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2.5.1 Product Development Rationale

2.5.1.1 Pharmacological Class

MK-0518 (also known as raltegravir and as L-000900612) is a human immunodeficiency virus (HIV) integrase strand transfer inhibitor active against HIV type 1 (HIV-1).

2.5.1.2 Chemical and Pharmaceutical Properties

The final market image (FMI) is the [redacted]% poloxamer 407 formulation, which contains [redacted]% drug loading (as salt) and the following: microcrystalline cellulose (diluent), dibasic calcium phosphate (diluent), lactose monohydrate (diluent), hypromellose (binder/stabilizing agent), poloxamer 407 (surfactant), magnesium stearate, and sodium stearyl fumarate (lubricants), and a [redacted] film coat.

The FMI, referred to as "Phase II/III/FMI poloxamer formulation" in [Sec. 2.7.1], was used in all Phase III studies. The [redacted]% poloxamer formulation used in all Phase II and some late Phase I studies differs from the FMI only in the color and thickness of the film coating (white for Phase II versus pink for Phase III), and in the debossing used for the Phase III formulation.

2.5.1.3 Indications

MK-0518 has not yet been licensed in any country. The proposed prescribing information includes the following indication:

> MK-0518 is indicated in combination with other anti-retroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

2.5.1.4 Scientific Background

2.5.1.4.1 Public Heath Burden of HIV-1-Related Clinical Disease

HIV-1 is the etiologic agent of the Acquired Immunodeficiency Syndrome (AIDS). Productive infection with HIV results in the establishment of life-long infection that, if untreated, ultimately leads to AIDS and death. Approximately 40 million people are living with HIV/AIDS worldwide, and AIDS continues to be a leading cause of mortality with approximately 3 million deaths per year as of end of Dec-2005 [Ref. 5.4: 372].

2.5.1.4.2 Current HIV-1-Treatment Landscape and Medical Need

The treatment for HIV infection has evolved rapidly. A significant breakthrough occurred in 1996 with the introduction of potent 3-drug combination regimens based on HIV protease inhibitors (PIs), subsequently known as highly active antiretroviral therapy (HAART), resulting in a significant decrease in the mortality and morbidity associated with AIDS [Ref. 5.4: 67, 236, 285]; non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens are also potent and constitute a form of HAART. Until the fusion entry inhibitor, enfuvirtide, became available, the antiretroviral agents (approximately 22) available for use in HAART targeted 2 enzymes in the viral life cycle: the reverse transcriptase and protease. Many infected patients have been

successfully treated with these combination therapies, experiencing profound and continuous viral suppression with in many cases substantial immune system recovery and halt of clinical progression [Ref. 5.4: 285].

HAART has enabled HIV infection to be managed as a chronic disease. As the number of patients treated with different combinations of antiretroviral therapies (ARTs) continues to grow, intolerance of complicated dosing regimens, long-term toxicities, and multi-drug resistance have emerged as issues and present a major challenge for treating physicians. Gastrointestinal intolerance has resulted in poor adherence. Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside reverse transcriptase inhibitors (NRTIs) alone or in combination with other ARTs [Ref. 5.4: 310]. Other major toxicities associated with HAART include hyperglycemia, insulin resistance, lipodystrophy, lipoatrophy, hyperlipidemia, and cardiovascular events [Ref. 5.4: 310]. Concerns regarding the long-term toxicities associated with chronic administration of many agents are of such significance that patients and physicians have elected to delay therapy until a substantial decline in immune function has occurred.

Recent efforts, therefore, have been focused on the development of better-tolerated formulations and on combination regimens with improved tolerance and convenience to improve patients' compliance, a crucial factor for treatment success. A major remaining challenge is intra-class resistance, which has become common and which limits the optimization of subsequent antiretroviral regimens in patients failing current therapies; e.g., in one study, as many as 78% of treated-patients harbor virus that has reduced susceptibility to at least one therapeutic class, with over 50% resistant to multiple classes [Ref. 5.4: 109]. In addition, primary transmission of multiple-drug resistant HIV has been reported [Ref. 5.4: 1, 426]. The most urgent current medical need is in patients infected with multi-drug resistant virus who have few remaining treatment options. In these patients, therapy is more successful if an agent from an ART class to which the patient has not been previously exposed is combined with at least one other active ART [Ref. 5.4: 160, 248, 425].

A compelling medical need exits for the development of an ART with a novel mechanism of action to address the issue of intra-class resistance. The HIV integrase presents such a new therapeutic target. It is 1 of the 3 HIV-1 enzymes required for viral replication and catalyzes the stepwise process resulting in the integration of the HIV deoxyribonucleic acid (DNA) into the genome of the host cell. This ordered series of reactions includes the assembly of integrase in a stable complex with the viral DNA, the endonucleolytic processing of the viral DNA ends, and strand transfer or joining of the viral and cellular DNAs. Integration is required for stable maintenance of the viral genome as well as efficient viral gene expression. To date, there have been no approved drugs targeting this enzyme. MK-0518 is oral drug, which is the first HIV integrase strand transfer inhibitor with demonstrated safety and efficacy in treatment-naïve and heavily pretreated patients. Based on the favorable tolerability/safety and potent efficacy data presented in this Application, MK-0518 promises to be an important addition to the current armamentarium for the treatment of HIV infection.

2.5.1.5 Overview of Clinical Development Program

The MK-0518 clinical development program has progressed through 3 key phases; it is consistent with formal guidance received from the U.S. Food and Drug Administration (FDA) and the European Union (EU) Committee for Medicinal Products for Human Use (CHMP) as summarized in [Sec. 2.5.1.6]:

1) The ***Phase I*** program included an evaluation of the safety, tolerability, and pharmacokinetics (PK) of different doses of MK-0518 in uninfected subjects as well as evaluation of food effect, relevant drug-drug interaction studies, and studies in special populations (hepatic and renal insufficiency) (see [Sec. 2.5.3]). The Phase I program allowed for selection of doses of MK-0518 to be studied in combination therapy with currently licensed ARTs in Phase II and Phase III (see [Sec. 2.5.2], [Sec. 2.5.3], [Sec. 2.7.3.1.3.4.1-trxexp], and [Sec. 2.7.3.1.3.4.2-trxexp]).

2) In ***Phase II***, proof-of-efficacy in HIV-infected patients was established after 10 days of monotherapy (Protocol 004 – Part I) prior to evaluation of safety and efficacy of different doses of MK-0518 in chronic combination therapy with other ARTs, in both treatment-naïve (Protocol 004 – Part II) and treatment-experienced patients who have failed anti-retroviral therapies with triple-class resistant virus (Protocol 005) [Table 2.5: 1]. The Phase II data in conjunction with drug-drug interaction studies provided data to select the Phase III dose, 400 mg twice daily (b.i.d.) without regard to food (see [Sec. 2.5.4.3.2]).

3) In ***Phase III***, the safety, tolerability, and efficacy of MK-0518 400 mg b.i.d. in combination therapy was confirmed in treatment-experienced patients who failed anti-retroviral therapies with triple-class resistant virus (Protocols 018 and 019) ([Table 2.5: 1] and [Sec. 2.5.4.3.3]).

Although the initial emphasis has been in treatment-experienced patients to address the unmet medical need, data from 204 treatment-naïve patients are also presented to fully characterize the safety and efficacy profile of MK-0518. Studies in the expanded access environment and a Phase III study in treatment-naïve patients (Protocol 021) are ongoing at the time of this Application.

The clinical trials were conducted in accordance with current standard research approaches with regard to design, conduct, and analysis of such trials. The Clinical Study Report (CSR) and Data Analysis Plan (DAP) for each study were available to prepare this Clinical Overview. All trials were conducted following appropriate Good Clinical Practice guidelines and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed. Data presented in this Application and information presented in this Clinical Overview were subject to audit by Merck Worldwide Quality Assurance Resources groups based on approved Standard Operating Procedures (SOPs) in effect at the time of the audit.

Table 2.5: 1

Summary of MK-0518 Phase II/III Clinical Development Program

Protocol	Phase	Location	Pivotal / Supportive	Primary Endpoints	Duration	MK-0518 b.i.d. (Oral)	N (Pts)	Comparator (Oral)	N (Pts)
Treatment-Naïve Patients									
004 (Part I)	II	U.S./Int.	Supportive	Safety, Efficacy at Day 10	10 days	100 mg	7	Placebo	7
						200 mg	7		
						400 mg	6		
						600 mg	8		
004 (Part II)	II	U.S./Int.	Supportive	Safety, Efficacy at Week 24	48 wks with extension; total duration: 144 wks	100 mg + TFV + 3TC	39	EFV+ TFV + 3TC	38
						200 mg + TFV + 3TC	40		
						400 mg + TFV + 3TC	41		
						600 mg + TFV + 3TC	40		
Treatment-Experienced Patients									
005	II	U.S./Int.	Supportive	Safety, Efficacy at Week 24	48 wks with extension for an additional 96 wks†	200 mg + OBT	43	Placebo + OBT	45
						400 mg + OBT	45		
						600 mg + OBT	45		
018 (BENCHMRK-1)	III	Int.	Pivotal	Efficacy and Safety at Week 16	48 wks with extension; total duration: 152 wks	400 mg + OBT	232	Placebo + OBT	118
019 (BENCHMRK-2)	III	U.S./Int.	Pivotal	Efficacy and Safety at Week 16	48 wks with extension; total duration: 152 wks	400 mg + OBT	230	Placebo + OBT	119

† When the Phase III dose was selected, the protocol was amended to allow all patients, including those in control arm, to receive open-label MK-0518 400 mg b.i.d. after at least 24 weeks of double-blind therapy.
Note: All studies were double-blind (with in-house blinding), randomized, controlled; all had population pharmacokinetics (PK) and integrase resistance evaluation.
N = patients randomized and treated; Pts = patients; U.S. = United States; Int.= International; PK = Pharmacokinetics; TFV = tenofovir; 3TC = lamivudine; EFV = efavirenz.
OBT = Optimized Background Therapy.

[Ref. 5.3.5.1: P004, P005, P018, P019]

2.5.1.6 Regulatory Guidance and Advice

Regulatory agency advice was sought at key points during development. Formal guidance received from the US FDA and the EU CHMP is summarized:

United States: The clinical development program was reviewed and discussed with FDA [redacted] This marketing Application meets agreements reached at these meetings.

[redacted]

Europe: A formal CHMP Scientific Advise (SA) procedure was concluded on [redacted] 20[redacted] [Ref. 5.4: 296]. The Applicant believes that this submission fulfills the criteria outlined in the SA. In general, the CHMP felt that the efficacy and safety data would need to be sufficiently convincing of the fact that the drug could adequately cover an unmet medical need in treatment-experienced patients. A summary of the CHMP response follows:

[redacted]

＊：新薬承認情報提供時に置き換えた。

2.5.2 Overview of Biopharmaceutics

Three (3) formulations, each containing the most stable of the 3 identified forms of the potassium salt of MK-0518 (Form C), were evaluated in the development program. These included: (1) a rapidly disintegrating tablet used for the initial Phase I studies (Phase I lactose formulation); (2) an erodible tablet containing [redacted]% poloxamer 407, used for further Phase I studies (Phase I poloxamer formulation); and (3) an erodible tablet containing [redacted]% poloxamer 407, used for Phase II and III studies, as well as late Phase I studies (Phase II/III/FMI poloxamer formulation). The initial Phase I lactose formulation was developed as a probe, fit-for-purpose, formulation to initiate clinical studies with the intent to continue with formulation development. Consequently, the Phase I poloxamer ([redacted]%) formulation was developed, which possessed improved PK and physical properties, including a lower peak-to-trough ratio and the advantage of increasing drug loading from [redacted]% (Phase I lactose) to [redacted]% allowing a 400-mg potency tablet. However, [redacted] of this formulation necessitated slight modifications leading to the development of the Phase II/III FMI formulation containing [redacted]% poloxamer. The FMI formulation, consisting of the 400-mg potency Phase II/III/FMI poloxamer formulation with a [redacted] film coat, was used in the Phase III studies. The Phase II/III/FMI poloxamer formulation used in the Phase II studies and the late Phase I studies differs from the formulation used in Phase III studies only in the color and thickness of the film coating (white [Phase II]; pink [Phase III]), and in the debossing used for the formulation in the Phase III studies.

Biopharmaceutic performance between various formulations was compared in 2 clinical studies. Comparison of the biopharmaceutic properties between 3 candidate Phase II formulations (Phase II lactose, calcium phosphate, and Phase I poloxamer) relative to the Phase I lactose formulation indicated that the Phase I poloxamer formulation had superior PK properties (Protocol 007 [Ref. 5.3.3.1: P007], [Sec. 2.7.2.2.1.1.2]). The performance of a A* formulation and a B* formulation was assessed in Protocol 020 [Ref. 5.3.3.1: P020] (see [Sec. 2.7.1.2.1.2]). The A* formulation had an overall favorable PK profile supporting possible further development while the B* formulation was found to provide no advantage over the Phase I poloxamer formulation.

The absolute bioavailability of the MK-0518 FMI formulation was not determined. In an oral clinical absorption, distribution, metabolism, and excretion (ADME) study, an average of approximately 32% of the radiolabeled oral dose (consisting of parent compound and metabolite) administered was recovered in urine (Protocol 011 [Ref. 5.3.3.1: P011], [Sec. 2.7.2.2.1.3]), which provides a minimum value for the absolute bioavailability of the MK-0518 ADME formulation, and data in animals suggest that the bioavailability may be on the order of 60 to 70% [Sec. 2.7.1.1].

While there was little to no effect of food on the PK of either the Phase I lactose formulation or the Phase I poloxamer formulation, food influenced the PK of the Phase II/III/FMI poloxamer formulation. The extent of absorption of MK-0518 for the Phase II/III/FMI formulation, as assessed by area under the concentration time curve from 0 to infinity ($AUC_{0-\infty}$), was similar in the fed (high-fat meal) and fasted states (Protocol 028 [Ref. 5.3.3.1: P028]), although food appeared to slow the rate of absorption and extend the duration of absorption; this resulted in an approximately 34% decrease in maximum plasma concentration (C_{max}), an 8.5-fold increase in trough plasma concentration at 12 hours ($C_{12\ hr}$), and a 7.3 hour delay in time to maximum plasma concentration (T_{max}). A cross-study comparison ([Sec. 2.7.1.3.1]) of multiple-dose PK suggests that the magnitude of the food effect on the Phase II/III/FMI poloxamer formulation is diminished following multiple-dosing and when administered with a standard, rather than high-fat, meal. Food appears to increase PK variability somewhat over the fasted state and, consequently, a similar lower range of individual $C_{12\ hr}$ values was observed in the cross-study comparison, suggesting that food does not consistently increase $C_{12\ hr}$ values. On the basis of the clinical significance criteria (see [Sec. 2.7.2.1.3]), food does not have a clinically meaningful effect on the PK profile of MK-0518, relative to fasted administration. While the available data indicate that, on average, $C_{12\ hr}$ is increased by administration with food, there is no evidence that this increase would provide a therapeutic advantage, given the associated increase in PK variability. This is supported further by Pharmacokinetic/pharmacodynamic (PK/PD) analyses that suggest, at most, a modest association of drug concentration with viral response in this concentration range (see [Sec. 2.7.2.3.4]). Finally and importantly, it should also be noted that the Phase II dose-ranging efficacy studies and the pivotal Phase III efficacy studies were conducted with dosing without regard to food using the MK-0518 Phase II/III/FMI poloxamer formulation. In light of the favorable safety and efficacy data obtained in Phase II and Phase III in studies utilizing MK-0518 administered without respect to food, it is appropriate to label MK-0518 for administration without respect to food.

2.5.3 Overview of Clinical Pharmacology

The clinical pharmacology program (described in [Sec. 2.7.1] and [Sec. 2.7.2]) characterized the initial safety and tolerability as well as PK characteristics of MK-0518. The program includes 18 Phase I studies conducted worldwide and included healthy male and female subjects, patients with hepatic insufficiency, and patients with renal insufficiency and a full PK evaluation of a subset of HIV patients enrolled in a Phase II study. The analysis of PK includes a composite analysis across many of the Phase I studies as well as a limited population PK analysis of data from the Phase I and the Phase II/III program in HIV-infected individuals. A thorough QTc study was also conducted to rigorously assess the effect of MK-0518 on the QTc interval.

MK-0518 was generally well tolerated up to 1600 mg administered as single doses and 800 mg administered every 12 hours (q12 hr) for 10 days. There were no serious adverse experiences (SAEs). All adverse experiences were generally transient and mild to moderate in intensity. There were 2 discontinuations due to study drug (including MK-0518 and co-administered agents). No clinically important abnormalities were noted in routine blood and urine chemistry panels, complete blood count, electrocardiograms, and physical examinations including vital signs. In the thorough QTc study, there was no statistically significant effect on QTc intervals relative to placebo following a single supratherapeutic dose of 1600 mg MK-0518.

In an ADME study, MK-0518 was found to be primarily eliminated by metabolism with a small component (~9% of the administered dose eliminated as parent compound) of elimination via renal excretion. Parent compound and the phenolic hydroxyl glucuronide metabolite were the only radioactive species detected in clinical samples. In an in vitro system, the expressed human uridine diphosphate glucuronosyltransferase (UGT) isozymes 1A1, 1A3, and 1A9 converted MK-0518 to its glucuronide in the presence of uridine diphosphate glucuronic acid as the cofactor. The formation of the glucuronide metabolite correlated highly with estradiol 3-glucuronidation (a probe substrate for UGT1A1), while correlation with UGT marker activities for UGT1A3 and 1A9 was weak. Formation of the glucuronide metabolite in human liver microsomes was inhibited by UGT1A1 substrates, while no inhibitory effect was observed with a UGT1A3/1A4 substrate. The data collectively indicate that the major mechanism of clearance of MK-0518 in humans is glucuronidation mediated by UGT1A1, with a minor contribution of renal excretion of unchanged parent compound.

MK-0518 displays dose proportional PK over the dose range 100 to 800 mg. At the clinical dose of 400 mg, the apparent terminal elimination half-life is approximately 9 hours with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Steady-state is generally reached in approximately 2 days and accumulation is slight with multiple-dose administration; the estimated AUC accumulation ratio was 1.05 with twice daily dosing. MK-0518 is relatively rapidly absorbed with a median time to maximum plasma concentration (T_{max}) of ~3 hours in the fasted state. There was no clinically meaningful effect of food on the extent of MK-0518 absorption, but food slowed the rate of absorption of the Phase II/III/FMI formulation, see [Sec. 2.5.2] and [Sec. 2.7.1].

For the purposes of assessing the impact of extrinsic and intrinsic factors (e.g., concomitant drugs, gender, age, body mass index, hepatic function, renal function, race, and HIV status) on MK-0518 PK, an increase in MK-0518 AUC of 2-fold or greater or a decrease in MK-0518 concentration at 12 hours postdose ($C_{12\ hr}$) of 60% or greater was considered a clinically meaningful alteration in MK-0518 PK (see the rationale for bounds in [Sec. 2.7.2.1.3]). Gender, age, body mass index, race, HIV status, moderate hepatic insufficiency, and severe renal insufficiency had no clinically meaningful effect on MK-0518 pharmacokinetics. No dose adjustment is required for MK-0518 based on any of these demographic factors.

MK-0518 has a low propensity to be involved in drug-drug interactions as a victim or as a perpetrator. In vitro results indicated that MK-0518 is not an inhibitor of the major cytochrome P450 (CYP) isozymes, including CYP3A4; major UGTs; and P-glycoprotein. Additionally, MK-0518 is not an inducer of CYP3A4. In clinical studies, MK-0518 did not meaningfully alter the PK of midazolam, providing evidence that MK-0518 has a low propensity for perpetrating drug interactions with substrates of CYP3A4. Additionally, MK-0518 was demonstrated not to meaningfully alter the PK of tenofovir (TFV), TMC125, and lamivudine (3TC). A number of clinical studies were conducted with agents known to be broad inducers and inhibitors of drug metabolizing enzymes including UGT1A1. The selection of compounds examined in the MK-0518 program was based on the history of their respective drug interaction profiles with the overall objective to bracket the most potent inhibitors and inducers with the potential to cause respective increases and decreases in MK-0518 plasma concentrations.

Atazanavir is a known inhibitor of UGT1A1 and was selected to assess the most substantial increases in MK-0518 PK. As anticipated, MK-0518 plasma levels were increased with co-administration of atazanavir but the increases were modest and not clinically meaningful. Co-administration of TFV was also shown to result in modest increases in MK-0518 concentrations that were not clinically meaningful. Of note, concomitant use of MK-0518 with these modest inhibitors, atazanavir and TFV, was well tolerated in the Phase II and Phase III studies. Based on these data, inhibitors such as atazanavir and TFV may be co-administered with MK-0518 without adjustment in the dose of MK-0518.

Ritonavir had no clinically meaningful effect on the pharmacokinetics of MK-0518. Ritonavir has been reported to be an inducer of glucuronidation, as well as an inhibitor of CYP3A4 and CYP2D6 metabolism, and an inhibitor of the transporter P-gp. Based on preclinical and in vitro data, the main route of elimination for MK-0518 is glucuronidation mediated by UGT1A1. Ritonavir (100 mg twice-daily) had no effect on the pharmacokinetics of MK-0518, despite the potential for induction of UGT1A1 by ritonavir. Due to the multiple effects of ritonavir on enzymes and transporters noted above, a balance of competing effects of induction and inhibition cannot be ruled out, although, again based on preclinical and in vitro data, it is not anticipated that the pharmacokinetics of MK-0518 would be altered by inhibition of CYP3A4, CYP2D6, and/or P-gp. Based on these data, ritonavir may be coadministered with MK-0518 without dose adjustment.

Efavirenz and TMC-125 had a modest influence on the pharmacokinetic profile of MK-0518. For efavirenz and TMC-125, there is evidence of a modest reduction in $C_{12\ hr}$ (21% and 34% mean decrease, respectively), which is probably due to slight induction of UGT1A1; however, the point estimates and 90% CIs for these effects indicate that the magnitude of these effects are small and not likely to be clinically meaningful. Although the lower bound of the CI (0.34) for TMC-125 was less than the defined clinically significant bound of 0.4 due to a wide 90% CI, if the true change in MK-0518 $C_{12\ hr}$

were on the order seen of the lower bound of the 90% CI, then this overall level of induction should have resulted in more substantial decreases in other associated pharmacokinetic parameters than those observed. The lack of substantive effect on AUC, C_{max}, and T_{max} suggests the overall effect is minor and is unlikely to be clinically meaningful. Based on these data, efavirenz and TMC-125 may be coadministered with MK-0518 without dose adjustment.

Rifampin was selected as a representative broad potent inducer of drug metabolizing enzymes including UGT1A1. Rifampin decreased mean MK-0518 trough levels ($C_{12\ hr}$) by 61%, consistent with a clinically meaningful reduction. Mean $AUC_{0-\infty}$ and C_{max} values decreased by 40% and 38%, respectively. A doubling of the dose of MK-0518 should be considered when MK-0518 is co-administered with the strong inducers rifampin, phenytoin or phenobarbital.

Tipranavir, a known inducer of drug metabolizing enzymes, modestly decreased plasma levels of MK-0518, including MK-0518 $C_{12\ hr}$ which was decreased by an average of 51 to 55% with less of an effect on $AUC_{0-12\ hr}$ (24% decrease) and C_{max} (18% decrease). Although this result is borderline for clinical significance for $C_{12\ hr}$, there are considerable safety and efficacy data available for the concomitant use of tipranavir and MK-0518 from the Phase III studies, which support the efficacy of this combination. There was no clinically meaningful difference in the efficacy profile of MK-0518 with or without co-administration of tipranavir. Based on these data, tipranavir may be coadministered with MK-0518 without dose adjustment.

Initial efficacy data in conjunction with MK-0518 PK data were assessed in a Phase II study in HIV infected patients (Protocol 004). The pharmacokinetic parameter values of MK-0518 monotherapy at doses of 100, 200, 400, and 600 mg administered twice daily generally resembled the values observed in uninfected subjects in the Phase I studies. The doses selected for the initial Phase II study were based on PK data collected in the early Phase I studies compared with an in vitro 95% inhibition concentration (IC_{95}) of 33 nM against HIV-1 in the presence of 50% human serum. The PK along with safety and efficacy data from the dose-ranging studies in Phase II, which demonstrated no dose-related toxicities ([Sec. 2.7.4]) and a good margin of efficacy ([Sec. 2.7.3-trxexp]), were the basis for selection of the Phase III dose of 400 mg administered twice daily, dosed without regard to food.

Population PK data were obtained in most patients enrolled in the Phase II and Phase III efficacy studies. PK/PD evaluations of the potential relationship between various MK-0518 PK measures and a variety of efficacy measures were conducted and no clinically meaningful associations were identified for any of these comparisons. Given the high proportion of favorable outcomes achieved with MK-0518 therapy in the Phase II and Phase III studies, the lack of PK/PD correlations with measures of longer-term response suggest that the range of concentrations obtained in the Phase II and Phase III studies

falls near the top of the concentration-response curve, where treatment response has, at most, only a modest concentration dependence. This analysis indicates that MK-0518 concentrations throughout the range of clinical experience from Phase II and Phase III are likely associated with a similar high level of efficacy.

In summary, the Applicant has thoroughly defined the PK of MK-0518 in uninfected adults and HIV-infected patients of both genders and in subjects with defined degrees of renal and hepatic insufficiency. In addition, adequate drug-drug interaction data were also available to support the relevant section in the proposed Product Circular. No dose adjustment is warranted in patients with moderate and mild hepatic insufficiency or severe renal insufficiency, or in patients who need to use other licensed ARTs in combination with MK-0518. However, it is recommended to double the dose of MK-0518 to 800 mg b.i.d. when MK-0518 is co-administered with rifampin, phenytoin, or phenobarbital.

2.5.4 Overview of Efficacy

In this section, the efficacy results are discussed in [Sec. 2.5.4.3], after comments on the relevance of the patient population (see [Sec. 2.5.4.1]), and on the methods for efficacy assessment (see [Sec. 2.5.4.2]). This Application has provided compelling efficacy data of MK-0518 which includes data from 877 treatment-experienced patients (Protocols 005, 018, and 019) and from 198 treatment-naïve patients (Protocol 004) (see [Ref. 5.3.5.1: P004] and [Sec. 2.7.3-trxexp]). The primary focus in the integrated efficacy analysis was on the treatment-experienced patients who received MK-0518 400 mg b.i.d. (see [Sec. 2.7.3.3.2.1-trxexp]); in this analysis, data from the 2 pivotal Phase III studies are combined (699 patients) and displayed next to the supportive data from the 400 mg b.i.d. arm of Protocol 005 (including 45 patients on MK-0518 and 45 patients on placebo), to demonstrate consistency of treatment effect between the Phase II and Phase III treatment-experienced studies. Efficacy data from treatment-naïve patients (see [Sec. 2.7.3.2.1-trxexp]; [Sec. 2.7.3.5.1-trxexp]) provide support for the selected dose of MK-0518 as well as evidence of long-term efficacy.

2.5.4.1 Relevance of the Patient Population

The patients studied are particularly relevant to support the proposed indication and patients were included with a range of active OBT. The treatment-experienced studies included patients who had failed prior therapy with HIV documented to be resistant to at least 1 drug in each of the 3 classes of ARTs (NRTI, NNRTI, and PI) at screening. All patients had advanced HIV disease (≥80% of all patients had AIDS) and extensive prior ART experience (median of 10 years duration) (see [Table 2.7.3-trxexp: 10] and [Table 2.7.3-trxexp: 11]). In Protocol 005, the median baseline CD4 cell count was 196 cells/mm^3 and 246 cells/mm^3 for the MK-0518 group and placebo group, respectively, while in Protocols 018 and 019 the median baseline CD4 cell count for the MK-0518 400 mg group and placebo group was 119 cells/mm^3 and 123 cells/mm^3, respectively, with

approximately 32% of patients in both groups having CD4 cell counts of ≤50 cells/mm^3 at baseline. In order for the results of the Phase III studies to be most informative for the likely patient population in clinical practice, the studies appropriately allowed the inclusion of patients regardless of CD4 cell counts, patients with hepatitis B and/or C virus co-infection (see [Table 2.7.3-trxexp: 10]), and patients with abnormal baseline laboratory values (e.g., ALT/AST up to 5 times the upper limit of normal) [Ref. 5.3.5.1: P018, P019]. Overall, there was a broad representation of gender, race, geographic region, and viral subtype [Ref. 5.3.5.1: P018, P019] (see [Table 2.7.3-trxexp: 10]). Furthermore, the studies appropriately allowed patients in the Phase III studies to utilize investigational agents (i.e. darunavir and tipranavir) in the OBT, subject to local regulatory agencies' approval, in order to maximize the chance that the patient would receive an effective regimen. As a consequence, patients in the Phase III studies generally had more active OBTs than those in the Phase II study. In Protocol 005, 71% (32/45) of patients receiving MK-0518 400 mg b.i.d. and 51% (23/45) receiving placebo had GSS of 0 (see [Table 2.7.3-trxexp: 11]). In contrast, in both Protocols 018 and 019 combined, 25% (115/462) of patients receiving MK-0518 400 mg b.i.d. and 27% (65/237) of patients receiving placebo had GSS of 0 (see [Table 2.7.3-trxexp: 11]). The nature of the GSS score is discussed in [Sec. 2.7.3.3.1.3-trxexp].

The inclusion of treatment-naïve patients in the Phase II program (Protocol 004) provides a patient population with no complications from prior antiretroviral treatment and with predefined combination therapy. This allows fuller evaluation of the safety and efficacy of MK-0518 because this may be difficult to completely assess in treatment-experienced patients with severe underlying diseases, complicated background medical conditions, and heterogeneous OBT in the treatment regimen.

2.5.4.2 Methods for Efficacy Assessment

2.5.4.2.1 Study Design

The study design of the 3 protocols in treatment-experienced patients is described in [Sec. 2.7.3.1.3-trxexp]. All are double-blind, with in-house blinding, randomized, superiority trials evaluating MK-0518 versus placebo, both in combination with OBT ([Table 2.5: 1]).

Protocols 018 and 019 were 2 identical Phase III pivotal studies that evaluated MK-0518 400 mg b.i.d. versus placebo (2:1 randomization MK-0518:Placebo).

Protocol 005 was a dose-ranging Phase II supportive study evaluating 3 doses of MK-0518 (200, 400, and 600 mg b.i.d.) versus placebo (1:1:1:1 balanced randomization) for at least 24 weeks. Because preliminary PK data suggested that co-administration of MK-0518 with atazanavir increased overall exposure to MK-0518, 2 substudies were conducted in Protocol 005; Substudy A for patients who did not receive atazanavir in their OBT and Substudy B for patients who received atazanavir in their OBT. The MK-0518 600 mg arm of Substudy B provided an opportunity to evaluate the safety and

efficacy of MK-0518 with the highest exposure. Testing for homogeneity of treatment effect showed no statistically significant difference between Substudy A and Substudy B for each of the 3 doses of MK-0518 tested versus placebo, thus permitting the combination of data from both substudies [Ref. 5.3.5.1: P005]. In [redacted]20[redacted] after the Phase III dose of 400 mg b.i.d. was selected, Protocol 005 was amended to allow all patients (including the placebo group) who had completed at least 24 weeks of therapy in the double-blind, dose-ranging phase to receive the Phase III dose in an open-label extension. Patients were not unblinded as to their originally randomized arm and changes in OBT were not permitted. Some patients were in the double-blind, dose-ranging phase longer than 24 weeks depending on time of enrollment and time of IRB/ERC approvals. This open-label extension provided important, long-term efficacy data of MK-0518 in treatment-experienced patients (see [Sec. 2.7.3.5.1.2-trxexp] and [Sec. 2.5.4.3.4]).

Consistent with the treatment guidelines and regulatory recommendations [Ref. 5.4: 67, 310, 395], the optimization of background therapy was encouraged in the studies in treatment-experienced patients. Both genotypic and phenotypic resistance testing were performed at screening to provide necessary information for the selection of OBT for each patient. In Phase III, the Applicant allowed the use of recently validated drugs (i.e. tipranavir and darunavir) in order for the patients to receive the best OBT. To accurately assess the efficacy of MK-0518, change of OBT was not permitted except for toxicity management or after patients had confirmed virologic failure.

A superiority design is considered appropriate in this patient population that had limited treatment options. In Phase III, the 2:1 randomization MK-0518:placebo allowed the most information to be gained for MK-0518 and also allowed more patients to receive an additional potentially active study medication. As a consequence, however, the control group in the clinical development program is smaller than with a 1:1 randomization.

One of the challenges in the interpretation of efficacy and safety data in the treatment-experienced studies of the Phase III design is the heterogeneous OBT; such heterogeneity is inevitable considering the different patterns of resistance of the patients' HIV strains. The efforts were made to achieve balance of in both treatment groups by stratification with factors known to impact efficacy endpoints, such as use of enfuvirtide in OBT and degree of patients' HIV resistance to PIs. In addition, the efficacy analyses (see [Sec. 2.7.3.3-trxexp]) took into account the other baseline prognostic factors such as use of enfuvirtide and darunavir in OBT. The contribution of the OBT to therapy was assessed by the GSS and the phenotypic sensitivity score (PSS). These scores were generated using the results from the genotypic and phenotypic resistance assay of the patients' HIV at screening; the Phenosense GT assay (Monogram Biosciences) was utilized for Phase II and Phase III studies. The baseline GSS and PSS were defined as the total ARTs in the OBT to which the patient's viral isolate showed genotypic and phenotypic sensitivity, respectively. Because there is no widely agreed upon clinical cutoff, enfuvirtide use in enfuvirtide-naïve patients was counted as an active drug and added to the GSS and PSS.

Because the resistance testing for darunavir was not available at the time of Phase III initiation, darunavir use in darunavir-naïve patients was counted as an active drug and added to the GSS and PSS; this convention is conservative since the degree of darunavir contribution in a regimen could be over-estimated due to cross-resistance within the PI class.

It is common in treatment-experienced studies of new agents to allow patients with virologic failure to switch to open-label active study drug; in previous studies [Ref. 5.4: 7, 8, 425], a switch to an open-label active study drug treatment group was allowed after study Week 8. A switch at study Week 8 provides challenges in the interpretation of efficacy (i.e. is there sufficient time to achieve efficacy) and safety data, given the short duration of the double-blind portion. To balance the need for generating appropriate double-blind data yet at the same time avoiding maintaining patients under suboptimal treatment for too long, patients in Protocols 005, 018, and 019 with documented virologic failure were allowed to switch to the "open-label post virologic failure" arm (referred to in [Sec. 2.7.3-trxexp] and [Sec. 2.7.4] as OLPVF) and receive MK-0518 after receiving at least 16 weeks of double-blind study therapy. All patients who switched were appropriately considered as virologic failures in the efficacy analyses.

Protocol 004, conducted in treatment-naïve patients, was a multi-center, double-blind (with in-house blinding) randomized dose-ranging, controlled study with 2 Parts: Part I compared MK-0518 monotherapy at doses ranging from 100 to 600 mg b.i.d. with placebo for 10 days. Part II initiated once Part I was complete and compared the same doses of MK-0518 with a standard-of-care comparator, EFV 600 mg once daily, both in combination with TFV and 3TC (see [Sec. 2.7.3.1.3.1-trxexp]). Forty eight week data contributes long term efficacy data in this patient population as described in [Sec. 2.7.3.2.1-trxexp].

2.5.4.2.2 Endpoints

HIV RNA and CD4 cell counts are well accepted surrogate markers for efficacy in clinical trials of HIV therapeutics [Ref. 5.4: 29, 395, 427] and have been used to support the efficacy of MK-0518 in this Application; the Phase III studies were not powered to evaluate clinical endpoints (e.g., progression to AIDS-defining conditions [ADC] and/or death). Over the past several years, the treatment of heavily treatment-experienced patients has evolved, impacting the choice of primary study endpoints in clinical trials; e.g., enfuvirtide (in 2003) demonstrated superiority of efficacy by using the change of HIV RNA from baseline as primary endpoint [Ref. 5.4: 7, 8], but with subsequent availability of more potent PIs, the primary efficacy measurements have changed to include proportion of patients with at least 1 $\log_{10}$ copies/mL decrease or with HIV RNA <400 copies/mL [Ref. 5.4: 248, 425]. Recently, treatment guidelines have recommended proportion of patients with HIV RNA <50 copies/mL as the ultimate goal [Ref. 5.4: 67, 310]. This evolution is reflected in the MK-0518 development program; Protocol 005 (designed [redacted] 20[redacted]) utilized change of HIV RNA from baseline as the primary

efficacy endpoint, while Protocols 018 and 019 (designed [redacted]) utilized the proportion of patients with HIV RNA <400 copies/mL. In considering the integrated efficacy data for treatment-experienced patients, the more stringent virologic endpoints of HIV RNA <400 and <50 copies/mL have been appropriately used by the Applicant [Sec. 2.7.3-trxexp]. Time-to-loss-of-virologic-responses (TLOVR), which is the time between randomization and the first HIV RNA value >400 copies/mL (non-responders who did not achieve HIV RNA <400 copies/mL are assigned a time of zero), was used to assess the durability of antiretroviral effect (see [Sec. 2.7.3.1.5.3-trxexp]).

The primary time point was Week 16 in Phase III and Week 24 in Phase II. Initially the Phase III protocols were written with primary time point at Week 24 but were subsequently amended to a primary time point of Week 16 (the amendment occurred prior to frozen file for Week 16). This change in the timing of the primary and secondary efficacy analyses reflected review of preliminary analyses of the ongoing Phase II studies. These analyses indicated that regimens containing MK-0518 appeared to be highly potent and generally well tolerated with 2 observations of particular interest: (1) in treatment-naïve patients the MK-0518 regimens achieved an HIV viral load <50 copies/mL more quickly than the efavirenz group with the efficacy results seen at Week 16 sustained through Week 24 [Ref. 5.3.5.1: P004]; and (2) in a treatment-experienced population comparable to the Phase III studies, MK-0518 in combination with OBT demonstrated superior, potent antiviral efficacy as compared to placebo with OBT with the efficacy results seen at Week 16 sustained through Week 24 [Ref. 5.3.5.1: P005]. As noted in [Sec. 2.5.1.6], Week 16 is considered an acceptable primary time point for studies in this patient population by the US FDA and the EU CHMP. It is important to note that while the primary efficacy analysis in pivotal Phase III studies was undertaken using Week 16 data from all enrolled patients, Week 24 data from approximately 60% of enrolled patients are also reported and were entirely consistent with the Week 16 results [Ref. 5.3.5.1: P018, P019] (see [Sec. 2.7.3.3.2.1-trxexp]).

In all Phase II and III studies, sparse Population PK samples were collected and an assessment of PK/PD was performed [Sec. 2.5.3]. MK-0518 resistance was also well characterized [Sec. 2.5.4.4].

The statistical approaches to analyze the efficacy of MK-0518 in this Application are consistent with current scientific and regulatory guidelines (see [Sec. 2.7.3.1.5-trxexp] and [Table 2.7.3-trxexp: 7]) and are described in detail in [Sec. 2.7.3.1.5.3-trxexp]. Three (3) different analytic approaches were used to handle missing data in the analyses of proportion of patient with HIV RNA <400 copies/mL and <50 copies/mL: 1) Non-completer = Failure (NC = F) where patients who prematurely discontinued assigned treatment regardless of reason were considered as failures thereafter; 2) Treatment-Related Discontinuation = Failure (TRD = F) where patients who prematurely discontinued assigned treatment due to lack of efficacy or adverse experiences (AEs) were considered as failures thereafter; and patients who prematurely discontinued assigned treatment, for reasons other than lack of efficacy or AEs, were excluded from

the analyses and 3) Observed Failure (OF) where patients who prematurely discontinued assigned treatment due to lack of efficacy were considered as failures thereafter; patients who prematurely discontinued assigned treatment, for reasons other than lack of efficacy, were excluded from the analyses. All approaches gave similar results because the discontinuation rate was low. For proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL, the Application presents results from the NC = F analysis (with other methods supportive), and for change from baseline in HIV RNA, CD4 cell counts, efficacy by prognostic factors and by subpopulations, and resistance-associated mutations versus potential prognostic factors, this Application presents the OF analysis, which considers the pure antiretroviral effect of the treatment, was used.

2.5.4.3 Efficacy Results

2.5.4.3.1 Overview

The pivotal (Protocols 018 and 019) and supportive (Protocols 004 and 005) studies provide robust and compelling evidence of the clinical efficacy of MK-0518 used in combination with other ARTs in the treatment of HIV-infected patients. MK-0518 doses of 100 to 600 mg (Protocol 004) and 200 to 600 mg (Protocol 005) all produce similar antiretroviral effect. In particular, there are compelling data in HIV-infected patients failing current therapies with HIV strains resistant to at least one drug in each of 3 oral classes of ARTs. In all 3 studies in treatment-experienced patients, the primary hypothesis analysis demonstrated that MK-0518 had superior antiretroviral efficacy compared with placebo, all in combination with OBT, for the primary efficacy and all secondary efficacy parameters. The antiretroviral effect was sustained through at least 48 weeks of treatment in the Phase II study. The Phase III studies provided confirmation of the superior antiretroviral effect of MK-0518 400 mg b.i.d. versus placebo, all in combination with OBT, at Week 16; data at Week 24 in approximately 60% of patients showed similar results. All subgroup efficacy analyses confirmed consistency of treatment effect of MK-0518 versus that of placebo. It is of particular note that the efficacy of MK-0518 was demonstrated even in patients with no active OBT (GSS or PSS = 0) in both Phase II and Phase III. In patients receiving MK-0518 with enfuvirtide and darunavir as first use in OBT in Phase III, >90% achieved HIV RNA <400 copies/mL and >80 % achieved HIV RNA <50 copies/mL. In treatment-experienced patients failing therapies with triple-class resistant virus, this level of virologic suppression, which is comparable to that observed in treatment-naïve HIV infected patients [Ref. 5.4: 53], is unprecedented. Additional efficacy analyses by gender, race (White, Black, and Hispanic), viral sub-type (B versus non-B clade), and geographic region (North America, Central/South America, Asia Pacific, and Europe) demonstrated consistently potent efficacy of MK-0518 as compared to placebo. MK-0518 was only evaluated in 9 patients 65 years or older, limiting any conclusions about use in elderly patients.

Although the data in treatment-naïve patients are limited to the Phase II study, through at least 48 weeks of therapy in combination with TFV and 3TC, MK-0518 results in antiretroviral effects comparable with those demonstrated by efavirenz, a current standard of care for treatment-naïve patients. It is of particular interest that MK-0518 produced a more rapid reduction in viral load than the efavirenz-based regimen.

2.5.4.3.2 Efficacy in Dose-Ranging Studies

The Phase II dose-ranging studies support the dosing recommendation of MK-0518 at 400 mg b.i.d. without regard to food, and with no dose adjustment in combination with other licensed ARTs.

In ***treatment-naïve patients*** (MK-0518 doses of 100, 200, 400, and 600 mg), 85 to 95% achieved HIV RNA <50 copies/mL at Week 24, which was sustained beyond Week 48 (see [Sec. 2.7.3.2.1-trxexp]) [Ref. 5.3.5.1: P004]. Immunological benefits as measured by increases in CD4 cell counts were also demonstrated at all doses studied (see [Sec. 2.7.3.2.1-trxexp]) [Ref. 5.3.5.1: P004]. The antiretroviral effects demonstrated for MK-0518 were comparable to those demonstrated by the efavirenz-based regimen, one of the current standards of care for treatment-naïve patients. Interestingly, the MK-0518 regimens resulted in a more rapid reduction in viral load than the efavirenz-based regimen.

In ***treatment-experienced patients*** with limited active agents in OBT (MK-0518 doses 200, 400, and 600 mg), 70 to 71% achieved HIV RNA <400 copies/mL at Week 24 which was sustained beyond Week 48; 56 to 67% achieved HIV RNA <50 copies/mL (secondary efficacy endpoint) at Week 24, which was sustained beyond Week 48 (see [Section 2.7.3.5.1.2-txexp]) [Ref. 5.3.5.1: P005]. Immunological benefits, as measured by increases in CD4 cell counts, were also demonstrated at all doses studied (see [Sec. 2.7.3.5.1.2-trxexp]) [Ref. 5.3.5.1: P005]. The antiretroviral effects demonstrated for MK-0518 were superior to those seen in the placebo group [Ref. 5.3.5.1: P005]. Protocol 005 provides a stringent test of efficacy, because patients had extensive prior experience and limited treatment options (e.g., 72% of MK-0518-treated patients had GSS=0; 90% of patients had no active PI in the OBT; 26% of patients had prior enfuvirtide exposure). The efficacy in this study is, therefore, particularly notable with MK-0518 recipients, regardless of dose, experiencing potent antiretroviral activity as evidenced by the suppression of viral load to <50 copies/mL in 60% of patients receiving MK-0518 versus only 13% of patients receiving placebo. Even MK-0518-treated patients with GSS or PSS of 0 exhibited potent HIV suppression at Week 24 [Ref. 5.3.5.1: P005].

The dose of 400 mg b.i.d. for Phase III studies was appropriately selected, taking into account the potent efficacy observed with MK-0518 doses ranging from 100 to 600 mg b.i.d. in combination therapy with other ARTs and the results from drug interaction studies of MK-0518 with potent inducers of UGT1A1 (see [Sec. 2.7.3.1.3.4.2]). This dose will provide a margin of efficacy when MK-0518 is used in combination with ARTs that are inducers of UGT1A1 (e.g., tipranavir), because 100 mg was efficacious in Protocol 004 and 200 mg was efficacious in Protocol 005.

2.5.4.3.3 Efficacy in Treatment-Experienced Patients (Protocol 005, 018, 019)

2.5.4.3.3.1 Overall Efficacy

The integrated efficacy analysis for Protocol 005, the MK-0518 400 mg b.i.d. arm, and for Protocols 018 and 019 combined, demonstrated the consistently superior efficacy of MK-0518 400 mg b.i.d. plus OBT over placebo plus OBT at Week 16 (see [Table 2.5: 2]), as well as at Week 24 based on approximately 60% of patients enrolled in Phase III (see [Sec. 2.7.3.3.2.1.2-trxexp], [Table 2.7.3-trxexp: 14] and [Figure 2.7.3-trxexp: 11]). The MK-0518 400 mg b.i.d. arm from Protocol 005 was not combined with data from Protocols 018 and 019 because of differences in inclusion criteria and in ARTs used in OBT (see [Sec. 2.7.3.3-trxexp]). These data from all 3 studies in treatment-experienced patients provide a solid body of evidence of the potent efficacy of MK-0518 (see [Sec. 2.7.3.2-trxexp], [Sec. 2.7.3.3-trxexp], [Figure 2.5: 1] and [Figure 2.5: 2]). In each of the pivotal Phase III studies, the primary efficacy endpoint (percent of patients achieving HIV RNA <400 copies/mL) and all secondary endpoints demonstrated superiority of MK-0518 400 mg b.i.d. over placebo at the primary efficacy time point at Week 16 as well as at Week 24 based on approximately 60% of patients enrolled (see [Sec. 2.7.3.2.3-trxexp] and [Sec. 2.7.3.2.4-trxexp]). It is of note that in Protocols 018 and 019, the percentages of patients with virologic response receiving placebo was better than that observed in Protocol 005. This is most likely related to the permitted use of investigational or recently licensed ARTs in OBT in the Phase III studies; approximately 40% in the placebo group achieving HIV RNA <400 copies/mL at Week 24 is consistent with what was reported in patients receiving darunavir [Ref. 5.4: 160, 248].

Table 2.5: 2

Treatment Outcome at Week 16 (All Randomized and Treated Patients)
(The MK-0518 400 mg b.i.d. Group and the Placebo Group From Protocol 005, and Protocols 018 and 019 Combined)

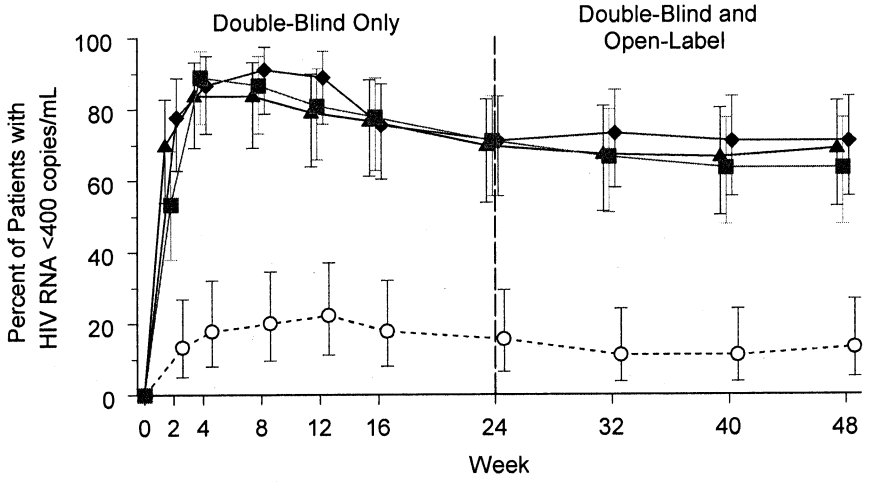
	Protocol 005		Protocols 018 and 019 Combined	
Outcome at Week 16	MK-0518 (N=45) n (%)	Placebo (N=45) n (%)	MK-0518 (N=462) n (%)	Placebo (N=237) n (%)
Patients with HIV RNA <400 copies/mL	35 (77.8)	8 (17.8)	355 (76.8)	99 (41.8)
Patients with HIV RNA <50 copies/mL	29 (64.4)	6 (13.3)	283 (61.3)	82 (34.6)
Patients with >1 Log_{10} drop in HIV RNA or HIV RNA <400 copies/mL	40 (88.9)	11 (24.4)	387 (83.8)	109 (46.0)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-2.06	-0.56	-1.88	-0.92
Mean CD4 cell count change from baseline (cells/mm^3)	110.3	29.7	83.9	35.6
Virologic Failure (confirmed)†	9 (20.0)	34 (75.6)	70 (15.2)	120 (50.6)
Non responder†	0 (0.0)	25 (55.6)	13 (2.8)	78 (32.9)
Rebound†	9 (20.0)	9 (20.0)	57 (12.3)	42 (17.7)
Death‡	0 (0.0)	0 (0.0)	6 (1.3)	3 (1.3)
Adjudicated AIDS-Defining Conditions§	N/A	N/A	11 (2.4)	5 (2.1)
Discontinuation due to clinical adverse events	0 (0.0)	0 (0.0)	7 (1.5)	5 (2.1)
Discontinuation due to laboratory adverse events	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Discontinuation due to other reasons‖	0 (0.0)	0 (0.0)	6 (1.3)	1 (0.4)

† Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).
‡ Includes available data beyond Week 16.
§ Potential cases identified for adjudication as of [redacted] 20[redacted] and occurring by Week 16.
‖ Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.
Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).
n (%) = Number (Percent) of patients in each category.
N/A = Not applicable

[Ref. 5.3.5.1: P005, P018, P019]

Figure 2.5: 1

Percent (95% CI) of Patients With HIV RNA <400 Copies/mL Over Time by Originally Randomized Treatment Group—Protocol 005
(Substudies A and B Combined; Entire Study Period)
(Non-Completer = Failure Approach)

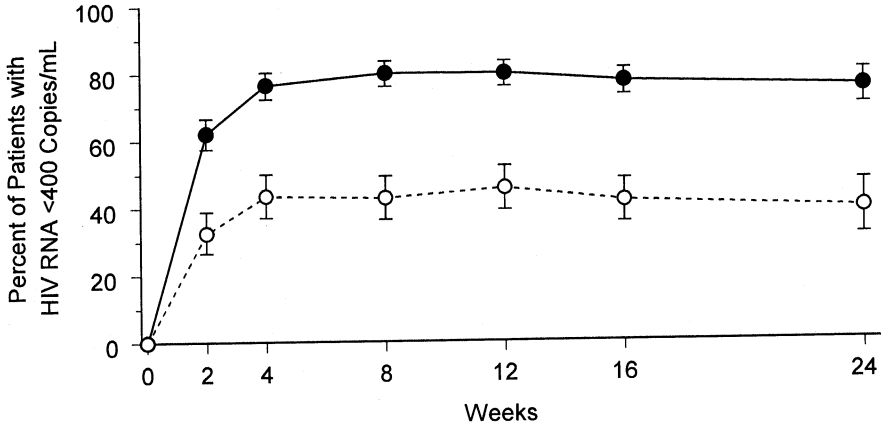


▲ MK-0518 200 mg b.i.d.	43	43	43	43	43	43	43	43	42	42
■ MK-0518 400 mg b.i.d.	45	45	45	45	42	45	45	45	44	44
◆ MK-0518 600 mg b.i.d.	45	45	45	45	45	45	45	45	45	45
○ Placebo	45	45	45	45	45	45	45	45	45	45

[Ref. 5.3.5.1: P005]

Figure 2.5: 2

Proportion of Patients With HIV RNA <400 Copies/mL (95% CI) Over Time
Protocol 018 and 019 Combined



Number of Contributing Patients							
● ISENTRESS + OBT	462	462	459	458	460	459	286
○ Placebo + OBT	237	237	237	236	237	237	150

m518p18p19CTD.r400 Mar. 22, 2007

[Ref. 5.3.5.1: P018, P019]

Furthermore, the efficacy data are consistent across all 3 studies conducted in different parts of the world and are further considered in [Sec. 2.5.4.3.3.2] and [Sec. 2.5.4.3.3.3] by the evaluation of several factors.

2.5.4.3.3.2 Efficacy by Baseline HIV RNA, Baseline CD4 Cell Count, Active PI in OBT, GSS, and PSS of OBT

Subgroup analyses using combined data from Protocols 018 and 019 evaluated efficacy of MK-0518 by baseline prognostic factors including baseline HIV RNA, baseline CD4 cell count, active PI in OBT, and GSS and PSS of OBT (see [Sec. 2.7.3.3.2.2-trxexp]). Taking into consideration that within each subgroup analysis there may be an imbalance in other prognostic factors between the MK-0518 group versus the placebo group, these analyses confirmed the consistent efficacy effect of MK-0518 in combination with OBT.

Specifically, MK-0518 demonstrated potent efficacy as compared to placebo across all of these baseline prognostic factors (see [Sec 2.7.3.3.2.2-trxexp], [Table 2.7.3-trxexp: 19], [Table 2.7.3-trxexp: 20], [Table 2.7.3-trxexp: 21], [Figure 2.7.3-trxexp: 12] and [Figure 2.7.3-trxexp: 16]). Consistent with Protocol 005, MK-0518 retained potent efficacy in patients with GSS=0 (functional monotherapy): 57% (63/111) and 45% (50/111) of those receiving MK-0518 achieved HIV RNA <400 copies/mL and HIV RNA <50 copies/mL, respectively, versus 10% (6/63) and 6% (4/63) of those receiving placebo (see [Table 2.7.3-trxexp: 19] and [Table 2.7.3-trxexp: 20]). However, functional monotherapy with MK-0518 should be avoided, in light of the fact that excellent efficacy was observed in patients with more active OBT (GSS>0): 82 to 92% and 64 to 76% of those receiving MK-0518 achieved HIV RNA <400 copies/mL and HIV RNA <50 copies/mL, respectively, at Week 16 (see [Table 2.7.3-trxexp: 19] and [Table 2.7.3-trxexp: 20]), results comparable to those observed in treatment-naïve patients [Ref. 5.4: 53].

Patients with lower baseline HIV RNA or with higher baseline CD4 cell counts showed overall better responses as compared to patients with higher baseline HIV RNA or with lower baseline CD4 cell counts, respectively; the treatment differences between MK-0518 and placebo, however, were consistent in direction and magnitude in all subgroups (see [Figure 2.7.3-trxexp: 12]). These findings are consistent with data from clinical trials with other ARTs [Ref. 5.4: 421].

2.5.4.3.3.3 Efficacy by Darunavir, Enfuvirtide, Darunavir and Enfuvirtide, and Tipranavir Use in OBT

Additional analyses to evaluate the effect of newly available ART for use in OBT were performed. The efficacy analysis by darunavir, enfuvirtide, darunavir and enfuvirtide, and tipranavir use in OBT demonstrated that MK-0518 had potent efficacy as compared to placebo across all subgroups (see [Sec 2.7.3.3.2.2-trxexp], [Table 2.7.3-trxexp: 22], [Table 2.7.3-trxexp: 23], [Table 2.7.3-trxexp: 24], [Fig 2.7.3-trxexp: 17], [Table 2.7.3-trxexp: 19], [Table 2.7.3-trxexp: 20], [Table 2.7.3-trxexp: 21] and [Figure 2.7.3-trxexp: 15]). Based on the results from the efficacy analyses by GSS and PSS of OBT, it is not surprising that when patients in the MK-0518 group had first use of darunavir and enfuvirtide, greater than 90% and 80% achieved HIV RNA <400 copies/mL and HIV RNA <50 copies/mL, respectively. Specifically, 98% and 89% of patients receiving MK-0518 with enfuvirtide and darunavir first use had HIV RNA <400 copies/mL and HIV RNA <50 copies/mL, respectively (see [Sec 2.7.3.3.2.2.1-trxexp], [Table 2.7.3-trxexp: 22] and [Table 2.7.3-trxexp: 23]).

In light of the potential impact of tipranavir-caused induction on the PK parameters of MK-0518, a detailed analysis of tipranavir use in the Phase III studies was undertaken. MK-0518 demonstrated potent efficacy as compared to placebo regardless of whether or not tipranavir was used as part of OBT (see [Sec 2.7.3.3.2.2.-trxexp], [Table 2.7.3-trxexp: 19], [Table 2.7.3-trxexp: 20], [Table 2.7.3-trxexp: 21] and [Figure 2.7.3-trxexp: 15]). If tipranavir was or was not used in the OBT in patients with tipranavir-sensitive HIV, 81%

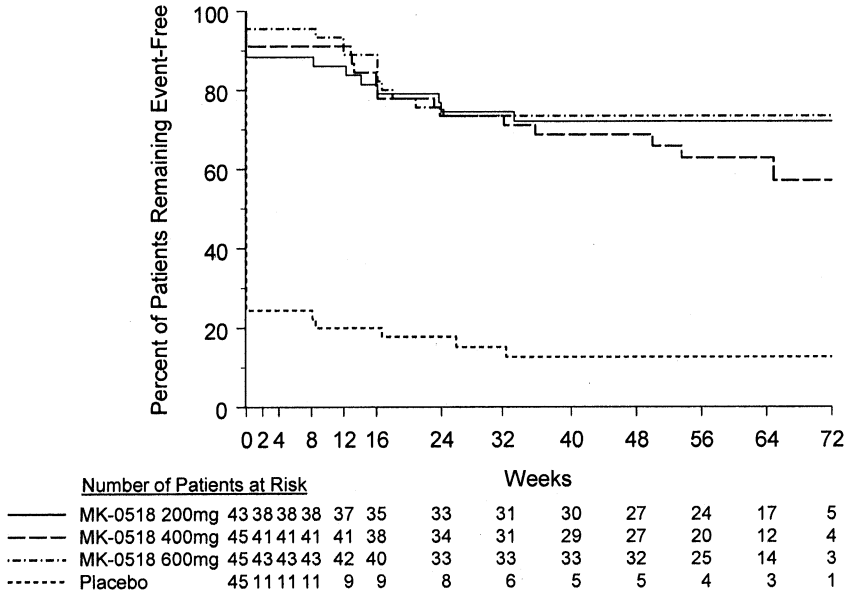
and 81% of patients on MK-0518, respectively, versus 50% and 44% of patients on placebo, respectively, achieved HIV RNA <400 copies/mL. The evaluation of MK-0518 in patients utilizing tipranavir in the setting of tipranavir-resistant HIV represents a strict test of the impact of tipranavir on the efficacy on MK-0518 because in these patients tipranavir would not be predicted to be adding substantive antiretroviral efficacy into the regimen and would modestly reduce MK-0518 levels (see [Sec. 2.5.3]); 62% of patients on MK-0518 versus 22% on placebo had HIV RNA <400 copies/mL. The response rates were lower in both groups as one would anticipate because tipranavir was no longer an active drug. Despite this, the magnitude of the treatment effect versus placebo was preserved in the MK-0518 group. Overall, these data support that the impact of tipranavir on MK-0518 PK is not clinically significant in the setting of combination therapy and support the dosing recommendation of MK-0518 without dose adjustment when used in combination with tipranavir.

2.5.4.3.4 Long-Term Efficacy

Long-term efficacy data from both Phase II studies demonstrate that potent antiretroviral effect of MK-0518 was sustained out to Week 48 for all patients and up to Week 72 for a small number of patients with available data are in [Sec. 2.7.3.5-trxexp]. In Protocol 005, the durability of antiretroviral activity was assessed using TLOVR (see [Figure 2.5: 3]), in addition to the percent of patients achieving HIV RNA <400 copies/mL and HIV RNA <50 copies/mL and the change from baseline in CD4 cell count [Ref. 5.3.5.1: P005]. This TLOVR analysis includes all data for patients randomized to MK-0518, and encompasses the 24-week double-blind portion of the study, the period between Week 24 and Week 48, which represents a mix of double-blind data and open-label extension data, and the period beyond Week 48 during which all patients remaining in study were receiving MK-0518 400 mg b.i.d. Only 3 patients lost virologic response after Week 48, noting that the number of patients with data beyond Week 56 is small. This is particularly noteworthy considering the limited treatment options available to patients in Protocol 005. The association between prognostic factors and TLOVR was evaluated using a Cox Proportional Hazards model [Ref. 5.3.5.1: P005]. Enfuvirtide use in OBT, baseline HIV RNA, and baseline GSS and PSS appeared to be strongly associated with TLOVR. Patients with enfuvirtide use in OBT, with baseline HIV RNA <50,000 copies/mL, and with GSS and PSS >0 showed a major reduction in hazard of loss of virologic response; the observation with enfuvirtide is consistent with recent clinical trials [Ref. 5.4: 160, 248].

Figure 2.5: 3

Time to Loss of Virological Response – Kaplan-Meier Approach
Protocol 005 All Doses (Substudies A and B Combined; Entire Study Period)



[Ref. 5.3.5.1: P005]

Similar durability was demonstrated in Protocol 004 (see [Sec. 2.7.3.5.1.1-trxexp]).

In addition to the Phase II data, TLOVR analysis from Protocols 018 and 019 combined, demonstrate that failures beyond Week 16 were uncommon based on available data up to Week 32; as noted in [Figure 2.7.3-trxexp: 27] and [Sec. 2.7.3.5.1.4-trxexp] 52 patients receiving MK-0518 plus OBT and 10 patients receiving placebo plus OBT completed 32 weeks and remained failure-free (see [Sec. 2.7.3.5.1.4-trxexp] and [Fig. 2.7.3-trxexp: 27]).

2.5.4.3.5 Efficacy in Special Populations

Efficacy analyses by gender, race, viral subtype (B versus non-B clade), and geographic region demonstrated potent efficacy of MK-0518 as compared to placebo and this efficacy did not appear different in any of the subgroups analyzed (see [Sec. 2.7.3.3.3-trxexp]). Given the limited number of patients 65 years or older studied (N=9), assessment of efficacy of MK-0518 in this patient population could not be made. There were no data in the pediatric patient population (age <16) and no data in pregnant HIV-infected women. The proposed Product Circular appropriately notes the lack of data in these patient populations and the inability to recommend the use of MK-0518 in these patients at present.

2.5.4.4 Resistance

In the development of any new ART, there is interest in evaluating in clinical trials whether the new ART is efficacious in patients with virus resistant to currently licensed compounds; preclinical data in [Sec. 2.6.2.2.2.2] and clinical data in [Sec. 2.5.4.3.3.2] have already demonstrated that MK-0518 retained potent activity against HIV strains resistant to NRTIs, NNRTIs, and PIs. There is also an interest in the identification of specific mutations that are associated with resistance and virologic failure. The resistance profile of MK-0518 was evaluated by performing genotypic resistance assays in patients who had virologic failure in the clinical trials (see [Sec. 2.7.3.5.2-trxexp]). Virologic failure was generally associated with mutation at either amino acid 148 (Q changed to H, K, or R) or amino acid 155 (N changed to H) in the HIV integrase. These mutations were usually observed in combination with 1 or more secondary mutations. There have been instances in which virologic failure occurred and no integrase mutations were observed. Most integrase mutations were detected by Week 16. These resistance mutations observed in patients were generally consistent with resistance mutations observed in vitro. Despite the emergence of integrase mutations within 16 weeks of therapy, the efficacy has been demonstrated to be robust and sustained through at least 48 weeks, even in a patient population with limited active ARTs in the OBT.

2.5.4.5 Conclusions Regarding the Clinical Efficacy of MK-0518

This Application provides compelling clinical efficacy data to support the proposed indication in the Product Circular. The virologic and immunologic benefits associated with MK-0518 were superior to those associated with placebo, all in combination with OBT. The potent and sustained antiviral effect, comparable to that observed historically in treatment-naïve patients, was particularly significant given that these patients had failed previous therapies with multi-drug resistant virus. The range of treatment-experienced patients included in Phase II and Phase III provided the opportunity to evaluate the efficacy of MK-0518 in a variety of combination regimens and is representative of the population in the proposed indication. The overall data provide

support that MK-0518 should not be reserved as a last-line agent in order to avoid functional monotherapy, because the greatest level of viral suppression were repeatedly demonstrated in patients who had other potent ARTs (e.g., enfuvirtide in enfuvirtide-naïve patients; darunavir in darunavir naïve patients) co-administered.

2.5.5 Overview of Safety

The safety database reported in [Sec. 2.7.4] permits a thorough examination of the safety profile of MK-0518. While the largest body of safety data is from the treatment-experienced patients in support of the proposed indication, there are also detailed safety data from uninfected subjects (18 Phase I studies) and treatment-naïve patients (Phase II dose-ranging study). This Application also provides reports of serious adverse experiences from ongoing studies including the Phase III treatment-naïve study (Protocol 021) and the expanded access environment (see [Sec. 2.7.4]). The overall data showed that MK-0518 is generally well-tolerated at all doses studied, including the dose of 400 mg b.i.d. proposed for the Product Circular.

2.5.5.1 Study Population and Extent of Exposure

The evaluation of safety of MK-0518 in HIV-infected patients presented in [Sec. 2.7.4] includes data from the Phase II and Phase III studies described in [Table 2.5: 1]. This evaluation includes data from 875 patients who were treated with MK-0518 for at least 16 weeks and up to 78 weeks (548 days) in combination regimens in the **2 Phase II studies and 2 Phase III studies** (see [Sec. 2.7.4.2.1.2] and [Sec. 2.7.4.1.3.2]). These 875 patients included the 755 patients who received MK-0518 by initial randomization, 114 patients from the placebo arms of Protocol 005, Protocol 018, and Protocol 019 who switched to OLPVF, and 6 patients from the Protocol 005 placebo group who received MK-0518 400 mg in the open-label extension phase per amendment. In addition, ongoing studies contribute safety data through serious adverse experience reports; these additional reports are all from the expanded access environment as there were no serious adverse experiences reported from the ongoing Phase III treatment-naïve study (see [Sec. 2.7.4.2.1.2.3.4]).

The safety evaluation focused primarily on data from: 1) from the ***double-blind treatment*** in which the control arm was either placebo or efavirenz; and 2) was supplemented by the evaluation of MK-0518 used in the ***open-label arms*** (The safety data from the open-label arms, which are not discussed in detail in this Overview of Safety, were generally consistent with the double blind comparative data.):

Double-Blind Treatment:

Data are derived from the Phase II dose-ranging studies and the integrated evaluation of the MK-0518 400 mg b.i.d. regimen in treatment-experienced patients. The Phase II dose-ranging studies provide information on the potential for dose-related toxicities. The treatment-naïve (Protocol 004 [N=198 with 160 patients randomized to 4 different doses

of MK-0518 and 38 to control]) and treatment-experienced (Protocol 005 [N=178 total with 133 patients randomized to 3 different doses of MK-0518 and 45 to control]) studies were evaluated separately due to the different patient populations. The mean (range) duration of treatment at any dose was 347.7 (5 to 473) days in treatment-naïve patients, and 349.5 (4 to 258) days in treatment-experienced patients, respectively. Safety data from Protocols 018 and 019 have been appropriately combined with the treatment-experienced patients receiving MK-0518 400 mg b.i.d. in Protocol 005 to provide the integrated safety data supporting the dose recommended for the proposed Product Circular (N=789 patients with 507 patients receiving MK-0518 400 mg b.i.d. and 282 receiving placebo).

Open-Label Arms:

Open-label data are available from the Phase II and Phase III studies. All of the treatment-experienced studies (Protocols 005, 018, and 019) allowed patients to enter an OLPVF arm in the event of virologic failure (N=177 with 114 coming from placebo groups and 63 from MK-0518 groups); the mean (range) number of days for patients on open-label MK-0518 400 mg b.i.d. was 76.7 (7 to 186 days). In addition, patients in Protocol 005 could continue in an open-label extension after at least 24 weeks of dose-ranging therapy (N=100); the mean (range) number of days for patients on open-label study drug at 400 mg b.i.d. (from end of double-blind/beginning of OL) was 126.8 (48 to 186) days [Ref. 5.3.5.1: P005].

In interpreting the safety data, it is important to note that the design of the clinical studies presented in [Sec. 2.5.4.2.1] resulted in imbalance of both the numbers of patients treated with MK-0518 versus comparator (randomization ratios were 3:1 or 4:1 in Phase II and 2:1 in Phase III studies) and the duration of treatment for MK-0518 versus comparator (e.g., open-label MK-0518 was offered to all treatment-experienced patients who had virological failure after at least 16-weeks of therapy). The overall extent of exposure to MK-0518, therefore, was substantially greater than that of the comparator regimens, particularly in the treatment-experienced population due to the open-label option. During double-blind treatment in Protocols 005, 018 and 019, the exposure to MK-0518 **400 mg b.i.d.** was 260.8 patient-years and to placebo was 126.6 patient-years. This difference in exposure to study drug is important to consider when evaluating the frequency of adverse experiences in the double-blind phase of the study. Unless specifically indicated, however, the frequencies (%) presented for adverse experiences are not adjusted for different duration of exposure.

2.5.5.2 Analysis of Adverse Experiences

The overall safety evaluation plan is described in [Sec. 2.7.4.1.1]. Briefly, monitoring of safety was done by the investigator(s) at each study visit. Subjects/patients who completed the study or discontinued early were requested to return for a 14-day post-therapy follow-up visit. Clinical adverse experiences were graded as mild, moderate, or

severe intensity by the investigator. No intensity is recorded for laboratory adverse experiences. A drug-related adverse experience was one that the investigator regarded as possibly, probably, or definitely related to study therapy. An adverse experience is considered serious if it fulfills the following criteria: results in death, is life threatening, results in a persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, other important medical event, cancer or overdose. In addition to the investigators' evaluation of laboratory adverse experiences, all laboratory values outside the normal range were assessed regardless of whether they were considered by the investigator to be or not to be a laboratory adverse experience. Guidelines for grading the severity of laboratory abnormalities are based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences (DAIDS Criteria).

2.5.5.2.1 Analysis of Adverse Experiences in Treatment-Experienced Patients

This is the key analysis supporting the proposed Product Circular indication (see [Sec. 2.7.4.2]).

2.5.5.2.1.1 Clinical Adverse Experiences

Review of the double-blind treatment-experienced population receiving MK-0518 400 mg b.i.d. showed that the overall clinical adverse experience profile of MK-0518 was similar to that of placebo, each given with OBT [Sec. 2.7.4.2]. As anticipated in this very sick patient population, at least one clinical adverse experience was reported in the majority of patients; the frequency of clinical adverse experiences, drug related clinical adverse experiences, serious clinical adverse experiences, serious drug-related clinical adverse experiences, and deaths were generally similar in both groups. A measure of the overall safety profile is the percent of patients who discontinued study therapy due to an adverse experience. Discontinuations due to clinical adverse experiences were uncommon and similar in both groups (1.6% [8/507] in MK-0518 versus 1.4% [4/282] in placebo group). In general, the frequency of specific clinical AEs with MK-0518 was relatively low. The most frequently reported clinical adverse experiences (reported in ≥10% of patients in one or more treatment groups), including those of all intensity and regardless of drug relationship, were diarrhea (15.6% [79/507] MK-0518; 19.1% [54/282] placebo), nausea (9.5% [48/507] MK-0518; 13.1% [37/282] placebo), and headache (8.7% [44/507] MK-0518; 11.7% [33/507] placebo) (see [Sec. 2.7.4.2.1.2.1.2]). Consistent with the Product Circular of the recently approved ARTs, the proposed Product Circular of MK-0518 also includes the most frequently reported overall drug-related clinical adverse experiences (reported in ≥2% of patients in one or more treatment groups) of moderate to severe intensity: diarrhea (3.7% MK-0518; 3.5% placebo), nausea (2.2% MK-0518; 3.2% placebo), injection-site reaction related to enfuvirtide use (8.7% [44/507] MK-0518; 9.6% [27/282] placebo), and headache (2.2% MK-0518; 1.4% placebo) (see [Sec. 2.7.4.2.1.2.1.2]).

In reviewing the clinical adverse experience profile of the MK-0518 group compared with that of the placebo group, rash (regardless of drug relationship) was reported more often in the MK-0518 group (6.7% [34/507] MK-0518; 3.9% [11/282] placebo); the incidence of drug-related rashes, however, were similar between the treatment groups: 2.0 %(10/507) for MK-0518 versus 2.5% (7/282) for placebo [Sec. 2.7.4.2.1.2.5]. This Application provides a detailed evaluation of the cases of rash (reported as follicular rash, generalized rash, macular rash, maculopapular rash, popular rash, pruritic rash, and rash) (see [Sec. 2.7.4.2.1.2.5]). Pruritus and hypersensitivity were also evaluated in detail. Rash was primarily mild to moderate in intensity, usually associated with other agents known to cause rash, and none led to discontinuation of study therapy. The incidence of pruritus was generally similar in both treatment groups and this adverse experience did not limit therapy. Hypersensitivity was described in 4 patients in the MK-0518 group and 4 patients in the placebo group. For the 4 patients in the MK-0518 group, 2 were able to continue study therapy, while the other 2 had therapy interrupted and upon rechallenge were able to resume MK-0518 therapy. Rash, macular rash, maculopapular rash, and hypersensitivity are appropriately noted as side-effects of MK-0518 in the proposed Product Circular.

In regards to lipodystrophy and lipoatrophy, which were already present in approximately 27.4% and 12.0% of patients pre-study, respectively, the frequency of lipodystrophy or lipoatrophy reported as adverse experiences during the study was low and similar between the MK-0518 and placebo groups: lipodystrophy was reported in 0.8% (4/507) of patients receiving MK-0518 versus 0.4% (1/282) of patients receiving placebo; lipoatrophy was reported in 0.2% (1/507) of patients receiving MK-0518 versus 0.4% (1/282) of patients receiving placebo ([Sec. 2.7.4.2.1.2.5] and [Appendix 2.7.4: 13]). Anthropomorphic measurements taken over 48 weeks in the Phase II treatment-naïve and treatment-experienced studies showed no particular trends of concern but are not a definitive test for lipodystrophy. Furthermore, lipodystrophy typically requires a longer period of treatment and observation to become apparent, while the duration of follow-up is limited for the MK-0518 Phase III studies. With these qualifications, however, there does not appear to be a pattern suggesting increased rates of lipodystrophy or lipoatrophy in patients receiving MK-0518.

In light of the potent efficacy demonstrated by the MK-0518-containing regimens, cases of Immune Reconstitution Syndrome (IRS), a syndrome that has been reported in HAART, were reviewed. There were 3 patients with IRS reported as serious adverse experiences (see [Sec. 2.7.4.2.1.2.5]). Study therapy was interrupted for only 1 patient. Two (2) had recovery and 1 had the IRS listed as ongoing at the time of the preparation of the Summary of Clinical Safety. IRS is appropriately listed under Precautions in the proposed Product Circular.

2.5.5.2.1.2 Laboratory Adverse Experiences and Laboratory Values

Safety laboratory results were assessed by 3 different approaches: (1) investigator-reported adverse experiences, including investigator assessment of potential causality; (2) review of changes from baseline of laboratory values using Predefined Limits of Change (PDLC); and (3) review of study therapy discontinuations due to laboratory adverse experiences. Overall, MK-0518 demonstrated an excellent safety profile with respect to safety laboratory parameters.

Review of the double-blind treatment-experienced population receiving MK-0518 400 mg b.i.d. showed that the overall laboratory adverse experience profile of MK-0518 was similar to that of placebo, each given with OBT. Laboratory adverse experiences were reported uncommonly (19.5% [99/507] MK-0518; 18.1% [51/282] placebo) in the double-blind cohort. There were 2 serious laboratory adverse experiences and 1 discontinuation due to a laboratory adverse experience in the MK-0518 group, compared with none in these categories for the placebo group. There were no serious drug related laboratory adverse experiences or deaths due to laboratory adverse experiences in either group. Of the tests performed in routine monitoring, the most frequently (incidence ≥1% in one or more treatment groups) reported laboratory adverse experiences, regardless of drug relationship, were alanine aminotransferase (ALT) increased (4.5% [23/507] MK-0518; 2.1% [6/282] placebo), aspartate aminotransferase (AST) increased (4.3% [22/507] MK-0518; 2.5% [7/282] placebo), blood triglycerides increased (3.6% [18/507] MK-0518; 3.2% [9/279] placebo), and creatinine phosphokinase increased (3.2% [16/507] MK-0518; 0.7% [2/282] placebo). Of the tests performed in routine monitoring, the most frequently (≥1% in one or more treatment group) reported laboratory adverse experiences that were considered drug-related were: ALT increased (3.2% [16/507] MK-0518; 0.7% [2/282] placebo), AST increased (2.6% [13/507] MK-0518; 1.1% [3/282] placebo), and blood triglycerides increased (2.6% [13/507] MK-0518; 1.1% [3/279] placebo).

Elevations in hepatic aminotransferases have been commonly described with most ART agents. In the MK-0518 studies, overall frequencies of elevated AST and ALT reported either as adverse experiences or objectively observed as PDLC were generally similar between the MK-0518 group and the placebo group and rarely limited therapy. Higher frequencies of these abnormalities were seen in patients with chronic viral hepatitis or tipranavir use, but these trends were observed to be similar in both the MK-0518 group and the placebo group.

There was no evidence of hyperglycemia following treatment with MK-0518, supporting the removal of the PI class warning in regards to diabetes mellitus/hyperglycemia from the proposed Package Circular.

In reviewing the laboratory adverse experience profile of the MK-0518 group compared with that of the placebo group, elevations in creatine kinase (regardless of drug relationship) were reported more often in the MK-0518 group (3.2% [16/507] MK-0518; 0.7% [2/282] placebo); the minority of these were reported as drug related (0.8% [4/507] MK-0518; 0.7% [2/282] placebo). In the MK-0518 group, these elevations were generally transient, often associated with increased physical exercise and did not limit therapy.

2.5.5.2.1.3 Summary

In summary, this safety evaluation demonstrated that MK-0518 400 mg b.i.d. was generally well tolerated in treatment-experienced patients. While not presented here, the open-label non-comparative safety data were generally consistent with double-blind comparative data.

2.5.5.2.2 Analysis of Adverse Experiences in Treatment-Naïve Patients

Safety data from uninfected subjects (N=315 subjects) enrolled in Phase I studies and from treatment-naïve HIV infected patients (N=198 patients) were also reviewed. Treatment-naïve patients generally do not have confounding factors such as advanced HIV disease or medical conditions resulting from complications of long-term HAART. In addition, heterogenous OBTs do not confound the safety evaluation in this population (TFV and 3TC was the fixed combination regimen in the Phase II study).

Safety data from Phase I studies indicate that MK-0518 was generally well tolerated in uninfected male and female subjects and in uninfected subjects with moderate hepatic or severe renal insufficiency.

In treatment-naïve patients, MK-0518 was generally very well tolerated in patients at all doses studied, ranging from 100 to 600 mg b.i.d. in combination with 3TC and TFV. No dose-related toxicities were observed, and the safety profile was similar to that observed in treatment-experienced patients. Of interest, there was no significant elevation of triglycerides, total cholesterol, or LDL-cholesterol over time in patients in the MK-0518 groups as compared with the efavirenz group. Given the interest in the HIV treating community in knowing whether MK-0518, a novel HIV integrase inhibitor, is associated with changes in serum lipid parameters, this information is important to disclose in the Product Circular.

2.5.5.2.3 Deaths, Serious Adverse Experiences, and Discontinuations

Serious adverse experiences occurred in comparable frequencies between the MK-0518 400 mg b.i.d. group and the placebo group (10.7% [54/507] MK-0518; 12.8% [36/282] placebo). Most of these were considered related to the underlying diseases since the frequencies of serious adverse experiences considered possibly drug-related were much lower and similar between the MK-0518 and placebo groups (1.6% [8/507] MK-0518; 1.8% [5/282] placebo). Most of the patients on MK-0518 (75% [6/8]) recovered from the serious drug-related adverse experiences and continued in the study.

Overall, adverse experiences leading to discontinuation were uncommon (≤1.6%) and generally balanced between treatment groups as noted in [Sec. 2.5.5.2.1].

For evaluation of deaths and serious adverse experiences of cancer discussed below, all patients in Phase II and III studies were included regardless of the MK-0518 doses received. In interpreting the data on Deaths and SAEs, it is important to consider that the overall extent of exposure to MK-0518 was substantially greater than that of the comparator regimens (see [Sec 2.5.5.1]) and that the treatment-experienced patients included in the development program had advanced HIV disease: ≥80% had AIDS at study entry and in Phase III, 32% of patients had baseline CD4 cell counts of ≤50 copies/mL. For comparative purposes, during the double-blind treatment period in Protocols 004, 005, 018, and 019, there were 758 patients receiving MK-0518 (all doses) versus 323 patients receiving placebo, with patient exposure (based on time on study) of approximately 510 patient-years versus 169 patient-years, respectively (exposure ratio of approximately 3:1 MK-0518:Placebo).

In the double-blind comparative period, there was a total of 8 deaths reported in 758 patients (1.1%) receiving MK-0518 versus 3/320 (0.96%) in placebo. The patient-year adjusted death rates were 1.568 and 1.771 per 100 patient-years for the MK-0518 and the comparator arms, respectively, resulting in a relative risk of 0.885 with an associated 95% CI of (0.21, 5.18) based upon an exact approach using binomial conditional distribution. There were 2 additional deaths during the open-label phase: one during the open-label extension period of Protocol 005 and one during the OLPVF (Protocol 019). None of the deaths were considered related to MK-0518 in combination with OBT. Most cases occurred in patients with low CD4 cell counts and were related to opportunistic infections or AIDS malignancies.

Ten (1.3% [10/758]) patients were reported to have an serious adverse experience of malignancy in the MK-0518 group and 1 (0.3% [1/323]) patients in the comparator group for data combined across Protocols 004, 005, 018 and 019 during double-blind phase. A complete evaluation of these malignancies is in [Sec 2.7.4.2.1.2.5]. None of the neoplasms was considered by the investigators to be drug related. In addition, 2 malignancies were reported in the pretreatment/screening period, consistent with a high background rate for cancers in this population. The patient-year-adjusted incidence rates

were 1.970 and 0.592 patients with malignancies per 100 patient-years for the MK-0518 arm and the comparator arm, respectively, resulting in a relative risk of 3.328 with an associated 95% CI of (0.47, 144.45) based upon an exact approach using binomial conditional distribution. In addition, there were 2 additional patients with neoplasms events from the open-label parts of the combined studies resulting in a total of 12 patients with neoplasms in the MK-0518 group and 1 patient in the comparator group. With increased numbers of patients and increased exposure to MK-0518 by including the open-label parts, the incidence rate (1.940 patients with malignancies per 100 patient-years) was not increased from the patient-year-adjusted incidence rate of 1.970 for the MK-0518 group during the double blind parts of the studies.

There does not appear to be any direct evidence of drug relationship to any of these events of cancer: most of these cancers (approximately 75%) were detected within 3 months of enrollment; the reported cancer diagnoses were varied, but are predominantly common AIDS defining conditions (lymphomas and Kaposi's sarcoma), or otherwise common in the HIV infected population (anal cancer related to human papillomavirus), or have other likely etiologies (chronic hepatitis B for the hepatic neoplasm; tobacco history for squamous cell carcinoma of the vocal cord).

Overall, the combined data do not suggest any specific cancer risk associated with MK-0518 treatment. As discussed in more detail in the Risk Management Plan, additional follow-up from ongoing studies in both treatment-naïve and treatment-experienced patients will provide additional data. A summary of these serious adverse experiences of malignancy is provided appropriately within the proposed Product Circular; this summary includes the statement that the relationship to raltegravir is unknown.

2.5.5.3 Safety in Special Groups and Situations

Safety in special groups and situations was evaluated primarily in the Phase III treatment-experienced studies where there were generally substantial proportions of patients with the subgroup of interest.

2.5.5.3.1 Intrinsic Factors

Adverse experiences and laboratory abnormality profiles were generally similar in patient subgroups based on gender (N for male = 445; for female = 62), age (N for <65 years = 498 and N for ≥ 65 years = 9), and race (N for White = 336; N for Black = 71; N for Hispanic = 58; N for Asian = 16; N for Multi-Racial = 26), taking into account small sample sizes for some categories (see [Sec. 2.7.4.5.1]). Limitations of the safety data in the elderly population (age ≥65) are acknowledged with appropriate wording in the proposed Product Circular.

2.5.5.3.2 Extrinsic Factors

Safety data were reviewed for subgroups of patients with hepatitis B and/or C virus co-infection, patients who used ARTs that are known to be associated with increased hepatic aminotransferases (tipranavir), and ARTs that have been shown to increase plasma levels of MK-0518 in Phase I drug interaction studies (atazanavir, TFV).

Patients with active hepatitis-B (based on positive HBsAg) and/or C (based on positive hepatitis C serology) virus co-infection showed a safety profile generally similar to that of the complement group without chronic viral hepatitis, although rates of AST and ALT elevations as adverse experiences and as PDLCs were slightly higher for both treatment groups in the co-infected population versus the complement. This information is important to the prescribing physician and is appropriately stated in the proposed Product Circular. A review of patients whose OBT included (or did not include) tipranavir was performed; slightly higher rates of AST and ALT elevations as adverse experiences and PDLC were seen for both treatment groups in those whose OBT contained tipranavir versus the complement. This is likely due to tipranavir itself which has a known association with LFT abnormalities [Ref. 5.4: 397]. It is not likely due to a drug-drug interaction because tipranavir modestly lowers exposure of MK-0518. The safety profile of patients receiving MK-0518 with TFV and/or atazanavir was generally similar to that of the complement population, suggesting that there is no increased toxicity apparent at the highest exposures to MK-0518 studied to date.

2.5.5.3.3 Overdose

The maximal dose of MK-0518 studied in Phase I was 1600 mg daily for 14 days (see [Sec. 2.7.4.5.5]). There is very limited information on overdose, noted in only 6 patients in Protocol 018 who received more than the prescribed daily dose of 800 mg. No adverse experiences were reported with these overdoses. The wording in the proposed Product Circular reflects the lack of data on overdose.

2.5.5.4 Limitations of the Safety Database

In this Application, there were no data from pediatric patients and pregnant women and insufficient data in patients above age of 65. These limitations of the safety database are appropriately acknowledged in the corresponding sections in the proposed Product Circular.

2.5.5.4.1 Risk Management Plan

A comprehensive Risk Management Plan is provided in this Application and is considered acceptable.

2.5.5.5 Worldwide Marketing Experience

MK-0518 has not yet been licensed in any country, and therefore, no postmarketing data are available.

2.5.5.6 Conclusions Regarding the Clinical Safety of MK-0518

MK-0518 treatment was generally well tolerated with relatively few serious drug-related adverse experiences and very few discontinuations in all subjects including uninfected subjects, treatment-naïve patients, and treatment-experienced patients with advanced HIV infection/AIDS. There was no evidence that higher doses or higher exposure due to drug-drug interactions led to increased drug toxicity. There was no evidence of hyperglycemia or lipodystrophy/lipoatrophy. There were no evidence of clinically significant increases of liver function test abnormalities in patients receiving MK-0518. MK-0518 was generally well tolerated in patients with co-existing chronic viral hepatitis. There was a numerically greater number of malignancies observed in the MK-0518 groups compared with the placebo group but there was no direct evidence of drug relationship to any of these events of cancer. Additional follow-up in the ongoing studies is warranted.

The proposed Product Circular clearly identifies all clinical and laboratory adverse experiences potentially related to MK-0518, and appropriately provides the safety information in hepatitis B and/or C co-infected patients, and the lack of lipid abnormalities in treatment-naïve patients. IRS is listed in Precautions. The proposed Package Circular also acknowledges lack of data in pediatric patients, in pregnant patients, and in patients with severe hepatic insufficiency and insufficient data in patients older than 65 and in case of overdose.

2.5.6 Benefits and Risks Conclusions

Medical Need for Treatment of HIV-Infected Patients With Triple-Class Resistant Virus

Despite the progress made with HAART over the last decade, there is still an urgent medical need for an effective ART for patients failing current therapies with multi-drug resistant virus (see [Sec. 2.5.1.4]). Although there are approximately 22 licensed ARTs, all except one belong to only 3 classes of ARTs (NRTIs, NNRTIs, and PIs) that target 2 HIV enzymes. There is significant cross-resistance within each class. Overcoming the increased levels of resistance and cross-resistance that follow each successive therapeutic failure is a major challenge faced by clinicians. Recent data [Ref. 5.4: 67] strongly indicate that a new ART from a novel class offers benefits to this patient population given lack of cross-resistance to exiting classes. MK-0518, the first HIV integrase strand transfer inhibitor, has provided convincing evidence of its benefits in HIV-1 infected patients, in particular those who are refractory to currently available treatment.

Impact of MK-0518 on the HIV Treatment Armamentarium

Benefits

The available efficacy data from all 3 Phase II and III trials in treatment-experienced patients support the conclusion that MK-0518 has potent antiretroviral effect in the targeted patient population. The 48-week results from Protocol 005 suggest that this potent antiretroviral effect is sustained. Potentially of most significance is the observation that MK-0518, in combination with at least one more active potent ART, such as enfuvirtide or darunavir, produces a high degree of remarkable viral suppression which has only been previously possible in treatment-naïve patients [Ref. 5.4: 53]. To date, rescue antiretroviral therapy in patients failing previous regimens has been inadequate, given that patients generally do not have more than one active ART in the regimen. Functional monotherapy quickly leads to therapeutic failure and further development of resistance. The landscape for HIV treatment in heavily-treatment-experienced patients is evolving rapidly with the possibility of having more than one new agent available in approximately the same timeframe to allow truly effective combination therapy. Thus, the timing for access of MK-0518 is extremely important for these patients, so that the most recently approved ARTs can partner with MK-0518 for the construction of an effective combination therapy.

In addition to efficacy benefits, the favorable tolerability and safety profile of MK-0518 to date in this advanced-HIV patient population provides a significant therapeutic benefit. Toxicity is an important barrier to effective antiretroviral therapy and accounts for the most common reasons for treatment failure [Ref. 5.4: 204, 367]. The rate of discontinuation due to adverse experiences in all studies in the clinical development program for MK-0518 was low. In treatment-naïve patients in whom it is feasible to assess the potential impact on lipid levels, MK-0518 treatment was not associated with increases in serum cholesterol, triglycerides, or LDL-C, suggesting an important potential advantage over ritonavir-boosted regimens.

The low propensity of MK-0518 for drug interaction represents another important benefit. In situations where MK-0518 is co-dosed with ARTs that may lower or raise its plasma exposure, the high margin of efficacy and safety exhibited in the dose-ranging studies, supports the administration of MK-0518 without dose adjustment. This would simplify the dosing instructions for MK-0518, and potentially facilitate compliance. In addition, the low pill burden (one pill twice daily) may also facilitate compliance, an important factor for therapeutic success.

Risks

Consistent with all clinical development programs for HIV drugs, the safety database is relatively limited both in terms of size and of duration. Overall, MK-0518 has been generally well tolerated with low discontinuation rates due to adverse experiences. The adverse experience profile, clinical and laboratory, of MK-0518 in combination with other ARTs is similar to that of placebo with ARTs. No specific safety issues were identified that would preclude the approval of MK-0518 for the proposed indication. Although there was a numerically greater number of neoplasms reported in the MK-0518 treatment groups, a thorough review of the data does not provide any direct evidence of drug relationship to any of these events of cancer. This risk, however, must continue to be actively assessed. The current database should be supplemented with 48-week data from Protocols 018 and 019 when available. As MK-0518 is the first in a new class of ARTs, an appropriate postmarketing monitoring plan should be established, which includes longer-term safety data from ongoing clinical trials (Protocols 004, 005, 018, 019, which are currently planned for a total of 3 years duration; and the Phase III treatment-naïve study for a total of 96-weeks).

Overall Benefits/Risks Assessment

Overall, the data presented in this Application support a significant benefit for MK-0518 in combination therapy with other ARTs for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Taking into account the observed safety profile, the benefits/risks ratio of MK-0518 for the requested indication is positive.

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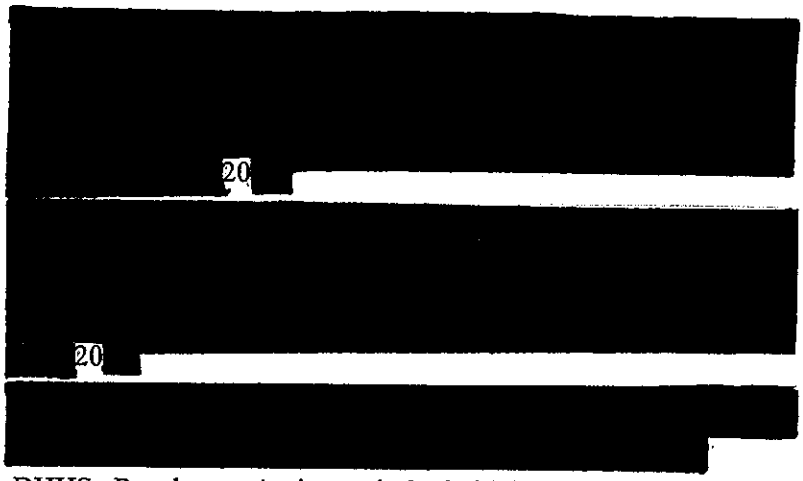

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