0	0.2		
BRONCHITIS ACUTE NOS				1.4	1.5
BRONCHITIS NOS				7.5	7.1
BRONCHOSPASM	0	0	0.2		
CATARRH				0	0.5
CHEST TIGHTNESS				1.4	1
CHOKING	0	0	0.2	0	0.5
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0	0.2		
COUGH	6.9	6.5	5.8	9.5	9.2
COUGH AGGRAVATED				0	0.5
DRY THROAT				0.7	0.5
DYSPHONIA	0	0.2	0	0.7	0.5
DYSPNOEA	1.4	0.9	1.8	2.7	2.6
DYSPNOEA EXACERBATED				0	0.5
DYSPNOEA EXERTIONAL	0	1.2	0.7		
DYSPNOEA NOS				2	1.5
EPISTAXIS	0.7	0.2	0.3	2.7	2
HAEMOPTYSIS	0	0.2	0.3		
HICCUPS	0.7	0	0.2	0.7	0.5
HYPOXIA	0	0	0.2		
INTERSTITIAL LUNG DISEASE	0	0	0.2		
LARYNGEAL OEDEMA	0	0	0.2		
LOWER RESPIRATORY TRACT INFECTION NOS				0.7	1
LUNG DISORDER	0.7	0	0.2		
LUNG INFILTRATION	0	0	0.2		
MAXILLARY SINUSITIS				0	0.5
NASAL CONGESTION	2.1	1.2	0.8	4.8	5.1
NASAL DISCOMFORT				1.4	1
NASAL SEPTUM PERFORATION	0.7	0	0		
NASAL ULCER	0	0.2	0		
OROPHARYNGEAL SWELLING				0.7	0.5
PHARYNGEAL ERYTHEMA	0.7	0.2	0	0.7	0.5
PHARYNGEAL HAEMORRHAGE				0.7	0.5
PHARYNGEAL INFLAMMATION	0	0.2	0		
PHARYNGOLARYNGEAL PAIN	0.7	1.6	1.2	3.4	2.6
PLEURISY	0	0	0.2	0.7	0.5
PLEURITIC PAIN	0	0.2	0		
PNEUMOCYSTIS CARINII PNEUMONIA				0.7	0.5
PNEUMONIA NOS				4.1	3.1
PNEUMONITIS				0.7	0.5
POSTNASAL DRIP	0.7	0.2	0		

	PRODUCTIVE COUGH	0.7	0.9	0.5	1.4	1.5
	PULMONARY CONGESTION	0	0.2	0		
	PULMONARY EMBOLISM	0.7	0	0.3		
	PULMONARY HAEMORRHAGE	0	0	0.2		
	PULMONARY OEDEMA	0	0	0.2		
	RALES	0	0.5	0.2	0.7	0.5
	RESPIRATORY FAILURE	0.7	0	0		
	RESPIRATORY TRACT CONGESTION	0	0	0.2		
	RESPIRATORY TRACT INFECTION NOS				2	2
	RHINITIS ALLERGIC	0.7	0.7	1.2		
	RHINITIS ALLERGIC NOS				0.7	0.5
	RHINITIS NOS				1.4	2
	RHINORRHOEA	0.7	1.2	0.7	2	2
	RHONCHI	0	0.2	0	0	0.5
	SINUS CONGESTION	0	1.2	0.7	3.4	2.6
	SINUSITIS ACUTE NOS				1.4	1
	SINUSITIS CHRONIC NOS				0.7	0.5
	SINUSITIS NOS				4.8	3.6
	SLEEP APNOEA SYNDROME	0	0	0.3		
	SNEEZING	0	0.2	0.3	0	1
	THROAT IRRITATION	0	0	0.2	0.7	0.5
	TONSILLAR DISORDER				0.7	0.5
	TONSILLAR HYPERTROPHY	0.7	0.2	0.2		
	TONSILLITIS ACUTE NOS				0	1
	UPPER RESPIRATORY TRACT CONGESTION	0	0.5	0.2		
	UPPER RESPIRATORY TRACT INFECTION NOS				12.9	11.2
	UPPER RESPIRATORY TRACT INFECTION VIRAL NOS				0	0.5
	WHEEZING	0	0	0.3	2	2.6
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ACNE	1.4	1.9	1.2		
	ACNE CYSTIC				0.7	0.5
	ACTINIC KERATOSIS	0	0	0.3	0.7	0.5
	ALOPECIA	0	0.5	1		
	ALOPECIA AREATA	0	0.2	0		
	BLISTER	0	0	0.3	0.7	0.5
	CELLULITIS STAPHYLOCOCCAL				0.7	0.5
	DECUBITUS ULCER	0	0	0.3		
	DERMAL CYST	0	0.2	0.3		
	DERMATITIS	0.7	0.7	0.7	1.4	1
	DERMATITIS ACNEIFORM	0.7	0	0.2		
	DERMATITIS ALLERGIC	0.7	0	0.3	0.7	1
	DERMATITIS CONTACT	0.7	0	0.7	1.4	1.5

DERMATITIS EXFOLIATIVE				0	0.5
DERMATITIS MEDICAMENTOSA				5.4	4.6
DERMATITIS PSORIASIFORM	0	0	0.2		
DERMATOSIS	0	0	0.2		
DRUG ERUPTION	0.7	0	0.2		
DRY SKIN	0.7	1.4	1	4.1	5.1
DYSHIDROSIS	0.7	0.2	0	0	0.5
ECZEMA	1.4	0.9	1.7	3.4	3.1
EOSINOPHILIC PUSTULAR FOLLICULITIS	0.7	0.2	0.2	0.7	0.5
EPIDERMAL NAEVUS				0.7	0.5
ERYTHEMA	1.4	1.2	0.7	5.4	5.1
ERYTHEMA NODOSUM	0	0.2	0		
FUNGAL RASH				0.7	0.5
GRANULOMA SKIN	0	0	0.2		
GUTTATE PSORIASIS	0	0.2	0		
HEAT RASH	0	0.2	0		
HIDRADENITIS	0	0.2	0		
HYPERHIDROSIS	0.7	0.7	0.7	0.7	1
HYPERKERATOSIS	0	0.5	0.3		
HYPOAESTHESIA FACIAL	0	0.2	0		
HYPOTRICHOSIS	0.7	0	0		
IMPETIGO NOS				0.7	0.5
INGROWING NAIL	0.7	0	0	1.4	1
INGROWN HAIR	0	0.2	0	0.7	0.5
INTERTRIGO	0	0.2	0		
LEUKOPLAKIA	0.7	0.2	0		
LICHEN PLANUS				0.7	0.5
LIPOATROPHY	0.7	0.2	0.8	2	3.1
LIPODYSTROPHY ACQUIRED	0	0.2	0.2	0.7	0.5
LIPOHYPERTROPHY	2.8	1.4	1.3	0.7	0.5
NAIL DISCOLOURATION	0	0.2	0.2		
NAIL DISORDER	0	0.2	0		
NAIL PIGMENTATION	0	0.5	0		
NEURODERMATITIS	0	0	0.2		
NIGHT SWEATS	1.4	3	2.6	6.1	5.6
PALMAR ERYTHEMA	0	0	0.2		
PENILE ULCERATION				0.7	0.5
PHOTODERMATOSIS	0	0.2	0		
PHOTOSENSITIVITY REACTION NOS				0	0.5
PIGMENTATION DISORDER	0	0	0.2		
PITYRIASIS				0.7	0.5
PITYRIASIS ROSEA				0.7	0.5

POLYMORPHIC LIGHT ERUPTION	0	0	0.2	0	0.5
PRURIGO	2.1	0.9	1.3	1.4	1
PRURITUS	3.4	2.8	4.6	3.4	5.1
PRURITUS GENERALISED	1.4	0.2	0	1.4	1.5
PSORIASIS	0	0.5	0		
PURPURA	0	0.2	0.2		
RASH	11.7	7.9	5.5	2	1.5
RASH ERYTHEMATOUS	0	0.2	0.3	0.7	0.5
RASH FOLLICULAR	0	0	0.2		
RASH GENERALISED	1.4	0.5	0		
RASH MACULAR	0.7	0.9	1.3	1.4	1
RASH MACULO-PAPULAR	1.4	1.4	0.8	3.4	3.1
RASH NOS				2	1.5
RASH PAPULAR	2.1	0.9	0.7	3.4	3.6
RASH PRURITIC	0.7	1.2	0.2	0.7	0.5
RASH SCALY				0.7	0.5
ROSACEA	0	0.2	0.5		
SCAB	0	0.2	0		
SEBACEOUS HYPERPLASIA	0	0	0.2		
SEBORRHOEA	0	0.2	0	1.4	1.5
SEBORRHOEIC DERMATITIS	0.7	1.9	1	4.1	4.1
SKIN BURNING SENSATION	0	0.2	0		
SKIN CHAPPED				0.7	0.5
SKIN DEPIGMENTATION	0.7	0	0		
SKIN DESQUAMATION NOS				1.4	1
SKIN DISCOLOURATION	0	0	0.3		
SKIN HYPERPIGMENTATION	0	0	0.5	0.7	1.5
SKIN HYPOPIGMENTATION				0.7	0.5
SKIN INFLAMMATION	0	0.2	0		
SKIN LESION	0.7	0.7	1.2	0.7	0.5
SKIN LESION NOS				0.7	0.5
SKIN NODULE	0	0.2	0	0.7	0.5
SKIN REACTION	0	0.2	0		
SKIN ULCER	0	0	0.5	0.7	0.5
SKIN WARM				0.7	0.5
SPIDER NAEVUS				0	0.5
STEVENS-JOHNSON SYNDROME	0	0	0.2		
SUBCUTANEOUS NODULE	0.7	0.2	0.2		
SWEAT GLAND INFECTION				0	0.5
SWEATING INCREASED				1.4	1
SWELLING FACE	0.7	0.2	0	1.4	2
URTICARIA	0	0	0.3		

	VIRAL RASH NOS				0.7	0.5
	XERODERMA	0	0	0.2		
SOCIAL CIRCUMSTANCES	DRUG ABUSER	0	0	0.2		
	ANAL SKIN TAG EXCISION	0.7	0	0		
	ANGIOPLASTY				0.7	0.5
	BENIGN TUMOUR EXCISION				0.7	0.5
	CARTILAGE GRAFT	0	0.2	0		
	COLOSTOMY	0	0	0.2		
	CORONARY ANGIOPLASTY	0	0.2	0		
	CORONARY ARTERIAL STENT INSERTION	0	0.2	0		
	CORONARY ARTERY SURGERY				0.7	1
	DENTAL OPERATION NOS				0.7	0.5
	DRUG DETOXIFICATION	0	0.2	0		
	DRUG IMPLANTATION	0	0.2	0		
	ENDODONTIC PROCEDURE				0	0.5
SURGICAL AND MEDICAL PROCEDURES	FULGURATION	0.7	0	0		
	HIP ARTHROPLASTY	0	0	0.2	1.4	1
	INFUSION	0	0.2	0		
	MALIGNANT TUMOUR EXCISION	0	0.2	0		
	MOLE EXCISION	0	0.2	0		
	NAIL OPERATION	0	0.2	0		
	NASAL SINUS DRAINAGE				0.7	0.5
	NERVE BLOCK				0.7	0.5
	POLYPECTOMY				0.7	0.5
	SKIN NEOPLASM EXCISION	0	0	0.2		
	SURGERY				0	0.5
	TOOTH EXTRACTION	0	0.2	0.2	0.7	0.5
	TOOTH EXTRACTION NOS				0.7	0.5
	WART EXCISION	0.7	0	0		
	WISDOM TEETH REMOVAL				0.7	0.5
VASCULAR DISORDERS	AORTIC STENOSIS				0.7	0.5
	BLOOD PRESSURE FLUCTUATION	0	0.2	0.2		
	DEEP VEIN THROMBOSIS	0.7	0.2	0.2	0.7	0.5
	FEMORAL ARTERY OCCLUSION	0	0	0.2		
	FLUSHING	0.7	0.2	0.2		
	HAEMATOMA	0	0.2	0		
	HAEMATOMA NOS				0	0.5
	HAEMORRHAGE	0	0	0.2		
	HOT FLUSH	0	0	0.5	0	0.5
	HYPERTENSION	5.5	3.7	3	2.7	2.6
	HYPERTENSION NOS				0.7	1

HYPERTENSIVE CRISIS	0	0.2	0		
HYPOTENSION	0	0.9	0.5	1.4	1
HYPOTENSION NOS				1.4	1
MICROANGIOPATHY	0	0.2	0		
ORTHOSTATIC HYPOTENSION	0	0.2	0.2	0	0.5
PALLOR	0	0.2	0.2		
PERIPHERAL VASCULAR DISORDER	0	0	0.2		
PETECHIAE				1.4	1
PHLEBITIS	0	0.2	0.5		
SHOCK	0	0	0.2		
THROMBOPHLEBITIS	0	0	0.2	1.4	1
THROMBOSIS	0	0	0.2		
VARICOSE ULCERATION				0.7	0.5
VARICOSE VEIN				0.7	0.5
VASCULAR INSUFFICIENCY	0	0	0.2		
VASCULITIS	0	0	0.2		
VENOUS INSUFFICIENCY	0	0	0.2		

Appendix II

Comparison of treatment-emergent abnormalities of select laboratory tests among the highest quartile and lower 3 quartiles of etravirine exposure and placebo treated subjects in DUET trials

Laboratory test or examination name	Worst toxicity grade[††]	Highest Quartile (DUET) N=145 (%)	Lower Quartiles (DUET) N=431 (%)	Placebo Subjects (DUET) N=604 (%)
ALANINE AMINO TRANSFERASE	GRADE 0	58.9	70.3	71.0
CREATININE	GRADE 0	71.6	82.6	83.4
HAEMOGLOBIN	GRADE 0	90.8	92.1	86.8
LOW DENSITY LIPOPROTEIN CALCULATED	GRADE 0	50.4	57.1	60.4
ALANINE AMINO TRANSFERASE	GRADE 1	27.0	20.9	21.4
CREATININE	GRADE 1	15.6	11.1	9.9
HAEMOGLOBIN	GRADE 1	5.0	4.4	8.3
LOW DENSITY LIPOPROTEIN CALCULATED	GRADE 1	21.3	25.5	22.0
ALANINE AMINO TRANSFERASE	GRADE 2	13.5	6.5	6.0
CREATININE	GRADE 2	10.6	5.3	4.8
HAEMOGLOBIN	GRADE 2	3.5	2.1	3.6
LOW DENSITY LIPOPROTEIN CALCULATED	GRADE 2	16.3	11.1	9.4
ALANINE AMINO TRANSFERASE	GRADE 3	2.1	1.9	1.3
CREATININE	GRADE 3	5.0	0.9	1.5
HAEMOGLOBIN	GRADE 3	2.1	0.9	0.7
LOW DENSITY LIPOPROTEIN CALCULATED	GRADE 3	7.8	4.9	6.1
ALANINE AMINO TRANSFERASE	GRADE 4	1.4	0.5	0.3
CREATININE	GRADE 4	0.0	0.0	0.3
HAEMOGLOBIN	GRADE 4	1.4	0.5	0.7
LOW DENSITY LIPOPROTEIN CALCULATED	GRADE 4	0.0	0.0	0.0

[††] Categories are mutually exclusive with one grade per patient per laboratory test or examination name.
Data source: lbad.xpt, dmad.xpt and run75 NONMEM POPPK analyses

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/s/

Pravin Jadhav
1/17/2008 11:19:45 PM
BIOPHARMACEUTICS

Jogarao Gobburu
1/18/2008 05:50:52 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-187	Submission Date: July 18, 2007
Brand Name	INTELENCE
Generic Name	ETRAVIRINE
Reviewer	Vikram Arya, Ph.D.
In Vitro Metabolism Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Pharmacometrics Reviewer	Pravin Jadhav, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	DAVP
Sponsor	Tibotec
Relevant IND(s)	IND 63, 646
Submission Type; Code	505 (b) (1), 1P
Formulation; Strength(s)	Tablet ; 100 mg
Dosing regimen	200 mg b.i.d.
Indication	Treatment of HIV-1 infection

Table of Contents

1 Executive Summary

Etravirine (TMC125), a substituted diarylpyrimidine derivative, is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Etravirine is proposed for the treatment of HIV-1 infection

The recommended dose is 200 mg b.i.d.

The sponsor collected pivotal efficacy and safety data from 2 identical, ongoing 48-week (with optional 48 week treatment extension period), randomized, double blind, placebo-controlled clinical trials: **TMC125-C206 (DUET-1)** and **TMC125-C216 (DUET 2)**. DUET-1 and DUET 2 trials were designed to evaluate the long term efficacy, tolerability, and safety of TMC125 in treatment experienced patients. The subjects received TMC125 200 mg b.i.d. (as formulation F060) in addition to an optimized background regimen (OBR) or placebo (in addition to the optimized background regimen). The OBR consisted of darunavir/ritonavir 600/100 mg b.i.d. and at least 2 other investigator selected antiretroviral agents (NRTIs with or without enfuvirtide). The primary analysis, performed when all subjects completed 24 weeks of treatment or dropped out earlier, provided key efficacy and safety data in the treatment experienced patient population.

1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics Information provided by the Sponsor is acceptable. All the subjects enrolled in the pivotal clinical trials (TMC125-C206 and TMC125-C216) received darunavir/ritonavir 600/100 mg b.i.d. which was shown to reduce the systemic exposures of etravirine by approximately 40 %. As the pivotal efficacy and safety data were collected at these "reduced" etravirine exposures, the lack of data to support dosing recommendations for TMC125 when dosed with drugs that do not decrease TMC125 exposures represented a major omission. The language in the package insert and a post-marketing commitment address this omission.

1.2 Phase IV Commitments

The following postmarketing commitments (PMCs) will provide further information regarding the safe and effective use of etravirine in the target population.

1. Conduct an *in vivo* drug-drug interaction study between etravirine and fluconazole.

2. Conduct an *in vivo* drug-drug interaction study between etravirine and buprenorphine/naloxone.

In addition to the post marketing commitments outlined above, the following post marketing commitment (requested by the clinical division with input from the clinical pharmacology team) is expected to provide further information regarding the safe and effective use of INTELENCE:

Conduct a 48-week clinical study of treatment-experienced patients enrolling at least 200 subjects to evaluate safety and pharmacokinetics of etravirine when given with drug combinations that do not contain darunavir/rtv. Submit an interim report including analyses of 12-week safety data and supportive efficacy data with the Safety Update submission for the traditional approval supplemental new drug application for etravirine.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Etravirine is proposed for the treatment of HIV-1 infection

Etravirine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent polymerase activities by causing a disruption of the enzyme's catalytic site. This binding to the reverse transcriptase results in a non-competitive inhibition of the HIV-1 reverse transcriptase. The proposed oral dose of etravirine is 200 mg twice daily (two 100 mg tablets) following a meal.

The sponsor conducted 36 clinical trials to characterize the biopharmaceutics (10 trials), pharmacokinetics (4 trials), potential of darunavir to prolong the QT interval (1 trial) special populations (hepatic impairment; 1 trial), mass balance study (1 trial) and drug-drug interaction potential (19 trials) of TMC125. In addition, the sponsor developed a population pharmacokinetic model using data from healthy and HIV-1 infected subjects. This model was used to obtain the pharmacokinetic parameters based on sparse sampling from subjects enrolled in the two pivotal phase III trials.

Exposure Response

Virologic success

- The effect of TMC125 exposures on the viral load was analyzed as a binary variable. The effect of TMC125 exposures and various prognostic factors on viral load was evaluated. A subject's viral susceptibility to the protease inhibitor darunavir was the strongest predictor of success. All subjects in the phase III trials (TMC125 and placebo groups) received darunavir plus low dose ritonavir (DRV/rtv) plus at least 2 other antiretroviral drugs.
- There was a modest dependency of virologic success on baseline viral load, baseline CD4+ cell count, compliance, phenotypic sensitivity score, C_{min} (of TMC125), AUC (of TMC125), and IQ (ratio between steady-state trough concentration and the baseline IC_{50} value; IQ combines the drug concentration and the susceptibility of a patient's virus to TMC125). The predicted likelihood of response as a function of the C_{min} and IQ of TMC125 showed an initial increase and seemed to reach a plateau. The proportion of patients with virologic success (viral load < 400 copies/mL) was 52 % in the placebo treated patients, 59 % in the group with median IQ of 47 (range 0.3-161), 75 % in the group with median IQ of 295 (range 161-487), 85 % in the group with median IQ of 833 (range 487-1409) and 89 % in the group with median IQ of 2583 (range 1409-11402).

- Simulations were conducted to assess the effect of doubling TMC125 exposures (C_{min}) in patients with IQ < 400. The probability of virologic success increased to 77 % from 74.5 % by doubling the exposure. The marginal increase of 2.5 % was observed. There were more failures in patients with higher resistance to DRV even if they achieved a relatively higher TMC125 IQ. On the other hand, less number of failures were seen in patients with less resistance to DRV and a relatively low TMC125 IQ. In order to achieve the response rate seen in phase III trials, it is important that the patient's drug regimen include at least one fully active and strong agent, for example DRV, while adding TMC125 to the patient's antiretroviral regimen.

Safety

The incidence of rash has been previously observed with other NNRTIs. In addition, there were several cases of rash identified throughout the development of TMC125. Therefore, the occurrence of rash and its association with systemic exposure of TMC125 was evaluated in detail.

- A total of 167 records (from 141 subjects) of rash and rash type events were identified. In the pooled DUET analyses, the proportion of subjects with rash (any type) was higher in TMC125 group (15 %) compared to the placebo group (8 %). The trend was similar in individual studies, however, the proportion of subjects with rash (any type) was higher (18 %) in DUET-1 compared to DUET-2 (12 %).

- Rash with TMC125 treatment mostly emerged during the first weeks of treatment. For the rashes in the TMC125 group, the median time to onset was 12 days (range 1 to 231 days) and the median duration was 11 days (range 1 to 171 days). The predicted likelihood of response (rash) as a function of TMC125 AUC showed an increase with increasing AUC. The proportion of patients with rash was 8 % in the placebo treated patients, 10 % in the lowest quartile of TMC125 AUC (median = 2413, range = 145-3026 hr•ng/mL), 13 % in the 2nd quartile of TMC125 AUC (median = 3805, range = 3026-4525 hr•ng/mL), 14 % in the 3rd quartile of TMC125 AUC (median = 5462, range = 4525-6530 hr•ng/mL) and 17 % in the last quartile of TMC125 AUC (median = 8882, range = 6530-64164 hr•ng/mL).

Benefit-risk assessment for rash

- Based on exposure-virologic success relationship, TMC125 IQ of > 400 does not lead to incremental benefit in virologic success. An IQ of 400 corresponds to C_{min} of ~200 (400 multiplied by median IC_{50} (0.5)). It was also established that incidence of rash increases with increasing exposures.
- In the DUET trials, no incidence of Stevens-Johnson syndrome was observed in subjects who received TMC125. Rash events appeared in the first few weeks of the treatment. Therefore, in the pharmacometric reviewer's opinion, the exposures of TMC125 should not exceed the exposures achieved in DUET trials. It will be

beneficial to identify characteristics of patients who might be susceptible to TMC125 induced rash.

Absorption

- Etravirine is a low to intermediate permeability compound. Etravirine is thought to permeate cell membranes predominantly *via* a passive trans-cellular diffusion mechanism (provided solubility and dissolution rate are not limiting).

- The mean systemic exposure (AUC_{last}) of TMC125 was increased by 105 % when TMC125 was administered under fed conditions (standardized breakfast; 561 kcal, 15 gms of fat) as compared to when TMC125 was administered under fasted conditions. Other meals increased TMC125 exposure to a similar extent.

- The results of the drug-drug interaction study with drugs that alter the intra-gastric pH (ranitidine and omeprazole; TMC125-C120) suggest that there is no effect of changes in pH on the absorption of TMC125. There was approximately a 40 % increase in the systemic exposures of TMC125 (a CYP2C19 substrate) in the presence of omeprazole, however, this may be attributed to the inhibition of CYP2C19 by omeprazole.

- The absolute bioavailability of TMC125 is unknown.

- The results of trial TMC125-C228 showed that the mean systemic exposures of TMC125 after oral administration of TMC125 200 mg b.i.d. as formulation F060 (F060 was used in the pivotal phase 3 trials) were significantly higher than the mean systemic exposures after oral administration of TMC125 800 mg b.i.d. as formulation TF035 (TF035 was used in phase 2b trials). However, the results of the same trial showed that the individual exposures of TMC125 after multiple dosing in HIV-1 infected subjects were in the same range between TMC125 200 mg b.i.d. as formulation F060 and TMC125 800 mg b.i.d. as formulation TF035.

- The results of study TMC125-C173 showed that systemic exposures of TMC125 were similar after administration of TMC125 as a tablet dispersed in water (1 tablet of TMC125 100 mg, formulation F060, dispersed in 100 mL of water) or as a solid form (1 tablet of TMC125 100 mg, formulation F060).

Distribution

- The *in vitro* plasma protein binding of TMC125, determined by equilibrium dialysis, is approximately 99 % (trial TMC125-NC143). TMC125 is extensively bound to human albumin (87.9 % to 99.7 % at concentrations of 0.1 to 6.0 g/100 mL) and α1-acid glycoprotein (69.2 % to 99.0 % at concentrations of 0.02 to 0.20 g/100 mL).

- The apparent volume of distribution for the central compartment (V_2/F) when TMC125 was modeled with a sequential zero- and first-order absorption and 2-compartment disposition model was 422 L.

- The distribution of TMC125 into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

- The *in vitro* metabolism of TMC125 was studied in human hepatic microsomes. The results of the *in vitro* assessment showed that CYP3A and CYP2C (CYP2C9 and CYP2C19; to a lesser extent) enzymes play a major role in the biotransformation of TMC125.

- The results of the mass balance study (TMC125-C130) showed that most of the administered ^{14}C-TMC125 related radioactivity after oral administration of a single 800 mg dose of the capsule formulation TF002 (TMC125 in PEG 4000) was excreted in the feces. At 168 hours after dosing, a mean of 93.7 % of the administered radioactivity was recovered in the feces, and a mean of 1.2 % of the administered radioactivity was recovered in the urine. The unchanged drug accounted for the majority of the radioactivity in the feces (81.2 % to 86.4 % of the dose). The % of dose excreted in the feces as metabolite 8 ranged from 3.8 % to 9 % of the dose and as metabolite 12 was up to 0.7 % of the dose. No unchanged drug was recovered in the urine.

Excretion

- The results of the mass balance study showed that after a single dose administration of TMC125, the majority of the radioactivity was excreted in the feces. The limited excretion of TMC125 through the renal route suggests that renal elimination is a minor route for TMC125 elimination.

Intrinsic Factors

- Based on population PK analyses, no dose adjustment is needed based on hepatitis B &/or C co-infection, gender, race, and age (age range 18-77 years).

- No dose adjustment of TMC125 is required in subjects with mild or moderate hepatic impairment. TMC125 was not evaluated in subjects with severe hepatic impairment.

- In view of the limited renal excretion of TMC125 (< 2 % as metabolites and no excretion of unchanged drug in the urine), a study to investigate the exposure to TMC125 in subjects with renal impairment was neither conducted nor needed.

Extrinsic Factors

Drug-Drug Interactions

TMC125 is a substrate of CYP3A4, CYP2C9 and CYP2C19. Therefore, co-administration of TMC125 with drugs that are inducers/inhibitors of these enzymes may alter the therapeutic effect or adverse event profile of TMC125. TMC125 is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19, therefore, co-administration of TMC125 with drugs that are substrates of CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse event profile of the co-administered drugs.

Etravirine is a p-gp substrate. In addition, the results of the *in vitro* studies with ^{3}H-paclitaxel showed that TMC125 has weak P-gp inhibitory properties (IC_{50} of 24.2μM {10,500 ng/mL}). The sponsor is planning to determine the *in vivo* p-gp induction/inhibition properties of TMC125 in trial TMC125-C180 (drug-drug interaction study with digoxin).

The drug-drug interaction studies were conducted using various doses and formulations of TMC125. However, the drug-drug interaction trials that provide information to be included in the package insert were conducted either with formulation TF035 (800 mg b.i.d.) or with the to-be-marketed formulation F060 (200 mg b.i.d.). The use of a different dose (800 mg b.i.d.) and different formulation (TF035) should not alter the interpretation of most drug interaction studies.

Table 1 shows the established and other potentially significant drug interactions based on which, alterations in dose or regimen may be recommended. The interactions between TMC125 and the drug preceding the asterisk (*) sign were evaluated in a clinical study; the interactions between TMC125 and other drugs (not preceding the asterisk sign) are predicted.

Table 1: Established and other potentially significant drug interactions: alterations in dose or regimen may be recommended based on drug interaction studies or predicted interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz* nevirapine*	↓ etravirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE™ with efavirenz or nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and other NNRTIs should not be co-administered.

Delavirdine	↑ etravirine	Combining two NNRTIs has not been shown to be beneficial. INTELENCE™ and delavirdine should not be co-administered.
HIV-Antiviral Agents: Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)		
didanosine*	↔ etravirine ↔ didanosine	The combination of INTELENCE™ and didanosine can be used without dose adjustments, however, didanosine should be administered on an empty stomach (2 hours before or 2 hours after a meal) and TMC125 should be administered following a meal.
HIV-Antiviral Agents: Protease Inhibitors (PIs)		
ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with ritonavir 600 mg b.i.d. may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and ritonavir 600 mg b.i.d. should not be co-administered.
atazanavir/ritonavir*	↑ etravirine ↓ atazanavir	Concomitant use of INTELENCE™ with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with atazanavir/ritonavir is anticipated to be about 100% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. INTELENCE™ and atazanavir/ritonavir should not be co-administered.
darunavir/ritonavir*	↓ etravirine ↔ darunavir	The mean systemic exposure (AUC) of etravirine was reduced by about 37% when INTELENCE™ was co-administered with darunavir/ritonavir. Because all subjects in the Phase 3 trials received darunavir/ritonavir as part of the background regimen and etravirine exposures from these trials were determined to be safe and effective, INTELENCE™ and darunavir/ritonavir can be co-administered without any dose adjustments.
fosamprenavir/ritonavir*	↑ amprenavir	Due to a significant increase in the systemic exposure of amprenavir, the appropriate doses of the combination of INTELENCE™ and fosamprenavir/ritonavir have not been established. INTELENCE™ and fosamprenavir/ritonavir should not be co-administered.
lopinavir/ritonavir* (soft gel capsule)	↑ etravirine ↓ lopinavir	The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be about 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. The safety profile at these increased etravirine exposures is unknown, therefore, INTELENCE™ and lopinavir/ritonavir should be co-administered with caution.
saquinavir/ritonavir*	↓ etravirine ↔ saquinavir	The mean systemic exposure (AUC) of etravirine was reduced by about 33% when INTELENCE™ was co-administered with saquinavir/ritonavir. Because the reduction in the mean systemic exposures of etravirine in the presence of saquinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, INTELENCE™ and saquinavir/ritonavir can be co-administered without any dose adjustments.

tipranavir/ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with tipranavir/ritonavir may cause a significant decrease in the plasma concentrations of etravirine. This may result in loss of therapeutic effect of INTELENCE™. It is not recommended to co-administer tipranavir/ritonavir and INTELENCE™.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE™. INTELENCE™ and antiarrhythmics should be co-administered with caution. Drug concentration monitoring is recommended, if available.
Anticoagulants: warfarin	↑ Warfarin	Warfarin concentrations may be increased when co-administered with INTELENCE™. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with INTELENCE.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ etravirine	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE™ should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™.
Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ etravirine ↔ fluconazole ↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	Posaconazole is a potent inhibitor of CYP3A4 and fluconazole is a potent inhibitor of CYP2C9; both may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE™ may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE™. Voriconazole is a CYP2C19 substrate and CYP3A4, CYP2C9 and CYP2C19 inhibitor. Concomitant use of voriconazole and INTELENCE™ may increase plasma concentrations of both drugs. Dose adjustments for itraconazole, ketoconazole or voriconazole may be necessary depending on other co-administered drugs.
Antiinfectives: clarithromycin*	↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Clarithromycin exposure was decreased by INTELENCE™; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
Antimycobacterials: rifampin, rifapentine	↓ etravirine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE™ should not be used in combination with rifampin or rifapentine as co-administration may cause significant decrease in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™.

Antimycobacterials: rifabutin*	↓ etravirine ↓ rifabutin ↓ 25-*O*-desacetylrifabutin	If INTELENCE™ is NOT part of a regimen consisting of Protease Inhibitor/ritonavir, rifabutin at a dose of 300 mg q.d. is recommended If INTELENCE™ is part of a regimen containing darunavir/ritonavir or saquinavir/ritonavir, rifabutin should not be co-administered due to the potential for significant reduction in etravirine exposure.
Benzodiazepines: diazepam	↑ diazepam	Concomitant use of INTELENCE™ with diazepam may increase plasma concentrations of diazepam. A decrease in diazepam dose may be needed.
Corticosteroids: Dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
Estrogen-based Contraceptives: ethinylestradiol* norethindrone*	↔ etravirine ↑ ethinylestradiol ↔ norethindrone	The combination of estrogen- and/or progesterone-based contraceptives and INTELENCE™ can be used without any dose adjustments.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓ etravirine	Concomitant use of INTELENCE™ with products containing St. John's wort may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™. INTELENCE™ and products containing St. John's wort should not be co-administered.
HMG-CoA Reductase Inhibitors: atorvastatin*	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin	The combination of INTELENCE™ and atorvastain can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on clinical response.
fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	↔ etravirine ↑ fluvastatin, ↓ lovastatin, ↔ pravastatin, ↔ rosuvastatin, ↓ simvastatin	No interaction between pravastatin or rosuvastatin and INTELENCE™ is expected. Lovastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE™ may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin is metabolized by CYP2C9 and co-administration with INTELENCE™ may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for these HMG-CoA reductase inhibitors may be necessary.
H_2-Receptor Antagonists Ranitidine* Cimetidine Famotidine	↔ etravirine	INTELENCE™ can be co-administered with H_2-receptor antagonists without any dose adjustments.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↓ etravirine	Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected when co-administered with INTELENCE™.
Narcotic Analgesics:	↔ etravirine	INTELENCE™ and methadone can be co-administered

methadone*	↔ methadone	without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Phosphodiesterase Type 5 (PDE-5) Inhibitors: sildenafil*, vardenafil, tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	INTELENCE™ and sildenafil can be co-administered without dose adjustments, however, the dose of sildenafil may need to be altered based on clinical effect.
Proton Pump Inhibitors: omeprazole*	↑ etravirine	INTELENCE™ can be co-administered with proton pump inhibitors without any dose adjustments.
↑ = increases, ↓ = decreases, ↔ = no change		

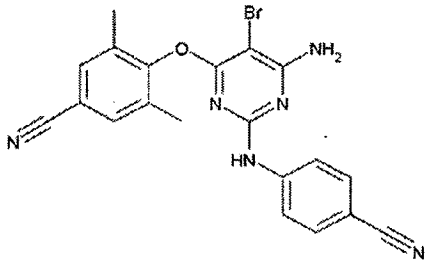
2 Question based review (QBR)

2.1 General Attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Etravirine (TMC125), a substituted diarylpyrimidine derivative, is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

The chemical name for TMC125 is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidinyl]oxy]-3,5-imethylbenzonitrile. The molecular formula for etravirine is $C_{20}H_{15}BrN_6O$ and its molecular weight is 435.28. Etravirine has the following structural formula:



The composition of the proposed to-be-marketed formulation (F060) is shown below.

Table 1: Composition of the proposed to-be-marketed formulation (F060)

Component	Reference to Quality Standard	Function	Quantity per Unit (mg/tablet)
TMC125	Non-compendial	Active ingredient	100.0
Hypromellose (HPMC)[a]	USP		
Microcrystalline cellulose[b]	NF		
Colloidal silicon dioxide	NF		
Croscarmellose sodium	NF		
Magnesium stearate	NF		
Lactose monohydrate	NF		
Total tablet weight:			800

[a] Also referred to as "HPMC" in the dossier

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Etravirine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent polymerase activities by causing a disruption of the enzyme's catalytic site. This binding to the reverse transcriptase results in a non-competitive inhibition of the HIV-1 reverse transcriptase.

Etravirine is proposed for the treatment of HIV-1 infection

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed oral dose of etravirine is 200 mg twice daily (two 100 mg tablets) following a meal. In addition, based on the results of study TMC125-C173, INTELENCE™ whole tablets dispersed in water are expected to provide systemic exposures similar to the systemic exposures observed after administration of TMC125 swallowed as a tablet.

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor collected pivotal efficacy and safety data from 2 identical, ongoing 48-week (with optional 48 week treatment extension period), randomized, double blind, placebo-controlled clinical trials: TMC125-C206 (DUET-1) and TMC125-C216 (DUET 2). DUET-1 and DUET 2 trials were designed to evaluate the long term efficacy, tolerability, and safety of TMC125 in treatment experienced patients. The subjects received TMC125

200 mg b.i.d. (as formulation F060) in addition to an optimized background regimen (OBR) or placebo (in addition to the optimized background regimen). The OBR consisted of darunavir/ritonavir 600/100 mg b.i.d. and at least 2 other investigator selected antiretroviral agents (NRTIs with or without enfuvirtide). The primary analysis, performed when all subjects completed 24 weeks of treatment or dropped out earlier, provided key efficacy and safety data in the treatment experienced patient population.

In total, 1203 subjects were randomized and treated in these ongoing Phase III trials, of which 599 subjects were in the TMC125 group and 604 subjects were in the placebo group. There were no important differences between the 2 pooled treatment groups with respect to demographic parameters and baseline disease characteristics. The trial populations had advanced HIV disease and documented resistance to currently available NNRTIs.

Table 2 shows the outcome of treatment at week 24 of the DUET 1 and DUET 2 trials (pooled analysis).

Table 2: Outcome of treatment at Week 24 of the DUET 1 and DUET 2 Trials (Pooled Analysis)

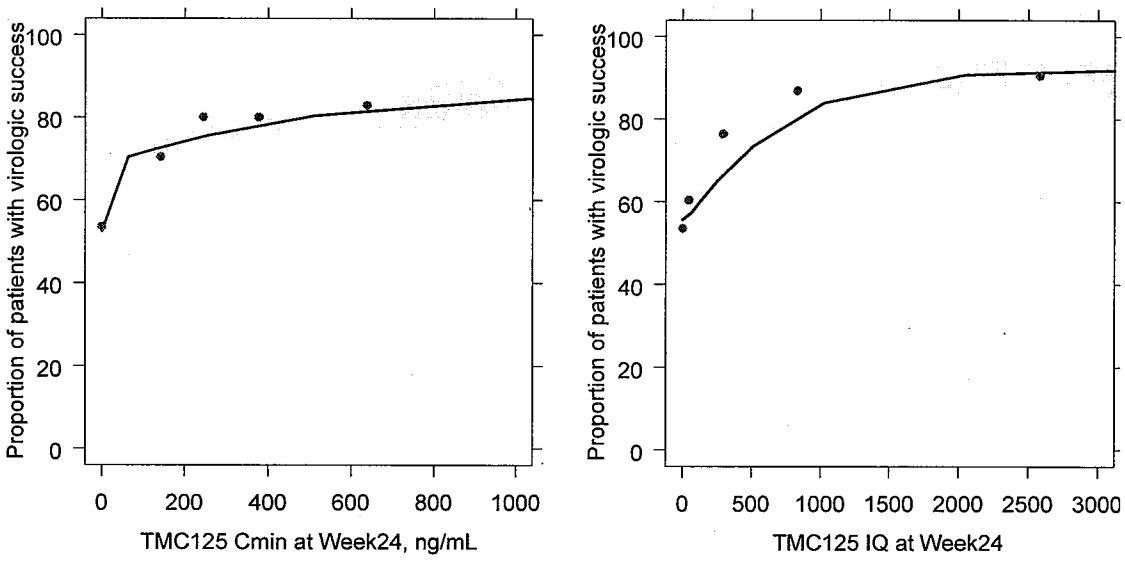
Table 11: Outcomes of Treatment at Week 24 of the TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)		
	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE™ + BR N=599	Placebo + BR N=604
Virologic Responders at Week 24 Viral Load < 50 HIV-1 RNA copies/mL	358 (59.8%)	243 (40.2%)
Virologic Failures (VF) at Week 24 Viral Load ≥ 50 HIV-1 RNA copies/mL	190 (31.7%)	320 (53.0%)
Death*	9 (1.5%)	16 (2.6%)
Discontinuations before Week 24†:		
due to VF	2 (0.3%)	3 (0.5%)
due to Adverse Events	28 (4.7%)	11 (1.8%)
due to other reasons	12 (2.0%)	11 (1.8%)
* all deaths, including the follow-up period † all discontinuations up to and including day 154 of the treatment period BR=background regimen		

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Viral load and CD4+ cell count are accepted as surrogate markers for efficacy in trials with antiretroviral (ARV) agents. In DUET 1 (TMC125-C206) and DUET 2 (TMC125-C216) trials, the primary efficacy parameter was the proportion of subjects with

IQ seem to be more appropriate than C_{min} or AUC as the IQ accounts for C_{min} and fold change in TMC125. The predicted likelihood of response as a function of the C_{min} and IQ of TMC125 showed an initial increase and seemed to reach a plateau. The proportion of patients with virologic success (viral load < 400 copies/mL) was 52 % in the placebo treated patients, 59 % in the group with median IQ of 47 (range 0.3-161), 75 % in the group with median IQ of 295 (range 161-487), 85 % in the group with median IQ of 833 (range 487-1409) and 89 % in the group with median IQ of 2583 (range 1409-11402) (see figure below).

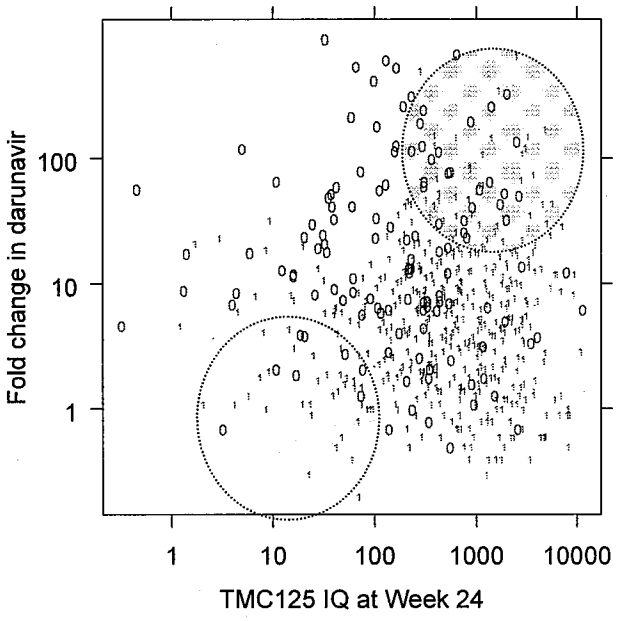
Figure 1: Median (95% CI) prediction of likelihood of response (viral load < 400 copies/mL) as a function of TMC125 Cmin (left panel-Model 3) and IQ (right panel-Model 4), based on the GAM models fitted to 500 bootstrap samples of the original data set. (circles: observed data, line and shaded area: model prediction)



The analysis indicates achieving a TMC125 IQ of at least 400 maximizes the probability of success, which confirmed findings from the end of phase II review by FDA.

Simulations were conducted to assess effect of doubling TMC125 exposures (C_{min}) in patients with IQ < 400. This was accomplished by doubling C_{min} in patients with IQ < 400 while keeping the rest of the data same. The new IQ was calculated. The probability of virologic success increased to 77 % from 74.5 % by doubling the exposure. The marginal increase of 2.5 % was observed. The reason for the small increase (2.5 %) was investigated. There were more failures in patients with higher fold change in DRV even if they achieved relatively higher TMC125 IQ. On the other hand, less number of failures were seen in patients with lower fold change in DRV and relatively low TMC125 IQ (see figure below).

Figure 2: Fold change in DRV and TMC125 IQ in relation to virologic success as defined by viral load <400 copies/mL. Each symbol is represented by an individual patient (Success=1 and Failure=0).



In order to achieve the response rate seen in phase III trials, it is important that patient's ART regimen should have at least one fully active and strong agent, for example DRV, when adding TMC125 to patient's ART.

2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

An exposure response relationship was observed for rash events. Rash events were of interest throughout the TMC125 development program.

A total of 167 records (from 141 subjects) of rash and rash type events were identified. In the pooled DUET analyses, the proportion of subjects with rash (any type) was higher in TMC125 group (15 %) compared to the placebo group (8 %). The trend was similar in individual studies, however, the proportion of subjects with rash (any type) was higher (18 %) in DUET-1 compared to DUET-2 (12 %).

confirmed undetectable viral load (< 50 copies/mL) at week 24. In addition, various secondary efficacy endpoints such as viral load < 400 copies/mL and effects on CD4+ cell count were also assessed.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the sponsor quantified the appropriate moieties in all the clinical pharmacology studies. Etravirine was quantified using sensitive and validated HPLC/MS/MS methods. In addition, concentrations of other moieties were also determined in the drug-drug interaction studies. It was not necessary to measure concentrations of etravirine metabolites, except for in the mass balance study, since based on the results of the *in vitro* studies, the EC_{50} values for the major metabolites (metabolite 12 and metabolite 8) against the NNRTI-resistant virus was significantly higher (metabolite 8 did not show any activity) than etravirine.

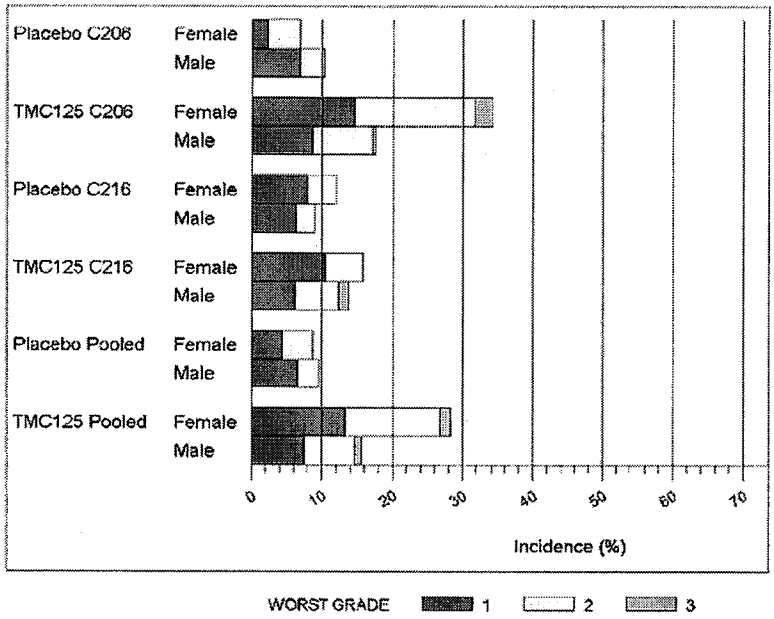
2.2.4 Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The exposure-response (efficacy) relationship was evaluated using data from the two Phase III trials, DUET 1 (TMC125-C206) and DUET 2 (TMC125-C216). The subjects were randomized 1:1 to TMC125 or placebo. All the subjects received the protease inhibitor darunavir with low dose ritonavir (DRV/rtv 600/100 mg b.i.d.) as part of an optimized background regimen (OBR) that included at least 2 other antiretroviral drugs. The effect of TMC125 exposures on viral load was analyzed as a binary variable (virologic success, viral load < 50 or viral load < 400 copies/mL) and the effect of TMC125 exposures and various prognostic factors on viral load was also evaluated. Based on the univariate graphical analyses and logistic regression analyses, the fold change in darunavir susceptibility was the strongest predictor of success. The fold-change in darunavir susceptibility indicates a subject's degree of resistance to darunavir i.e., a higher fold change indicates more resistance and a fold-change of 1 indicates no baseline resistance.

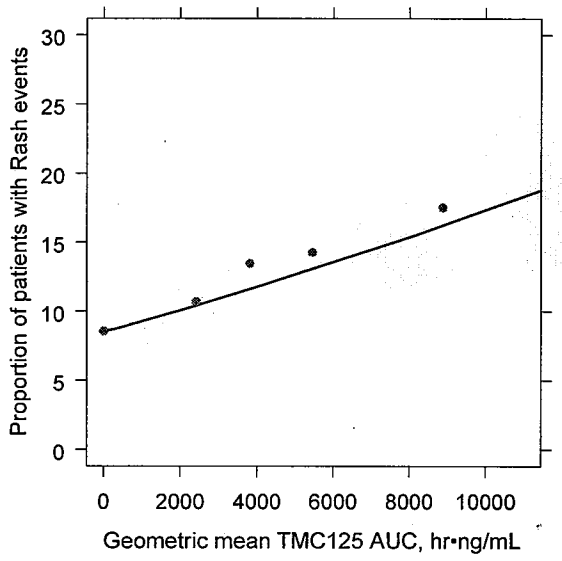
The proportion of patients with virologic success was lower (~ 16 % in the placebo and ~ 52 % in the TMC125 treated patients) at 42 (median of the last quantile) fold change in DRV resistance. On the other hand, the proportion of patients with virologic success (< 400 copies/mL) was higher (~85 % in the placebo and ~85 % in the TMC125 treated patients) at 1.1 (median of the first quantile) fold change in DRV resistance. There was a modest dependency of virologic success on baseline viral load, baseline CD4+ cell count, compliance, phenotypic sensitivity score, C_{min} (of TMC125), AUC (TMC125), and IQ (ratio between steady-state trough concentration and the baseline IC_{50} value; IQ combines the drug concentration and the susceptibility of a patient's virus to TMC125). The use of

Figure 3: Incidence of Rash by Gender and different grade types



Rash with TMC125 treatment mostly emerged during the first weeks of treatment. For the rashes in the TMC125 group, the median time to onset was 12 days (range 1 to 231 days) and the median duration was 11 days (range 1 to 171 days). The predicted likelihood of response (rash) as a function of TMC125 AUC showed an increase with increasing AUC. The proportion of patients with rash was 8 % in the placebo treated patients, 10 % in the lowest quantile of TMC125 AUC (median=2413, range=145-3026 hr•ng/mL), 13 % in the 2nd quantile of TMC125 AUC (median=3805, range=3026-4525 hr•ng/mL), 14 % in the 3rd quantile of TMC125 AUC (median=5462, range=4525-6530 hr•ng/mL) and 17 % in the last quantile of TMC125 AUC (median=8882, range=6530-64164 hr•ng/mL).

Figure 4: Median (95% CI) prediction of likelihood of response (rash event) as a function of TMC125 AUC, based on the GAM models fitted to 500 bootstrap samples of the original data set. (circles: observed data, line and shaded area: model prediction)



2.2.4.3. Does etravirine prolong QT or QTc interval?

In a double-blind, double-dummy, randomized, placebo- and active-controlled, 4- period crossover study, the effect of two different dose regimens of TMC125 (TMC125 200-mg and TMC125 400-mg) on QT/QTc intervals were compared with placebo. The QT intervals were measured on Day 1 and Day 8. The overall findings are summarized in table 3.

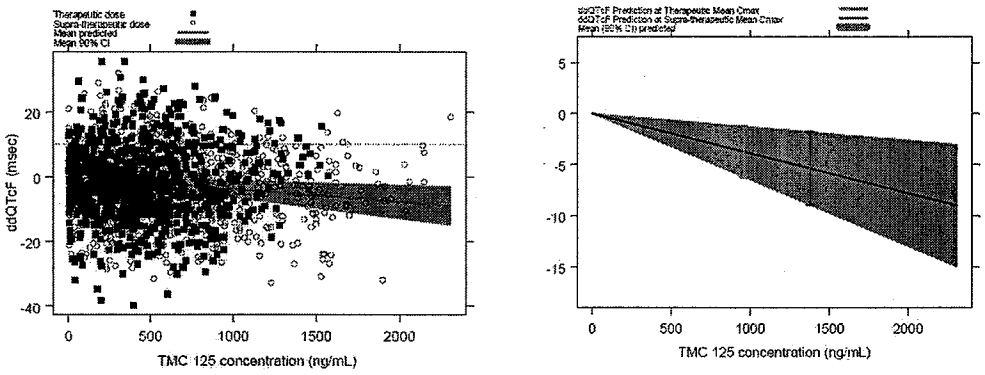
Table 3: FDA Analysis: The Point Estimate and the 90 % CIs Corresponding to the Largest Upper Bounds for TMC125 and the Largest Lower Bound for Moxifloxacin

Drug	Days	Time (h)	ΔΔQTcF (ms)	90% CI (ms)
TMC125 200-mg	1	4.5	0.2	(-2.4, 2.9)
TMC125 200-mg b.i.d.	8	6	0.5	(-2.2, 3.2)
TMC125 400-mg	1	6	0.2	(-2.1, 2.5)
TMC125 400-mg b.i.d.	8	0.5	-1.1	(-4.5, 2.4)
Moxifloxacin 400-mg	1	4	9.8	(5.5, 14.1)

The largest upper 90% bounds for QT_cF are below 10 ms for both TMC125 dosing regimens, indicating that there is no signal of QT prolongation. Assay sensitivity of the

study was confirmed since the largest Bonferroni-adjusted two-sided 90% lower bound for moxifloxacin on Day 1 is greater than 5 ms.

In fact, the study suggests TMC125 shortens the QTc intervals. The upper limits of the two-sided 90% CI of QT_cF between TMC125 and placebo were negative at multiple timepoints, including t_{max}. A linear mixed effects model was used to describe the relationship between TMC125 concentrations and ΔΔQTcF (see figure below).



According to this relationship, TMC125 shortens QTc. The mean (lower CI) ΔΔQTcF at mean C_{max} (~1378 ng/mL) after supratherapeutic dose is -5.7 (-9.25) ms.

The exposures achieved with supratherapeutic dose (400 mg b.i.d.) are expected to cover the increases in plasma concentrations due to drug-drug interactions, co-infection with hepatitis B and/or C, and mild-to-moderate liver impairment. When the exposures achieved in this trial were compared to those observed in the phase III studies, approximately 1 % of the HIV patients had higher plasma concentrations.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose selection was agreed upon between the sponsor and the agency at the end of phase 2 meeting. The review was done by Dr. He Sun. The dose selection for the registrational Phase III efficacy and safety trials with TMC125 in HIV-1 infected subjects (DUET-1 and DUET-2) was based on the antiviral activity (change in log_{10} plasma viral load from Baseline at Week 24), safety (incidence and severity of adverse events and laboratory parameters), pharmacokinetics, and pharmacokinetic/pharmacodynamic assessments that were obtained from the primary analysis of the Phase 2b dose-escalating trial TMC125-C203 and the Phase 2b dose-finding trial TMC125-C223, both conducted in HIV-1 infected subjects with previous NNRTI experience and/or resistance. These earlier trials were conducted using TMC125 administered as tablet formulation TF035 (TMC125 in HPMC, [redacted], and therefore a second stage of the dose selection process investigated the correspondence of TMC125 dosing between formulation TF035

and the final, selected formulation F060 (TMC125 in HPMC, spray-dried) to be used in the Phase 3 efficacy and safety trials and intended for commercialization.

The observation made in the end of phase 2 meeting review was confirmed in phase 3 that an IQ of at least 400 is required to maximize the probability of virologic success.

2.2.5. What are the PK characteristics of etravirine?

2.2.5.1. What are the single dose and multiple dose PK parameters?

The PK of etravirine was determined as a single dose (day 1) after oral administration of F060 in healthy subjects in two trials (TMC125-C168 and TMC125-C178). Table 4 shows the PK parameters.

Table 4: Single dose pharmacokinetic parameters of TMC125

	Mean ± SD; t_{max}: Median (Range)			
	100 mg	200 mg		400 mg
Parameter	TMC125-C168	TMC125-C168	TMC125-C178	TMC125-C178
N	23	24	39	39
t_{max}, h	4.0 (3.0 - 6.0)	4.0 (3.0 - 6.0)	4.08 (2.08 - 6.12)	4.08 (2.08 - 6.10)
C_{max}, ng/mL	143 ± 55	326 ± 121	370 ± 149	715 ± 264
AUC_{12h}, ng.h/mL	875 ± 409	-	2281 ± 1005	-
AUC_{24h}, ng.h/mL	1749 ± 819 [a]	2797 ± 1014	4562 ± 2010 [b]	6688 ± 2749

N = maximum number of subjects with data.
[a] For 100 mg TMC125 b.i.d., AUC_{24h} was calculated as 2 x AUC_{12h}.
[b] For 200 mg TMC125 b.i.d., AUC_{24h} was calculated as 2 x AUC_{12h}.

The mean exposure parameters (C_{max} and AUC) showed a dose proportional increase within the evaluated dose range (100 mg -400 mg). The mean exposure parameters observed in other studies where the pharmacokinetics of etravirine (100 mg administered as F060) was evaluated in healthy subjects were similar to the exposure parameters reported in table 4. The mean terminal half life of etravirine ranged from 25-60 hours.

Table 5 shows the multiple dose PK parameters in healthy subjects across two trials (TMC125-C168 and TMC125-C178).

Table 5: Multiple dose PK parameters in healthy subjects

	Mean ± SD; t_{max}: Median (Range)			
	100 mg b.i.d.	200 mg q.d.	200 mg b.i.d.	400 mg q.d.
Parameter	TMC125-C168	TMC125-C168	TMC125-C178	TMC125-C178
N	23	24	39	39
t_{max}, h	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)	4.08 (2.08 - 6.08)	4.08 (3.08 - 6.13)
C_{0h}, ng/mL	234 ± 92	167 ± 77	529.5 ± 172.5	382.1 ± 145.0
C_{max}, ng/mL	471 ± 141	659 ± 177	958.8 ± 278.1	1393 ± 385.9
AUC_{12h}, ng.h/mL	3925 ± 1251	-	8195 ± 2428	-
AUC_{24h}, ng.h/mL	7628 ± 2506	8054 ± 2748	16390 ± 4856 [a]	17220 ± 5009

N = maximum number of subjects with data.
[a] For 200 mg TMC125 b.i.d., AUC_{24h} was calculated as 2 x AUC_{12h}.

There was a dose proportional increase in the systemic exposures (AUC) of etravirine between total daily doses of 200 mg and 400 mg. Further, the systemic exposures were 200 % -700 % higher on day 8 (steady state) as compared to day 1.

2.2.5.2. How does the PK of etravirine and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetics of etravirine in HIV infected subjects was determined as part of the pharmacokinetic sub-study in DUET 1 and DUET 2 trials. In the pharmacokinetic sub-study, subjects participated in a 12-hour pharmacokinetic sampling period in addition to assessments required for the main study. Table 6 shows the PK parameters computed based on the intensive sampling.

Table 6: Summary of the Pharmacokinetic Parameters Computed Based on the Intensive Sampling in DUET 1 and DUET 2 trials

Parameter	Mean ± SD; t_{max}: Median (Range)	
	DUET-1	DUET-2
Week 4		
N	9	16
t_{max}, h	4.00 (0.08 - 6.08)	3.00 (2.00 - 6.00)
C_{6h}, ng/mL	298.9 ± 164.5	683.4 ± 1000
C_{12h}, ng/mL	296.8 ± 146.2	736.7 ± 1276
C_{min}, ng/mL	242.6 ± 148.6	570.7 ± 993.1
C_{max}, ng/mL	527.4 ± 174.7	1078 ± 1251
$C_{ss,av}$, ng/mL	366.5 ± 155.9	831.2 ± 1132
AUC_{12h}, ng.h/mL	4390 ± 1872	9974 ± 13640
FI, %	86.12 ± 36.24	84.60 ± 33.36
Week 24		
N	10	12
t_{max}, h	3.03 (2.02 - 6.03)	4.00 (1.02 - 6.00)
C_{6h}, ng/mL	397.3 ± 253.4	482.9 ± 685.0
C_{12h}, ng/mL	341.7 ± 285.3	506.9 ± 792.8
C_{min}, ng/mL	330.3 ± 261.5	469.1 ± 721.0
C_{max}, ng/mL	697.6 ± 398.5	874.2 ± 826.6
$C_{ss,av}$, ng/mL	489.6 ± 325.1	668.6 ± 769.2
AUC_{12h}, ng.h/mL	5840 ± 3891	8028 ± 9233
FI, %	85.84 ± 26.47	90.62 ± 40.63

N = maximum number of subjects with data.

A comparison of the pharmacokinetic parameters in healthy subjects (table 5) and HIV infected subjects suggests that the systemic exposures were lower in HIV subjects as compared to healthy subjects. The lower systemic exposures of etravirine in HIV infected subjects as compared to healthy subjects may be because HIV infected subjects in the DUET 1 and DUET 2 trials were administered darunavir/ritonavir as part of the optimized background regimen. The co-administration of darunavir/ritonavir and etravirine has been shown to reduce the systemic exposures of etravirine by ~ 40 % (Trial TMC125-C176).

2.2.5.3. What are the characteristics of drug absorption?

The comparison of the transepithelial permeation rates of TMC125 with the transepithelial permeation rates of reference compounds (alniditan, levocabastine, and theophylline) suggests that entravirine is a compound with low to intermediate permeability. Etravirine is thought to permeate cell membranes

predominantly *via* a passive transcellular diffusion mechanism (provided solubility and dissolution rate are not limiting).

The results of the drug-drug interaction study with drugs that increase the intra-gastric pH (ranitidine and omeprazole; TMC125-C120) suggest that there is no effect of increase in the pH on the absorption of TMC125. There was approximately a 40 % increase in the systemic exposures of TMC125 (a CYP2C19 substrate) in the presence of omeprazole, however, this may be attributed to the inhibition of CYP2C19 by omeprazole.

The absolute bioavailability of TMC125 is unknown.

2.2.5.4. What are the characteristics of drug distribution?

The *in vitro* plasma protein binding of TMC125, determined by equilibrium dialysis, is approximately 99 % (trial TMC125-NC143). TMC125 is extensively bound to human albumin (87.9 % to 99.7 % at concentrations of 0.1 to 6.0 g/100 mL) and α1-acid glycoprotein (69.2 % to 99.0 % at concentrations of 0.02 to 0.20 g/100 mL). At TMC125 concentrations of 100 and 1000 ng/mL, the blood to plasma concentration ratio in man was approximately 0.7, and the fraction of TMC125 distributed to the plasma water compartment was 0.0008, the fraction distributed to plasma proteins was 0.77, and the fraction distributed to blood cells was 0.23.

The apparent volume of distribution for the central compartment (V_z/F) when TMC125 was modeled with a sequential zero- and first-order absorption and 2-compartment disposition model was 422 L.

The distribution of TMC125 into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

The results of the mass balance study (TMC114-C130) showed that most of the administered ^{14}C-TMC125 related radioactivity after oral administration of a single 800 mg dose of the capsule formulation TF002 (TMC125 in PEG 400) was excreted in the feces. At 168 hours after dosing, a mean of 93.7 % of the administered radioactivity was recovered in the feces, and a mean of 1.2 % of the administered radioactivity was recovered in the urine.

The radioactivity recovered in the feces comprised of the parent drug and metabolite(s); unchanged TMC125 accounted for the majority of the radioactivity in the feces (81.2 % to 86.4 % of the administered dose). No unchanged radioactivity was recovered in the urine.

The results from other Phase I studies suggested minimal amount of TMC125 excretion in the urine. These results, in conjunction with the results from the mass balance study suggest that renal elimination is a minor route for TMC125 elimination.

2.2.5.6. What are the characteristics of drug metabolism?

The *in vitro* metabolism of TMC125 was studied in human hepatic microsomes. The results of the *in vitro* assessment showed that CYP3A and CYP2C (CYP2C9, CYP2C19; to a lesser extent) enzymes play a major role in the biotransformation of TMC125.

The major part of orally administered TMC125 was excreted unchanged in the feces (81.2-86.4 % of the dose). The most important phase-1 metabolic pathway of TMC125 in humans was hydroxylation of the methyl carbons of the dimethylbenzonitrile moiety. Both the mono and di-methyl hydroxylated metabolites (metabolites 12 and 8, respectively) and their glucuronides (metabolites 6 and 1, respectively) were formed. Overall, methyl hydroxylation accounted for 3.8-9.5 % of the dose. Aromatic hydroxylation at the dimethylbenzonitrile moiety (metabolite 13) was a very minor metabolic pathway in humans. In plasma, TMC125 represented the major fraction of the absorbed radioactivity at the three time points studied (2h, 4h, and 8h). Metabolite 1, 8 and 12 were detected in plasma; metabolite 8 amounted to one third to half of the TMC125 concentrations at the time points evaluated.

2.2.5.7. What are the characteristics of drug excretion?

See Section 2.2.5.5.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The single dose pharmacokinetics of TMC125 (administered as formulation F060) was evaluated at three dose levels (100 mg, 200 mg, and 300 mg) in HIV infected subjects (TMC125-C141). The results of the study showed a more than dose proportional increase in the systemic exposure (AUC_{last}) of TMC125 across the single-dose range evaluated (100-300 mg). Table 7 shows the pharmacokinetic parameters of TMC125 after single dose administration of 100 mg, 200 mg, and 300 mg in HIV infected subjects.

Table 7: Pharmacokinetic parameters of TMC125 after single dose administration of 100 mg, 200 mg, and 300 mg in HIV infected subjects

Panel 1	100 mg TMC125 F060 (Test)	800 mg TMC125 TF035 (Reference)
n	15	15
C_{max} (ng/mL)	37.6 ± 33.9	44.7 ± 48.5
AUC_{last} (ng.h/mL)	360 ± 562	392 ± 508
AUC_{∞} (ng.h/mL)	425 ± 641	470 ± 565
t_{max} (h)	4.00 [2.00 – 12.00]	3.00 [2.00 – 6.00]
$t_{1/2}$ (h)	7.89 ± 8.50	9.94 ± 10.28
Panel 2	**200 mg TMC125 F060 (Test)**	**1600 mg TMC125 TF035 (Reference)**
n	13	12
C_{max} (ng/mL)	131.4 ± 125.4	132.4 ± 207.2
AUC_{last} (ng.h/mL)	1059 ± 906	1285 ± 1887
AUC_{∞} (ng.h/mL)	1131 ± 955	1358 ± 1982
t_{max} (h)	4.00 [3.00 – 6.00]	5.00 [2.00 – 6.00]
$t_{1/2}$ (h)	15.83 ± 8.86	13.55 ± 9.32
Panel 3	**300 mg TMC125 F060 (Test)**	**2400 mg TMC125 TF035 (Reference)**
n	11	12
C_{max} (ng/mL)	257.7 ± 170.8	114.8 ± 81.6
AUC_{last} (ng.h/mL)	2434 ± 2221	1348 ± 1349
AUC_{∞} (ng.h/mL)	2831 ± 3090	1579 ± 1725
t_{max} (h)	3.00 [3.00 – 12.00]	4.00 [2.00 – 6.00]
$t_{1/2}$ (h)	21.55 ± 17.31	20.58 ± 16.69

Values are mean ± SD; for t_{max}: median [range]

The multiple dose pharmacokinetics of TMC125 (administered as formulation F060) was evaluated at two dose levels (100 mg b.i.d, and 200 mg b.i.d.) in HIV infected subjects (TMC125-C228). Table 8 shows the PK parameters after administration of 100 mg b.i.d. and 200 mg b.i.d. to HIV infected subjects.

Table 8: PK parameters after administration of 100 mg b.i.d. and 200 mg b.i.d. to HIV infected subjects

Pharmacokinetics of TMC125 mean ± SD, t_{max}: median (range)	100 mg TMC125 Test (F060)	800 mg TMC125 Reference (TF035)	200 mg TMC125 Test (F060)
Day 1			
N	33	32	27
t_{max}, h	4.00 (2.00-6.00)	4.00 (2.00-8.00)	4.00 (3.00-8.00)
C_{max}, ng/mL	54.9 ± 54.0	70.6 ± 72.7	125.9 ± 109.6
AUC_{12h}, ng.h/mL	312 ± 331	434 ± 437	745 ± 660
Day 8			
N	33	32	27
t_{max}, h	4.00 (0.00-6.00)	4.00 (0.00-6.00)	4.00 (2.00-8.00)
C_{0h}, ng/mL	86.3 ± 84.5	148.8 ± 119.3	235.9 ± 163.1
C_{min}, ng/mL	59.9 ± 63.8	125.8 ± 116.4	184.7 ± 128.1
C_{max}, ng/mL	170.9 ± 99.9	318.8 ± 245.8	451.3 ± 232.3
AUC_{12h}, ng.h/mL	1284 ± 958	2607 ± 2135	3713 ± 2069
$C_{ss,av}$, ng/mL	107.0 ± 79.8	217.3 ± 177.9	309.5 ± 172.4
FI, %	125.2 ± 47.7	94.9 ± 35.5	95.3 ± 31.4

The results of the study showed that the mean increase in systemic exposures (AUC_{last}) was greater than dose proportional to the increase in dose (within the dose range evaluated). Similarly, there was a dose proportional increase in the systemic exposures of etravirine between total daily doses of 200 mg and 400 mg in healthy subjects (see response to question 2.2.5.1.).

2.2.5.9. How do PK parameters change with time following chronic dosing?

The pharmacokinetics of TMC125 was determined in the pivotal phase III clinical trials (TMC125-C206 and TMC125-C216). Based on the samples collected in PK sub-study, the pharmacokinetic parameters were similar at week 4 and week 24.

Table 9: Pharmacokinetics of TMC125 was determined in the pivotal phase III clinical trials (TMC125-C206 and TMC125-C216)

Parameter	Mean ± SD; t_{max}: Median (Range) DUET-1	DUET-2
Week 4		
N	9	16
t_{max}, h	4.00 (0.08 - 6.08)	3.00 (2.00 - 6.00)
C_{0h}, ng/mL	298.9 ± 164.5	683.4 ± 1000
C_{12h}, ng/mL	296.8 ± 146.2	736.7 ± 1276
C_{min}, ng/mL	242.6 ± 148.6	570.7 ± 993.1
C_{max}, ng/mL	527.4 ± 174.7	1078 ± 1251
$C_{ss,av}$, ng/mL	366.5 ± 155.9	831.2 ± 1132
AUC_{12h}, ng.h/mL	4390 ± 1872	9974 ± 13640
FI, %	86.12 ± 36.24	84.60 ± 33.36
Week 24		
N	10	12
t_{max}, h	3.03 (2.02 - 6.03)	4.00 (1.02 - 6.00)
C_{0h}, ng/mL	397.3 ± 253.4	482.9 ± 685.0
C_{12h}, ng/mL	341.7 ± 285.3	506.9 ± 792.8
C_{min}, ng/mL	330.3 ± 261.5	469.1 ± 721.0
C_{max}, ng/mL	697.6 ± 398.5	874.2 ± 826.6
$C_{ss,av}$, ng/mL	489.6 ± 325.1	668.6 ± 769.2
AUC_{12h}, ng.h/mL	5840 ± 3891	8028 ± 9233
FI, %	85.84 ± 26.47	90.62 ± 40.63

N = maximum number of subjects with data.

2.2.5.10. What is the inter- and intra-subject variability in volunteers and patients, and what are the major causes of variability?

There was high inter-subject variability (expressed as % CV for AUC_{12h}) of steady state exposure of TMC125 after administration of TMC125 200 mg b.i.d. using formulation F060 in the two pivotal phase III clinical trials. The inter-subject variability was 80 % in TMC125-C206 (DUET-1) and 86 % in TMC125-C216 (DUET-2) based on population pharmacokinetics. The intersubject variability observed in the phase III trials was similar to the intersubject variability observed in previous phase II trials (irrespective of the dose/formulation used).

The high inter subject variability was further confirmed in the population pharmacokinetic model of TMC125 used for the pooled DUET trials, with inter-subject variability for clearance being 60.4 %. However, the inter-occasion

variability for this parameter was also high (40.1 %), indicating that variability in the pharmacokinetics of TMC125 within a subject was also high.

2.3 Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on population PK analyses, the sponsor concluded that no dose adjustment is needed based on intrinsic factors such as hepatitis B &/or C co-infection, gender, race, age (age range 18-77 years) and use of T-20 (extrinsic factor). The sponsor's analyses were replicated and additional empirical evidence was used to validate the findings. There were no major pharmacokinetic differences by subgroups to the extent requiring TMC125 dose adjustment.

As supportive analyses, two time windows (2-6 hrs and 10-14 hrs) were selected with reference to reported time since the last dose. The rationale was to capture the differences, if any, around the t_{max} (mean ~3 hrs) and around pre-dose time (dosing interval 12 hrs). TMC125 pharmacokinetics were not affected by body weight, age, creatinine clearance, hepatitis B infection, hepatitis C infection, race, sex, ENF and TDF to an extent requiring dose adjustment.

2.3.2. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1. Elderly

There was no clinical study conducted to specifically characterize the effect of age on the disposition of TMC125 however, the population pharmacokinetic analysis, based on the data from the pivotal phase III trials suggested that the pharmacokinetics of TMC125 are not considerably different across the age range (18-77 years; 33 subjects > 60 years old and 7 subjects > 65 years old) evaluated in HIV-1 infected subjects.

2.3.2.2. Pediatric Patients

[redacted] and the sponsor does not seek pediatric indication in this NDA.

2.3.2.3. Gender

Population pharmacokinetic analysis of TMC125 in HIV infected subjects indicated that gender had no apparent effect on the exposure to TMC125.

2.3.2.4. Race

Population pharmacokinetic analysis of TMC125 in HIV infected subjects indicated that race had no apparent effect on the exposure to TMC125.

2.3.2.5. Renal Impairment

The pharmacokinetics of TMC125 has not been studied in subjects with renal impairment. However, in view of the limited renal excretion of TMC125, the clearance of TMC125 is not expected to be significantly altered in subjects with renal impairment.

2.3.2.6. Hepatic Impairment

The pharmacokinetics of TMC125 was evaluated in subjects with mild or moderate hepatic impairment and compared with the pharmacokinetics of TMC125 in subjects with normal hepatic function (TMC125-C125). The results of the trial showed that no dose adjustment of TMC125 is required in HIV infected patients with mild or moderate hepatic impairment. The pharmacokinetics of TMC125 was not evaluated in subjects with severe hepatic impairment, therefore, TMC125 is not recommended for use in subjects with severe hepatic impairment. Table 10 shows the pharmacokinetic parameters of TMC125 after administration of TMC125 200 mg b.i.d. to healthy subjects, subjects with mild hepatic impairment, and subjects with moderate hepatic impairment.

Table 10: Pharmacokinetic parameters of TMC125 after administration of TMC125 200 mg b.i.d. to healthy subjects, subjects with mild hepatic impairment, and subjects with moderate hepatic impairment.

Pharmacokinetic parameter (Mean ± SD, t_{max}: median [range])	Panel A		Panel B	
	Healthy controls N = 8	Subjects with mild hepatic impairment N = 8	Healthy controls N = 8	Subjects with moderate hepatic impairment N = 8
Day 1				
C_{max}, ng/mL	498.8 ± 149.2	466.5 ± 157.8	413.9 ± 123.3	267.5 ± 100.6
t_{max}, h	4.0 (2.0 - 5.0)	4.5 (2.0 - 5.0)	5.0 (2.0 - 5.0)	5.0 (4.0 - 9.0)
AUC_{12h}, ng.h/mL	2972 ± 1105	2903 ± 816.1	2293 ± 663.9	1846 ± 808.0
Day 5				
C_{0h}, ng/mL	451.3 ± 117.4	437.5 ± 212.3	338.3 ± 84.51	406.5 ± 170.8
Day 6				
C_{0h}, ng/mL	525.5 ± 107.8	514.8 ± 191.2	408.1 ± 91.53	475.8 ± 274.9
Day 7				
C_{0h}, ng/mL	578.0 ± 90.62	541.4 ± 195.9	453.9 ± 105.8	536.9 ± 303.7
Day 8				
C_{0h}, ng/mL	618.6 ± 100.7	585.4 ± 186.4	491.6 ± 127.5	568.5 ± 336.5
C_{min}, ng/mL	593.8 ± 99.64	549.9 ± 192.1	461.6 ± 128.4	499.0 ± 293.4
C_{max}, ng/mL	1339 ± 356.9	1060 ± 267.8	1054 ± 193.5	817.6 ± 393.7
t_{max}, h	4.5 (3.0 - 5.0)	4.0 (3.0 - 6.0)	4.0 (4.0 -5.0)	5.0 (4.0 - 6.0)
AUC_{12h}, ng.h/mL	10650 ± 1688	9546 ± 2630	8584 ± 1560	7665 ± 4122
$t_{1/2terminal}$, h[a]	85.64 ± 27.44	86.73 ± 38.22	71.16 ± 27.50	189.9 ± 58.80
$C_{ss,av}$, ng/mL	887.5 ± 140.7	795.5 ± 219.2	715.3 ± 130.0	638.8 ± 343.5
FI, %	81.78 ± 23.49	67.94 ± 26.98	84.19 ± 17.36	54.15 ± 13.41

[a] Accurate determination not possible

2.4 Extrinsic Factors:

2.4.1. What extrinsic factors influence dose-exposure and/or –response, and what is the impact of any differences in exposure on response?

The extrinsic factors that were considered for their potential effect on the pharmacokinetics of TMC125 were the impact of concomitant food intake (described in section 2.5.3.), and the potential for drug-drug interactions.

2.4.2. Drug-Drug Interactions

2.4.2.1. Is there any *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, there is *in vitro* basis to suspect *in vivo* drug-drug interactions. See section 2.4.2.2. and section 2.4.2.3.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, TMC125 is a substrate of CYP3A and CYP2C (2C9 and 2C19) enzymes.

The *in vitro* metabolism of ^{14}C-TMC125 was studied in human liver microsomes (HLMs) in the presence of NADPH generating system. Two metabolites were formed, resulting from mono-hydroxylation at one of the methyl groups of the dimethylbenzonitrile moiety (metabolite 12), and from aromatic hydroxylation at the dimethylbenzonitrile moiety (metabolite 13). Based on the results of the different phenotyping approaches of TMC125 metabolism, the overall metabolism of TMC125 as well as formation of metabolite 12 and metabolite 13 was mainly catalyzed by CYP3A enzymes. The involvement of various CYP2C enzymes (CYP2C9 and CYP2C19) was also demonstrated however, different phenotyping approaches always did not provide consistent results. Taking into account the relative abundance of the various CYP isoforms, CYP3A4 enzymes play a major role in the *in vitro* biotransformation of TMC125.

2.4.2.3. Is TMC125 an inhibitor and/or inducer of CYP enzymes?

The inhibitory potential of TMC125 towards the various CYP enzymes was evaluated *in vitro* in trial TMC125-NC128. The various CYP probe substrates, selective towards CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A were incubated in the presence or absence of TMC125.

Table 11 shows the summary of results from study TMC125-NC128.

Table 11: Inhibition of CYP450 enzymes by TMC125

Cytochrome P450 Isoenzyme	Selected TMC125 Concentration		Type of Inhibition	Mean ± SD Inhibition Constant K_i	
	(µM)	(ng/mL)		(µM)	(ng/mL)
CYP1A2	11.5	5000	Competitive	7.0 ± 1.1	3045 ± 479
CYP2B6	50	21750	Non-competitive	83 ± 13	36105 ± 5655
CYP2C9	1.15	500	Competitive	0.58 ± 0.09	252 ± 39
CYP2C19	11.5	5000	Non-competitive	22 ± 4	9570 ± 1740
CYP2D6	50	21750	Competitive	15 ± 1	6525 ± 435
CYP3A	11.5	5000	Competitive	6.7 ± 1.1	2915 ± 479

CYP2C9 was most potently inhibited by TMC125. The K_i values for the other enzymes were at least 10-fold higher than the K_i value for CYP2C9, indicating a lower affinity of TMC125 towards the other enzymes evaluated in the study.

The induction potential of TMC125 towards the various CYP enzymes was evaluated *in vitro* in trial TMC125-NC164 and TMC125-NC238. The results of the trials indicated that TMC125 has the potential to induce CYP3A4.

The *in vivo* induction/inhibition potential of a single- and multiple-dose (14 days) TMC125 (administered as 200 mg b.i.d., formulation F060) towards CYP1A2, CYP2C9, CYP2D6, CYP3A4, and CYP2C19 enzymes was evaluated in a "cocktail" study (TMC125-C174). Table 12 shows the summary of the results of the study.

Table 12: Summary of results from study TMC125-C174

	LS means ratios (%) + 90% confidence intervals (%)				
Day 1	CYP1A2 Caffeine	CYP2C9 S-warfarin	CYP2D6 Dextromethorphan	CYP3A4 Midazolam	CYP2C19 Omeprazole
Parent	101.6 (95.58-108.1)	101.2 (98.26-104.2)	126.8 (102.7-156.6)	96.42 (90.01-103.3)	162.4 (100.2-262.9)
Metabolite	99.56 (93.99-105.5)	105.3 (91.57-121.2)	98.78 (93.35-104.5)	107.3 (101.6-113.4)	124.7 (75.85-204.9)
P/M [a]	102.1 (97.00-107.4)	96.07 (85.09-108.5)	128.4 (106.6-154.7)	89.83 (80.65-100.1)	130.2 (112.2-151.2)
Day 14	CYP1A2 Caffeine	CYP2C9 S-warfarin	CYP2D6 Dextromethorphan	CYP3A4 Midazolam	CYP2C19 Omeprazole
Parent	84.57 (78.20-91.46)	105.2 (93.43-118.5)	94.08 (71.98-123.0)	68.65 (64.04-73.59)	183.1 (78.25-428.6)
Metabolite	93.29 (88.31-98.54)	57.61 (44.01-75.41)	85.38 (77.57-93.97)	109.0 (100.4-118.3)	43.44 (19.74-95.60)
P/M [a]	90.55 (85.44-95.97)	181.6 (150.7-218.7)	111.6 (90.17-138.0)	63.04 (56.65-70.15)	432.4 (373.7-500.4)

[a] P/M: parent/metabolite ratio

Based on the results of the study, TMC125 was neither an inducer nor an inhibitor of CYP1A2 and CYP2D6. CYP3A4 enzyme activity was not changed by a single dose of TMC125, but was mildly induced by TMC125 at steady state, suggesting that TMC125 is a CYP3A4 inducer. The CYP2C19 enzyme activity was inhibited by single dose and to a greater degree, by steady state administration of TMC125,

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The sponsor conducted numerous drug-drug interaction studies (DDIs) to evaluate the effect of co-administering various classes of drugs on the systemic exposures of TMC125 and the effect of TMC125 on the systemic exposures of the co-administered drugs. The drugs selected to be co-administered with TMC125 in the drug-drug interaction studies were either other antiretroviral drugs or non-antiretroviral drugs that are frequently taken by HIV infected subjects.

The drug-drug interaction studies were conducted using various doses and formulations of TMC125. However, the drug-drug interaction trials that provide information to be included in the package insert were conducted either with formulation TF035 (800 mg b.i.d.) or with the to-be-marketed formulation F060 (200 mg b.i.d.). The use of a different dose (800 mg b.i.d.) and different formulation (TF035) should not alter the interpretation of most drug interaction studies due to the following considerations:

- The observed pharmacokinetic interaction (decrease in TMC125 exposures) in the presence of DRV/rtv was similar in trial TMC125-C139 (TMC125 800 mg b.i.d. using TF035 was evaluated) and TMC125-C176 (TMC125 100 mg b.i.d. using F060 was evaluated). Although 100 mg b.i.d. of TMC125 was used as the reference formulation in study TMC125-C176, the data from other trials indicates that the decrease in the exposure of TMC125 200 mg b.i.d. in the presence of DRV/rtv is expected to be similar to the decrease in the exposures of TMC125 observed in trial TMC125-C139.
- The observed pharmacokinetic interaction between tenofovir 300 mg q.d. and TMC125 was similar when TMC125 was given either as TMC125 800 mg b.i.d. formulation TF035 (TMC125-C138) or as TMC125 200 mg b.i.d. formulation F060 (TMC125-C177).
- The plasma concentrations of TMC125 after multiple dosing in HIV-1 infected subjects were in the same range between TMC125 800 mg b.i.d as formulation TF035 and TMC125 200 mg b.i.d. as formulation F060 (TMC125-C228).

Table 13: Drug Interactions: Pharmacokinetic Parameters for TMC125 in the presence of the co-administered drug

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	Exposure	Mean Ratio of Etravirine Pharmacokinetic Parameters 90% CI; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
Atazanavir	400 mg q.d.	14	↑	1.47 (1.36-1.59)	1.50 (1.41-1.59)	1.58 (1.46-1.70)
Atazanavir/ Ritonavir	300/100 mg q.d.	14	↑	1.30 (1.17-1.44)	1.30 (1.18-1.44)	1.26 (1.12-1.42)
Darunavir/ Ritonavir	600/100 mg b.i.d.	14	↓	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)
Lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	13	↑	1.15 (0.94-1.41)	1.17 (0.96-1.43)	1.23 (0.98-1.53)
Saquinavir/ ritonavir	1000/100 mg b.i.d.	14	↓	0.63 (0.53-0.75)	0.67 (0.56-0.80)	0.71 (0.58-0.87)
Tipranavir/ Ritonavir	500/200 mg b.i.d.	19	↓	0.29 (0.22-0.40)	0.24 (0.18-0.33)	0.18 (0.13-0.25)
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
Didanosine	400 mg q.d.	15	↔	1.16 (1.02-1.32)	1.11 (0.99-1.25)	1.05 (0.93-1.18)
Tenofovir disoproxil fumarate	300 mg q.d.	23	↓	0.81 (0.75-0.88)	0.81 (0.75-0.88)	0.82 (0.73-0.91)

Co-Administration With Integrase Strand Transfer Inhibitors						
Raltegravir	400 mg b.i.d.	19	↔	1.04 (0.97-1.12)	1.10 (1.03-1.16)	1.17 (1.10-1.26)
Co-Administration With Other Drugs						
Atorvastatin	40 mg q.d.	16	↔	0.97 (0.93-1.02)	1.02 (0.97-1.07)	1.10 (1.02-1.19)
Clarithromycin	500 mg b.i.d.	15	↑	1.46 (1.38-1.56)	1.42 (1.34-1.50)	1.46 (1.36-1.58)
Omeprazole	40 mg q.d.	18	↑	1.17 (0.96-1.43)	1.41 (1.22-1.62)	N.A.
Paroxetine	20 mg q.d.	16	↔	1.05 (0.96-1.15)	1.01 (0.93-1.10)	1.07 (0.98-1.17)
Ranitidine	150 mg b.i.d.	18	↓	0.94 (0.75-1.17)	0.86 (0.76-0.97)	N.A.
Rifabutin	300 mg q.d.	12	↓	0.63 (0.53-0.74)	0.63 (0.54-0.74)	0.65 (0.56-0.74)

CI = Confidence Interval; N = maximum number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decreases; ↔ = no change; q.d. = once daily; b.i.d. = twice daily

Table 14 shows the pharmacokinetic parameters for the co-administered drug in the presence of TMC125.

Table 14: Drug Interactions: Pharmacokinetic Parameters for the Co-administered Drugs in the Presence of TMC125

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	Exposure	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
Atazanavir	400 mg q.d.	14	↓	0.97 (0.73-1.29)	0.83 (0.63-1.09)	0.53 (0.38-0.73)
Atazanavir/ Ritonavir	300/100 mg q.d.	13	↓	0.97 (0.89-1.05)	0.86 (0.79-0.93)	0.62 (0.55-0.71)
Darunavir/ Ritonavir	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
Fosamprenavir/ Ritonavir	700/100 mg b.i.d.	8	↑	1.62 (1.47-1.79)	1.69 (1.53-1.86)	1.77 (1.39-2.25)
Lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	14	↓	0.85 (0.62-1.05)	0.80 (0.49-1.07)	0.92 (0.15-1.68)
Saquinavir/ Ritonavir	1000/100 mg b.i.d.	15	↔	1.00 (0.70-1.42)	0.95 (0.64-1.42)	0.80 (0.46-1.38)
Tipranavir/ Ritonavir	500/200 mg b.i.d.	19	↑	1.14 (1.02-1.27)	1.18 (1.03-1.36)	1.24 (0.96-1.59)
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
Didanosine	400 mg q.d.	14	↔	0.91 (0.58-1.42)	0.99 (0.79-1.25)	N.A.
Tenofovir disoproxil fumarate	300 mg q.d.	19	↔	1.15 (1.04-1.27)	1.15 (1.09-1.21)	1.19 (1.13-1.26)
Co-Administration With Integrase Strand Transfer Inhibitors						
Raltegravir	400 mg b.i.d.	19	↓	0.89 (0.68-1.15)	0.90 (0.68-1.18)	0.66 (0.34-1.26)

Co-Administration With Other Drugs				Cmax	AUC	Cmin
Atorvastatin	40 mg q.d.	16	↓	1.04 (0.84-1.30)	0.63 (0.58-0.68)	N.A.
2-hydroxy-atorvastatin		16	↑	1.76 (1.60-1.94)	1.27 (1.19-1.36)	N.A.
Clarithromycin	500 mg b.i.d.	15	↓	0.66 (0.57-0.77)	0.61 (0.53-0.69)	0.47 (0.38-0.57)
14-hydroxy-clarithromycin		15	↑	1.33 (1.13-1.56)	1.21 (1.05-1.39)	1.05 (0.90-1.22)
Ethinylestradiol	0.035 mg q.d.	16	↑	1.33 (1.21-1.46)	1.22 (1.13-1.31)	1.09 (1.01-1.18)
Norethindrone	1 mg q.d.	16	↔	1.05 (0.98-1.12)	0.95 (0.90-0.99)	0.78 (0.68-0.90)
R(-) Methadone	Individual dose regimen ranging from 60 to 130 mg/day	16	↔	1.02 (0.96-1.09)	1.06 (0.99-1.13)	1.10 (1.02-1.19)
S(+) Methadone		16	↔	0.89 (0.83-0.97)	0.89 (0.82-0.96)	0.89 (0.81-0.98)
Paroxetine	20 mg q.d.	16	↔	1.06 (0.95-1.20)	1.03 (0.90-1.18)	0.87 (0.75-1.02)
Rifabutin	300 mg q.d.	12	↓	0.90 (0.78-1.03)	0.83 (0.75-0.94)	0.76 (0.66-0.87)
25-*O*-desacetylrifabutin	300 mg q.d.	12	↓	0.85 (0.72-1.00)	0.83 (0.74-0.92)	0.78 (0.70-0.87)
Sildenafil	50 mg single dose	15	↓	0.55 (0.40-0.75)	0.43 (0.36-0.51)	N.A.
N-desmethyl-sildenafil		15	↓	0.75 (0.59-0.96)	0.59 (0.52-0.68)	N.A.

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decreases; ↔ = no change; q.d. = once daily ; b.i.d. = twice daily.

Table 15 shows the established and other potentially significant drug interactions based on which, alterations in dose or regimen may be recommended. The interaction between TMC125 and the drug preceding the asterisk (*) sign was evaluated in a clinical study; the interactions between TMC125 and other drugs (not preceding the asterisk sign) are predicted.

Table 15: Established and other potentially significant drug interactions: alterations in dose or regimen may be recommended based on drug interaction studies or predicted interaction

Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz* nevirapine*	↓ etravirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE™ with efavirenz or nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and other NNRTIs should not be co-administered.
Delavirdine	↑ etravirine	Combining two NNRTIs has not been shown to be beneficial. INTELENCE™ and delavirdine should not be co-administered.
HIV-Antiviral Agents: Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)		
didanosine*	↔ etravirine ↔ didanosine	The combination of INTELENCE™ and didanosine can be used without dose adjustments, however, didanosine should be administered on an empty stomach (2 hours before or 2 hours after a meal) and TMC125 should be administered following a meal.
HIV-Antiviral Agents: Protease Inhibitors (PIs)		
ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with ritonavir 600 mg b.i.d. may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and ritonavir 600 mg b.i.d. should not be co-administered.
atazanavir/ritonavir*	↑ etravirine ↓ atazanavir	Concomitant use of INTELENCE™ with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with atazanavir/ritonavir is anticipated to be about 100% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. INTELENCE™ and atazanavir/ritonavir should not be co-administered.
darunavir/ritonavir*	↓ etravirine ↔ darunavir	The mean systemic exposure (AUC) of etravirine was reduced by about 37% when INTELENCE™ was co-administered with darunavir/ritonavir. Because all subjects in