Table 2.7.4: 49

Listing of Patients Discontinued Due to Clinical Adverse Experiences—
Open Label Post Virologic Failure (Protocols 005, 018, and 019) - *Cumulative Data*

Study Number	AN	Gen-der	Race	Age	Period	Therapy	Total Daily Dose	Rela-tive Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontin-uance†	Intensity	Ser-ious	Drug Relation-ship	Action Taken	Outcome
MK-0518																
0180058	**7005**	**M**	**white**	**60 yr**	**OL Post Viral Fail**	**Off Drug 1 day**		**279**	**Septic shock**	**6 day**	**280**	**severe**	**Y**	**def not**	**discontinued PRx**	**recovered**

†Day study therapy was discontinued relative to the start of study therapy.
Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).
Adverse experience terms are from MedDRA Version 9.1.
Drug Relationship: def = definitely, def not = definitely not, poss = possibly, prob = probably, prob not = probably not.
Intensity: mod = moderate.

[Ref. 5.3.5.1: P005-Define, P018-Define, P019-Define]

2.7.4.2.1.2.5 Analysis of Adverse Experiences by Organ System or Syndrome in Phase II and Phase III Studies

Metabolic Disorders

Dyslipidemias, lipodystrophy, and hyperglycemia are common metabolic complications of antiretroviral therapy [Ref. 5.4: 269, 270, 307, 310, 323, 433, 434, 435, 442]. In the MK-0518 development program, in addition to collecting these occurrences as adverse experiences, fasting lipids and glucose were monitored routinely in all studies and abnormalities are reported according to the DAIDS toxicity grading criteria as described in [Sec. 2.7.4.3]. In addition, body circumference measurements were collected in the Phase II studies, Protocols 004 and 005, according to the method of the ACTG [Ref. 5.4: 457]and were reported in the Original Application.

Dyslipidemias

Protocol 004 is a dose-ranging study conducted in treatment-naïve patients for which there are 48-week follow-up data; after week 48, all MK-0518 doses were changed to 400 mg b.i.d. This study used a fixed nucleoside regimen in the combination therapy, which allowed clearer delineation of the potential of MK-0518 to cause dyslipidemia. In Protocol 004, during the SUR period, similarly low rates of metabolic adverse experiences were reported across all treatment groups as in the Original Application. Objective assessment of fasting lipids was performed using predefined limits of change according to the DAIDS toxicity criteria [Sec. 2.7.4.3.4]. During the SUR period there was a single Grade 3 abnormality (LDL cholesterol) and no Grade 4 lipid abnormalities in the MK-0518 group, these low rates are similar to the Application data. There is no update on the mean change from baseline and mean percent change from baseline in fasting lipids. These data suggest that MK-0518 is not associated with lipid abnormalities [Ref. 5.3.5.1: P004].

The data in treatment-experienced patients receiving MK-0518 400 mg b.i.d. or placebo (each with OBT) from Protocol 005 and the Phase III studies indicate that the frequency of dyslipidemias reported by investigators as adverse experiences and the frequency of lipid abnormalities reaching Grade 3 or 4 according to the DAIDS toxicity criteria,

were generally similar in the MK-0518 plus OBT groups for the Cumulative period and the Application period, as shown in [Sec. 2.7.4.2.1.2.1.2], [Sec. 2.7.4.3.2], and [Sec. 2.7.4.3.4]. It should be noted that interpretation of lipid changes in this population is difficult.

In summary, available data suggest MK-0518 does not appear to be associated with serum lipid abnormalities.

Lipodystrophy/ Lipoatrophy

As presented in the Original Application, data from Protocols 004 and 005, data suggest that MK-0518 is not associated with lipodystrophy over a period of 48 weeks.

In the Original Application period, in treatment-experienced patients receiving MK-0518 400 mg b.i.d. or placebo (each with OBT) from Protocol 005 and the Phase III studies, the frequency of lipodystrophy or lipoatrophy reported as adverse experiences was low (<1%) in both treatment groups. In the SUR period, there were no additional cases of lipoatrophy reported for this cohort. The number of patients with adverse experiences of lipodystrophy during the Cumulative period was 1.4% (7/507) of patients as compared to 0.8% (4/507) of patients during the Original Application period.

In summary, available data suggest MK-0518 is not associated with lipodystrophy or lipoatrophy.

Hyperglycemia

Fasting glucose was also routinely monitored in all studies. Hyperglycemia and diabetes mellitus were infrequently reported as adverse experiences in Protocol 004 and Protocol 005 in the Original Application. In the treatment-experienced MK-0518 400 mg b.i.d. cohort, hyperglycemia was reported as a clinical adverse experience in 0.4% (2/507) of patients in the MK-0518 group during the Cumulative Period as compared to 0.2% (1/507) during the Original Application period. Diabetes mellitus was reported in 1.0% (5/507) of patients on MK-0518 in both Cumulative and Original Application periods.

As reported in [Sec. 2.7.4.3], based upon the objective assessment of predefined limits of change, the rates of Grade 3 fasting hyperglycemia in treatment-experienced patients remained low; 1.4% for the MK-0518 group in the Cumulative Period vs. 1.0% for the MK-0518 group in the Original Application. No Grade 4 hyperglycemia was reported.

In summary, available data suggest MK-0518 is not associated with fasting hyperglycemia.

Central Nervous System (CNS) Adverse Experiences

No update is provided on CNS adverse experiences.

Rash

Rash was specifically examined as an umbrella term that included all terms reported for rash (i.e., rash, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, and rash pruritic) both overall and for those rashes considered by the investigator to be drug-related. The number (%) of patients with these specific clinical AE terms of rash (incidence >0% in one or more treatment groups) is presented for the Cumulative period in [Appendix 2.7.4: 54] and for the Original Application period in [Appendix 2.7.4: 55], for the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. The number (%) of patients with specific clinical AE terms of drug-related rash (incidence >0% in one or more treatment groups) is presented for the Cumulative period in [Appendix 2.7.4: 56] and for the Original Application period in [Appendix 2.7.4: 57]. Listing tables are provided for the Cumulative period for all rash in [Appendix 2.7.4: 58] and for drug-related rash [Appendix 2.7.4: 59]. New data from the SUR period are bolded in the listing tables.

Double-Blind Period

For the MK-0518 group, the overall proportion of patients with rash (including related terms) was 7.9% (40/507) in the Cumulative period as compared to 6.7% (34/507) in the Original Application period. During the Cumulative period for the MK-0518 group, one of the new rashes was considered drug-related by the investigator; there were no discontinuations due to rash, and no rashes were reported as serious adverse experiences.

Two (2) patients in the MK-0518 group (ANs 7053 and 8372) who had previously reported a rash during the Original Application period, reported another rash during the SUR period. Both of these rashes were of mild intensity, neither were drug related, and neither resulted in interruption of study therapy.

During the SUR period, 6 new patients reported rashes (ANs 15055, 15065, 16257, 16365, 16409, and 15103). All 6 rashes were of mild intensity, only one was reported as drug-related (in AN 16409), and none resulted in interruption of study therapy.

Investigators consider various clinical aspects of a rash in assessing its potential drug relationship such as localization, distribution, and appearance. Therefore, it is appropriate to consider the rash terms based on assessment of drug relationship. As shown in for the Cumulative Period in [Appendix 2.7.4: 56] and for the Original Application period in [Appendix 2.7.4: 57], in the MK-0518 group, the proportion of patients with drug-related rash was 2.2% (11/507) in the in the Cumulative Period and 2.0% (10/507) in the for the Original Application period.

AN 16409 was the one patient in the MK-0518 group who reported a drug-related rash during the SUR period. The rash was mild in intensity and did not result in study therapy interruption.

OLPVF phase

The number (%) of patients in the OLPVF phase with specific clinical AE terms of rash (incidence >0%) is presented for the Cumulative Period in [Appendix 2.7.4: 60] and for the Original Application period in [Appendix 2.7.4: 61]. A corresponding listing table for the Cumulative Period is presented in [Appendix 2.7.4: 62] with new data during the SUR period bolded.

There was one patient (AN 3867) who reported a macular rash (duration of 1 day) during the OLPVF phase in the Original Application period, but during the SUR period, the adverse experience term was changed to "skin discoloration", so this patient does not appear on the counts and listing tables for the Cumulative Period.

There were 7 new patients reporting rash during the SUR period (ANs 8301, 7120, 8299, 5019, 16247, 16234, and 16399). Of the 7 new patients reporting rash in the SUR period, 4 were considered drug-related (for ANs 8301, 7120, 15019, and 16399). Of the 4 patients, only 1 patient interrupted study therapy (AN 16399), and the investigator reported that the rash was related to the OBT of delavirdine, which was discontinued as part of the patient's OBT. The severity of the rashes was considered by the investigator to be mild to moderate for all MK-0518 patients in the OLPVF phase. Study therapy with MK-0518 was not discontinued due to the rash for any of the 7 patients.

One additional patient (AN 7025) who reported a rash in the Original Application period, reported another rash in the SUR period. Both rashes were reported during the OLPVF phase. This rash was of moderate intensity, was not drug-related, and did not result in interruption of therapy.

Darunavir in OBT

Because of a serious adverse experience of rash reported in the Original Application from an ongoing Phase I study of MK-0518 with darunavir and ritonavir, and the frequent use of darunavir in OBT in the Phase III studies, similar counts and listing tables were examined for rash as an umbrella term, overall and drug-related, based on whether or not the patient used darunavir in OBT in the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. In this cohort in the Cumulative Period, there were 294 patients who used darunavir in OBT and 495 patients who did not.

The number (%) of patients with these specific clinical AE terms of rash (incidence >0% in one or more treatment groups) among patients who used darunavir in OBT, is presented for the Cumulative period in [Appendix 2.7.4: 63] and for the Original Application period in [Appendix 2.7.4: 64], for the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. A corresponding listing table is provided for the Cumulative period in [Appendix 2.7.4: 65]. New data from the SUR period are bolded in the listing tables.

The number (%) of patients with specific clinical AE terms of drug-related rash (incidence >0% in one or more treatment groups) among patients who used darunavir in OBT, is presented in [Appendix 2.7.4: 66] and for the Original Application period in [Appendix 2.7.4: 67], for the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. A corresponding listing table is provided for the Cumulative period in [Appendix 2.7.4: 68]. New data from the SUR period are bolded in the listing tables.

For the MK-0518 group, among patients who used darunavir in OBT, the overall proportion of patients with rash was 13.5% (26/193) in the Cumulative Period and was 10.4% (20/192) in the Original Application period. Note: One (1) patient added darunavir to his/her OBT regimen during the SUR period, thus explaining the difference in the denominator for the 2 periods.

In the MK-0518 group, the proportion of patients with drug-related rash among patients who used darunavir in OBT for the MK-0518 group was 3.1% (6/193) in the Cumulative period and was 2.6% (5/192) in the Original Application period. The one additional drug-related rash (in AN 16409) was non-serious, mild in intensity, and did not result in discontinuation of study therapy.

For comparison, the number (%) of patients with these specific clinical AE terms of rash (incidence >0% in one or more treatment groups) among patients who did not use darunavir in OBT, is presented for the Cumulative Period in [Appendix 2.7.4: 69] and for the Original Application period in [Appendix 2.7.4: 70], for the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. A corresponding listing table is provided for the Cumulative period in [Appendix 2.7.4: 71]. New data from the SUR period are bolded in the listing tables.

The number (%) of patients with specific clinical AE terms of drug-related rash (incidence >0% in one or more treatment groups) among patients who did not use darunavir in OBT, is presented for the Cumulative Period in [Appendix 2.7.4: 72] and for the Original Application period in [Appendix 2.7.4: 73], for the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. A corresponding listing table is provided for the Cumulative period in [Appendix 2.7.4: 74]. New data from the SUR period are bolded in the listing tables.

In the MK-0518 group, among patients who did not use darunavir, the overall proportion of patients with rash during the Cumulative Period was 4.5% (14/314) and with drug-related rash was 1.6% (5/314). There were no new cases of rash or drug-related rash reported for these patients during the SUR period. In the MK-0518 group, the intensity of drug-related rash was mild-moderate for all patients, and all patients recovered from drug-related rash.

Summary

In summary, during the Cumulative Period the overall rate of rash remained somewhat higher in the MK-0518 group compared with placebo in the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. However, the character of rashes was generally similar in both treatment groups, most were mild to moderate in intensity and self-limited; none were serious or led to therapy discontinuation. Rashes considered to be drug-related by the investigator in both treatment groups were infrequent, all were mild to moderate in intensity, and most were self limited. All patients in the MK-0518 group with rash reported were able to continue therapy with MK-0518. Furthermore, when rashes were examined in the subgroup that used darunavir in OBT, there continued to be a slight excess in overall rashes. However, drug-related rashes occurred at similar low rates and mild to moderate intensity when MK-0518 was given with or without darunavir as part of OBT compared to placebo with or without darunavir in OBT.

In conclusion, while rash occurred somewhat more frequently in the MK-0518 group than in the placebo group, it was generally benign and did not limit study therapy. Coadministration of darunavir with MK-0518 did not increase the frequency of drug-related rash. The profile of rash adverse experiences for patients receiving MK-0518 during the Cumulative Period was similar to that during the Application period.

Pruritus

In the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort, pruritus (including adverse experiences reported as generalized pruritus, prurigo, and pruritus) was reported for the MK-0518 group, in 3.7% (19/507) of patients during the Cumulative Period and compared to 3.4% (17/507) of patients during the Original Application period.

There were no additional reports of pruritus in the in the OLPVF phase during the SUR period.

The occurrence of pruritus continues to appear to be balanced across the treatment groups; it was generally clinically benign and did not limit study therapy.

Hypersensitivity

During the SUR period, no new cases of hypersensitivity were reported in the MK-0518 group of the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort. In both the Cumulative and Application periods, in this cohort, 4 of 507, or 0.8%, of patients [AN 6404, AN 8380, AN 15100, and AN 16272] in the MK-0518 group reported clinical adverse experiences of drug hypersensitivity or hypersensitivity. Note: AN 6404 had adverse experiences of both hypersensitivity and drug hypersensitivity.

During the SUR period, there were 2 additional patients in the OLPVF phase reporting adverse experiences of hypersensitivity (ANs 3871 and 3223). Neither was considered serious or drug-related, and neither caused interruption of study medication. Both patients recovered from hypersensitivity; AN 3223 in 5 days and AN 3871 in 20 days. In the Original Application, 3 patients (AN 2990, AN 3292, and AN 16238) had drug hypersensitivity or hypersensitivity reactions reported in the OLPVF phase.

Overall, hypersensitivity reactions were reported infrequently in the Cumulative and the Application periods; they were considered by the investigator to be due to other medications (OBT or concomitant therapy) and did not lead to interruption of therapy. Of the 2 patients reported in the Application Period with serious hypersensitivity reaction who were rechallenged, both rechallenges were negative and patients were able to resume MK-0518 therapy. Therefore, based upon available data there does not appear to be significant hypersensitivity associated with MK-0518 therapy.

Aminotransferase (ALT/AST) elevations

Double-blind Period

In the treatment-experienced MK-0518 400 mg b.i.d. cohort, laboratory adverse experiences of increased serum ALT and increased serum AST were reported as follows:

- ALT increased: 4.7% (24/507) of patients in the Cumulative period as compared to 4.5% (23/507) of patients in the Original Application
- AST increased: 4.5% (23/507) of patients in the Cumulative period as compared to 4.3% (22/507) of patients in the Original Application

There were no serious adverse laboratory experiences of ALT or AST increased during the SUR period. Both ALT increased and AST increased seen in one patient (AN 15028) resulted in discontinuation, in the Original Application Period.

These rates are not adjusted for differing duration of time at risk in the 2 treatment groups.

OLPVF phase

In the OLPVF phase, laboratory adverse experiences of increased serum ALT and increased serum AST were reported as follows:

- ALT increased: 2.7% (6/223) of patients in the Cumulative period as compared to 0.6% (1/177) of patients in the Original Application
- AST increased: 2.2% (5/223) of patients in the Cumulative period as compared to 0.6% (1/177) of patients in the Original Application

In the SUR period for OLPVF, increased ALT in 2 patients, and increased AST in 2 patients, were recorded as drug-related, as compared to none reported in the Original Application Period. In the OLPVF phase, increased ALT and AST were not recorded as a serious adverse experience.

Predefined Limits of Change

In terms of the predefined limits of change for the treatment-experienced MK-0518 400 mg b.i.d. cohort, presented in [Sec. 2.7.4.3.1], serum ALT and AST increases were generally similar in the MK-0518 group during the Cumulative period compared with the Application period. For example, in the MK-0518 group Grade 3 serum AST increased was seen in 2.2% (11/507) of patients in the Cumulative period and in 2.0% (10/507) of patients in the Application period. Grade 3 serum ALT increased was seen in 3.0% (15/507) of patients in the Cumulative period and in 2.6% (13/507) of patients in the Application period. Similarly to the adverse experiences presented above, these rates are not adjusted for duration of exposure between the 2 treatment groups.

Of note, 17 of the 59 (28.3%) of patients in the MK-0518 group with Grade 2 or higher AST elevations had concurrent transient and self limited CPK elevations, some of which occurred in setting of increased physical exercise, suggesting the AST elevations in these patients were of muscle rather than liver origin.

Overall, the percentages of patients experiencing AST and/or ALT elevations reported as laboratory adverse experiences were comparable for the MK-0518 group during the Cumulative and Application periods and rarely limited study therapy. Similarly, the occurrence of AST and ALT abnormalities by assessment of predefined limits of change for the MK-0518 group was similar for the Cumulative and Application periods. In general for the Cumulative period as well as the Application period, the aminotransferase elevations in patients receiving MK-0518 were transient, resolved with or without interruption of therapy, and did not recur when therapy was re-introduced.

Creatine phosphokinase (CPK) elevations

Double-blind Period

In the treatment-experienced MK-0518 400 mg b.i.d. cohort, laboratory adverse experiences of increased CPK were reported in 3.7% (19/507) of patients in the Cumulative period as compared to 3.2% (16/507) of patients in the Original Application.

In this cohort, overall drug-related laboratory adverse experiences of increased CPK were reported in the MK-0518 group, in 1.2% (6/507) of patients during the Cumulative period, and 0.8% (4/507) of patients in the Original Application period.

These rates are not adjusted for differing duration of time at risk.

OLPVF phase

In the OLPVF phase, laboratory adverse experiences of increased CPK were reported in 2.2% (5/223) of patients in the Cumulative period as compared to 1.7% (3/117) of patients of patients in the Original Application period. There were no drug-related adverse experiences of CPK increased during the SUR period in the OLPVF phase; the only one drug-related CPK increase in the OLPVF phase was reported in the Original Application period.

During the Cumulative period, in the treatment-experienced MK-0518 400 mg b.i.d. cohort and during the OLPVF phase, there were no serious adverse experiences of increased CPK and no patients discontinued therapy due to increased CPK. Many of these elevations were isolated increases that returned to normal with time and elevations for several patients were noted by the investigators to be related to physical exercise.

Associated clinical adverse experiences

In the treatment-experienced MK-0518 400 mg b.i.d. cohort, CPK increases were also evaluated for associated clinical adverse experiences. As reported in the Original Application, one patient in the MK-0518 group (AN 15079) had elevated CPK reported as a laboratory adverse experience temporally associated with a clinical adverse experience of myositis, which was considered by the investigator to be due to ritonavir in OBT. The ritonavir dosage was reduced, and the next CPK result (performed 13 days later) had returned to baseline. The myositis resolved after 170 days.

Also reported in the Original Application, patient AN 16272 in the MK-0518 group, had elevated (Grade 3) CPK results temporally associated with a clinical adverse experience of myalgia. The myalgia was not considered by the investigator to be drug-related and did not cause an interruption of study therapy. The myalgia had not resolved at the time of the Protocol 019 database freeze for this SUR.

One patient in the MK-0518 group in Protocol 005 (AN 3256) reported a clinical adverse experience of myositis concurrently with the CPK increase. The myositis was not considered drug-related, did not result in discontinuation of study therapy, and resolved in 29 days.

One patient in the MK-0518 group in Protocol 019 (AN 16397) reported tendonitis with a duration of one month, at the same time as the CPK increase. The investigator indicated that the CPK increase was related to exercise. The tendonitis was not considered drug-related and did not result in discontinuation of study therapy.

In the SUR period, patient 16344, in the MK-0518 group in Protocol 019, reported musculoskeletal pain at the same time of the CPK increase. The investigator indicated that the CPK increase was related to exercise. The musculoskeletal pain was not considered drug-related, did not result in discontinuation of study therapy, and had not resolved at the time of the data freeze for this SUR.

Two (2) patients in the MK-0518 group (ANs 8257 and 16227) reported clinical adverse experiences of diabetes concurrently with the CPK increases. For AN 8257, the diabetes was an active background condition, was considered possibly drug-related, did not result in discontinuation of study therapy, and had not resolved at the time of the data freeze for this SUR. AN 16227 had elevated fasting serum glucose at the time of study entry (157 mg/dL). The diabetes was not considered drug-related, did not result in discontinuation of study therapy, and had not resolved at the time of the data freeze for this SUR. The investigator indicated that the CPK increase for this patient was related to exercise.

In summary, the occurrence of CPK elevations remained slightly more common in the MK-0518 group than in the placebo group during the Cumulative period similarly to the Application period. These elevations were generally transient, were not associated with clinically significant adverse experiences, and did not limit therapy. In at least some cases, the CPK elevations observed appeared to be due to increased physical exercise.

Immune Reconstitution Syndrome

Immune Reconstitution Syndrome (IRS) has been reported with highly active antiretroviral therapy regimens [Ref. 5.4: 310, 342, 343, 344, 389, 396, 439, 440].

There were no cases of IRS reported during double blind or OLPVF phase of the SUR period. As reported in the Original Application, there were 3 patients receiving MK-0518 who reported IRS as an adverse experience; 2 patients (AN 16239 and AN 16335) in the MK-0518 treatment group in the double-blind cohort, and 1 patient (AN 16233) in the OLPVF phase who was originally randomized to placebo.

The occurrence of IRS in this study population is not unexpected, in light of the prompt and potent antiretroviral response observed in the MK-0518 treatment group in highly immunodeficient patients.

Neoplasms

Based upon the observation of an increased frequency of malignant neoplasms for the MK-0518 versus comparator groups which was presented in the Application, the neoplasm analysis has been updated for the Cumulative period that again includes Protocols 004, 005, 018 and 019, and follows a similar organization: assessment of rate of malignancies identified in the double blind phase, both by diagnosis and overall, followed by as estimate of the rate when open label exposure is included. Adjustment for patient time at risk was performed, and time to event curves have also been updated. In addition to the analyses noted above, the data have been re-analyzed excluding those cancers known to be recurrent (either reported as recurrent in CTS, or a cancer diagnosis using a term reported in medical history at the same anatomic site).

Similar to other sections of the SUR, this section will focus on the cumulative data, but in contrast, will retain details provided in the Application for clarity and completeness. [Table 2.7.4: 50] has been updated such that 1) new terms or new cases of malignancy are bolded, 2) the results of adjudication of suspected AIDS defining conditions or deaths, if performed, are provided, 3) a "sponsor term" for diagnosis has been assigned for clarity based upon all data available in CTS or WAES to facilitate the analysis and discussion, and 4) recurrences are noted after diagnosis term.

The data available for the Cumulative Period indicate there were a total of 23 malignancies reported: 19 patients with 20 cancers in the MK-0518 groups, 1 patient with 1 cancer in the efavirenz group of Protocol 004, and 2 cancers that occurred pretreatment in the screening period of 2 patients who did not enroll in the studies (1 each from Protocol 019 and the Expanded Access Program [EAP]), of which 1 was fatal. None of the cancers were judged by the investigator to be drug-related. No cancers were reported in the MK-0518 groups in the blinded serious adverse event reports submitted from the ongoing Protocol 021, a Phase III study in ART-naïve patients. Two of the 20 cancers (both recurrent) in MK-0518 treated patients were reported in the SUR period, 1 on MK-0518 from Protocol 004 and 1 from the placebo group of Protocol 018 during OLPVF after 93 days on open label MK-0518. There were no additional deaths due to cancer during the SUR period.

The distribution by diagnosis of the 20 malignancies that occurred in 19 MK-0518-treated patients is as follows (allocation numbers of new cases in the SUR period are bolded in the text): 3 were Kaposi's sarcoma (KS; ANs 7026, 8256, and **0012**); 6 were lymphoma (2 Hodgkin's disease [HD; ANs 3281 and 3240] and 4 non-Hodgkin's lymphoma [NHL; ANs 7005, 8204, 15028, and 58]); 4 were squamous cell carcinoma (SCCa), of which 3 were cutaneous [AN 16365 - vocal cord SCCa in a smoker with hoarseness at study entry, AN 15090 - cutaneous and metastatic SCCa at the temple, AN 8321- recurrent cutaneous SCCa of the ear; AN **7024** – recurrent SCCa, details pending – information available after the SUR cutoff revealed this was cutaneous SCCa of the scalp); 3 were squamous cell carcinoma in situ (CIS) in anorectal region (AN 15084 - rectal polyp CIS on routine colonoscopy; AN 15113 and AN 18 - both anal SCCa CIS associated with papillomavirus infection); 1 was an anal cancer not further specified (AN 8288); 1 localized basal cell carcinoma of the face (AN 3281); 1 hepatocellular carcinoma attributed to chronic hepatitis B virus infection (AN 16239); and 1 rectal cancer (AN 8292), an adenocarcinoma found within 1 month of entry on evaluation of rectal bleeding; a stenosing lesion was found at 15 cm from anus. Seven (7) cancers were recurrent (1 HD [AN 3240], 1 NHL [AN 15028], 2 KS [AN 8256 and **0012**] and 3 SCCa [AN 8321, 15084 and **7024**). In one case, AN 15084, the sponsor categorized the AE of rectal cancer stage 0 as recurrent SCCa CIS since perianal Bowen's disease, a malignant condition, was recorded as medical history. Four (4) cancers were fatal (3 NHL [ANs 7005, 8204, and 15028] and 1 hepatocellular carcinoma [AN 16239]) as reported in the Application. The 2 cases reported in the EAP (AN 58, B cell lymphoma and AN 18, anal SCCa CIS) have only WAES data available and are not included in any of the patient time adjusted incidence analyses presented below.

Table 2.7.4: 50

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

CTS Cutoff (CTD): Protocol 004: [redacted]20
Protocol 005: [redacted]20
Protocol 018: [redacted]20
Protocol 019: [redacted]20
WAES Cutoff (CTD): [redacted]20

SUR Cutoff: [redacted]20

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm³)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
Protocols 004, 005, 018, 019 - CTS												
12	**55**	**M**	**MK-0518, 400 mg b.i.d.**	**004**	**V: Kaposi's sarcoma D: Kaposi's sarcoma B: Kaposi's sarcoma SP: Kaposi's sarcoma (recurrent)**	**409 (310 of Part II)**	**BL/Part I: 96 Day 10: 125 BL/Part II: 159 Week 2: 132 Week 4: 212 Week 8: 130 Week 12: 183 Week 16: 121 Week 24: 190 Week 32: 84**	**BL/Part I: Predose: 6,850 Day 10: <400/<50 BL/Part II: 8,390 Week 2: <400/<50 Week 4: <400/<50 Week 8: <400/<50 Week 12: <400/<50 Week 16: <400/<50 Week 24: <400/<50 Week 32: <400/<50**	**Tenofovir – 300 mg Lamivudine – 300 mg**	**Kaposi's sarcoma**	**Non-fatal**	**Not reported in WAES because the worsening condition did not meet any of the serious criteria other than cancer**

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
							Week 40: 152†† **Week 48: 128** **Week 60: 144** **Week 72: 186**	***Week 40: <400/<50††*** **Week 48: <400/<50** **Week 60: <400/<50** **Week 72: <400/<50**				
163	48	M	Efavirenz, 600 mg q.h.s.	004	V: squamous cell carcinoma D: Squamous cell carcinoma B: Squamous cell carcinoma SP: Squamous cell carcinoma (vocal cord)	207	BL: 168 Week 2: 197 Week 4: 180 Week 8: 150 Week 12: 155 Week 16: 184 *Week 24: 182††* Week 32: 168 Week 40: 181 Week 48: 220	BL: 22,300 Week 2: <400 /129 Week 4: <400/95 Week 8: <400/<50 Week 12: <400/<50 Week 16: <400/<50 *Week 24: <400/<50††* Week 32: <400/<50 Week 40: <400/<50 Week 48: <400/<50	Tenofovir – 300 mg Lamivudine – 300 mg.	Adenocarcinoma of colon Smoker (per WAES) CD4 lymphocytes decreased	Non-fatal	Location of squamous cell carcinoma: Vocal Cord (per WAES report) Treated with radiation therapy (per WAES)

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
3281	52	M	MK-0518, 200 mg b.i.d. (on Day 157 switched to 600 mg b.i.d. in open-label phase) (on Day 325 switched to optimal dose of 400 mg b.i.d. per protocol)	005	V: hodgkin's lymphoma D: Hodgkin's lymphoma B: Hodgkin's disease SP: Hodgkin's lymphoma V: cutaneous basalioma D: Basal cell carcinoma B: Basal cell carcinoma SP: Basal cell carcinoma	211 (55 of OLPVF) 254 (98 of OLPVF)	BL: 297 Week 2: 346 Week 8: 423 Week 12: 450 Week 16: 457 OLPVF (600 mg b.i.d.): Week 4: 346 *Week 8: 336††* Week 16: 430 Open Label Optimal (400 mg b.i.d.): Day 1: 118 Week 8: 225 Week 16: 263 Week 24: 335	BL: 23,700 Week 2: <400/<50 Week 4: <400/<50 Week 8: <400/<50 Week 12: <400/160 Week 16: 4,970 Week 16 (unscheduled visit 2 weeks post regular visit): 2,490 OLPVF (600 mg b.i.d.): Week 4: 42,500 *Week 8: 30,400††* Week 16: 12,200 Open Label Optimal (400 mg b.i.d.): Day 1: <400/<50 Week 4: 521 Week 8: <400/105 Week 16: 11,700 Week 24: 22,100	Fosamprenavir – 1400 mg Ritonavir – 200 mg Tenofovir disoproxil fumarate – 300 mg Emtricitabine – 200 mg	Chronic bronchitis	Non-fatal	Treated with chemotherapy and radiation therapy (per WAES) Basal cell carcinoma surgically removed (per WAES), patient recovered

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
3240	47	M	MK-0518, 400 mg b.i.d. (on Day 282 switched to 600 mg b.i.d. in open-label phase and on Day 295 switched to optimal dose of 400 mg b.i.d. per protocol)	005	V: Hodgkin's Lymphoma D: Hodgkin's lymphoma B: Hodgkin's disease SP: Hodgkin's Lymphoma (recurrent)	441 (147 of PVF Optimal	BL: 215 Week 2: 283 Week 4: 237 Week 8: 296 Week 12: 316 Week 16: 318 Week 24: 318 Week 32: 427 Visit aproximately one month post Week 32: 319 Open Label (600 mg b.i.d.) Visit approximately two months post Week 32 (Day 282): 311 Open Label Optimal (400 mg b.i.d.) Week 4: 320 Week 8: 324 *Week 16: 465††*	BL: 114,000 Week 2: 1,520 Week 4: <400/370 Week 8: <400/144 Week 12: <400/209 Week 16: <400/194 Week 24: 933 Week 32: 7,620 Visit approximately one-month post Week 32: 13,600 Open Label (600 mg b.i.d.) Visit approximately two months post Week 32: (Day 282): 18,900 Open Label Optimal (400 mg b.i.d.) Week 4: 6,950 Week 8: <400/238 *Week 16: <400/<50††*	Stavudine – 80 mg Emtricitabine (+) Tenofovir disoproxil fumarate – 1 tablet Darunavir – 1200 mg Ritonavir – 200 mg (patient was taking these OBT agents as of Day 407)	Hodgkins lymphoma diagnosed in 2004	Non-fatal	

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
7005	60	M	MK-0518, 400 mg b.i.d. (switched to open label post virologic failure on Day 251)	018	V: β cell lymphoma D: B-cell lymphoma B: B-cell lymphoma SP: B-cell lymphoma	76	BL: 7 Week 2: 105 Week 4: 175 *Week 8: 130††* Week 12: 139 Week 16: 14 Week 24: 43 Week 32: 7	BL: 372,000 Week 2: 1,860 Week 4: <400/201 *Week 8: <400/103††* Week 12: <400/168 Week 16: 92,600 Week 24: 21,800 Week 32: 68,100	Ritonavir – 200 mg Enfuvirtide – 180 mg abacavir sulfate (+) lamivudine – 1 tablet Darunavir – 1200 mg	Kaposi's Sarcoma Esophageal candidiasis PCP	Fatal (end stage AIDS) (per WAES report)/Lymph node biopsy/ Definitive/ B-cell lymphoma	Treated with chemotherapy
7024	**57**	**M**	**Placebo to MK-0518** **(switched to 400 mg b.i.d. open label post virologic failure on Day 184**	**018**	**V: recurrence of epidermoid carcinoma** **D: Epidermoid carcinoma** **B: Squamous cell carcinoma** **SP: Squamous cell Carcinoma** **(recurrent)** **(scalp)**	**277**	**BL: 28** **Week 2: 166** **Week 4: 107** **Week 8: 119** **Week 12: 84** **Week 16: 97** **UNSCH (Week 18): 63** **OLPVF - *(Week 4): 251††*** **OLPVF – (Week 8): 287** **OLPVF – (Week 16): 235**	**BL: 559,000** **Week 2: 171,000** **Week 4: 379,000** **Week 8: 337,000** **Week 12: 358,000** **Week 16: 495,000** **UNSCH: (Week 18): 565,000** **OLPVF - *(Week 4): 2,230††*** **OLPVF – (Week 8): <400/1,020** **OLPVF – (Week 16): <400/382**	**Ritonavir – 200 mg** **Lamivudine– 300 mg** **Darunavir- 1200 mg**	**Squamous cell carcinoma**	**Non-fatal**	**(post SUR cutoff – determined to be cutaneous SCCa of scalp).**

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
7026	42	M	MK-0518, 400 mg b.i.d.	018	V: Kaposis sarcoma D: Kaposi's sarcoma AIDS Related B: Kaposi's sarcoma AIDS Related SP: Kaposi's sarcoma	29	BL: 6 Week 2: 104 *Week 4: 325††* Week 8: 175 Week 12: 161 Week 16: 186 Week 24: 231 Week 32: 224	BL: 148,000 Week 2: 4240 *Week 4: 3110††* Week 8: 1890 Week 12: 962 Week 16: 1520 Week 24: 1270 Week 32: 4640	Ritonavir – 200 mg Darunavir – 1200 mg Enfuvirtide – 180 mg Emtricitabine (+) tenofovir disoproxil fumarate – 1 tablet	PCP Oral Candidiasis	Non-fatal/Visual inspection by exp. Clinician/pre-sumptive/ Kaposi's sarcoma	Suspected immune reconstitution syndrome CD4 6-104 (per WAES)
8204	45	M	MK-0518, 400 mg b.i.d.	018	V: liver and medulla T cell lymphoma D: T-cell lymphoma B: T-cell lymphoma SP: T-cell lymphoma	85	BL: 3 Week 2: 2 Week 4: 3 *Week 8: 5††* Week 12: Not available	BL: 235,000 Week 2: 28300 Week 4: 9830 *Week 8: 3410††* Week 12: 1,520,000	abacavir sulfate (+) lamivudine – 1 tablet ritonavir 200 mg fosamprenavir 1400 mg	Esophageal candidiasis CNS toxo MAC infection Pancreatitis (due to didanosine)	Fatal/Liver and osteo-medullary biopsies/ Definitive/ T cell lymphoma	Cause of death: disseminated mycobacterial infection, multiple organ failure, shock, and T cell lymphoma

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
8292	60	F	MK-0518, 400 mg b.i.d.	018	V: Rectal adenocarcinoma D: Rectal adenocarcinoma B: Rectal cancer SP: Rectal cancer	27	BL: 277 Week 2: 328 *Week 4: 323††* Week 8: 313 Week 12: 257 Week 16: 347 Week 24: 255	BL: 35,100 Week 2: <400/198 *Week 4: <400/<50††* Week 8: <400/<50 Week 12: <400/<50 Week 16: <400/<50 Week 24: <400/<50	Tipranavir – 1000 mg Ritonavir – 400 mg Abacavir sulfate – 600 mg Didanosine – 250 mg	PCP Herpes Zoster	Non-fatal	Rectal adeno-carcinoma and stenosing lesion 15 cm from anus, could not pass scope (per WAES)
8321	46	M	MK-0518, 400 mg b.i.d.	018	V: squamous cell carcinoma right ear D: Squamous cell carcinoma B: Squamous cell carcinoma SP: Squamous cell carcinoma (recurrent) (ear)	35	BL: 792 Week 2: 1140 *Week 4: 830††* Week 8: 628 Week 12: 1,395 Week 16: 988 Week 24: 1,085	BL: 10,700 Week 2: <400 / 57 *Week 4: <400/<50††* Week 8: <400/<50 Week 12: <400/<50 Week 16: <400/<50 Week 24: <400/<50	Emtricitabine (+) tenofovir disoproxil fumarate – 1 tablet Darunavir – 1200 mg Ritonavir – 200 mg	Squamous cell carcinoma diagnosed in 2005 Skin tumor, left shoulder (excised in 2000)	Non-fatal	Patient has had active squamous cell carcinoma at right ear since 2005. Required repeated excisions. (per WAES)

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
8256	46	M	MK-0518, 400 mg b.i.d.	018	V: kaposi sarcoma D: Kaposi's sarcoma AIDS related B: Kaposi's sarcoma AIDS related SP: Kaposi's sarcoma (recurrent)	110	BL: 9 Week 2: 27 Week 4: 24 Week 8: 69 Week 12: 9 *Week 16: 12††* Week 24: 14	BL: 627,000 Week 2: 20,100 Week 4: 566,000 Week 8: 590,000 Week 12: 700,000 *Week 16: 612,000††* Week 24: 397,000	abacavir sulfate (+) lamivudine – 1 tablet lopinavir (+) ritonavir – 2 tablets	Kaposi's Sarcoma Esophageal candidiasis Cryptococcosis MAC Chronic Herpes	Non-fatal/Gross appearance (physical examination)/ presumptive/ Kaposi's sarcoma	Treated with chemotherapy
8288	45	M	MK-0518, 400 mg b.i.d. (switched to open label post virologic failure on Day 178)	018	V: anal carcinoma D: Anal carcinoma B: Anal cancer SP: Anal carcinoma	181	BL: 34 Week 2: 70 Week 4: 89 Week 8: 80 Week 12: 101 Week 16: 67 *Week 24: 61††* Open Label Week 4: Not Available Week 8: 66	BL: 90,600 Week 2: 1,220 Week 4: <400/66 Week 8: <400/263 Week 12: 9,790 Week 16: 8,670 *Week 24: 11,800††* Open Label Week 4: 10,500 Week 8: 1,740	Abacavir sulfate (+) lamivudine – 1 tablet Tenofovir disoproxil fumarate – 300 mg Stavudine – 80 mg	Cryptococcosis	Non-fatal	Treated by surgery

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
16365	48	M	MK-0518, 400 mg b.i.d.	019	V: squamous cell carcinoma D: Squamous cell carcinoma B: Squamous cell carcinoma SP: Squamous cell carcinoma (vocal cord)	67	BL: 17 Week 2: 27 Week 4: 65 *Week 8: 56††* Week 12: 77 Week 16: 65	BL: 311,000 Week 2: <400 /539 Week 4: <400/<50 *Week 8: <400/<50††* Week 12: <400/<50 Week 16: <400/<50	Darunavir – 1200 mg Ritonavir – 200 mg lamivudine (+) zidovudine – 2 tablets tenofovir disoproxil fumarate – 300 mg	Tobacco user Hoarseness	Non-fatal	Location of squamous cell carcinoma: right vocal cord (per WAES report) Pre-existing hoarseness at the time of randomization. Biopsy performed to evaluate IRS possible (CD4 4-77 in 12 weeks (per WAES) RX: Surgery (per WAES)

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
16239	47	M	MK-0518, 400 mg b.i.d.	019	V: hepatocellular carcinoma D: Hepatic neoplasm malignant B: Hepatic neoplasm malignant SP: Hepatocellular carcinoma	69	BL: 198 Week 2: 385 Week 4: 201 *Week 8: 46††*	BL: 12,300 Week 2: <400/73 Week 4: <400/<50 *Week 8: <400/<50††*	Emtricitabine (+) tenofovir disoproxil fumarate – 1 tablet Saquinavir mesylate – 2000 mg Ritonavir – 200 mg	Chronic hepatitis B, Kaposi's Sarcoma, Wasting syndrome MAC infection Esophageal candidiasis	Fatal (cause of death per WAES report: hepatocellular carcinoma which was considered to be due to chronic hepatitis B infection)/ definitive herpes simplex esophagitis	Patient initially hospitalized for immune reconstitution syndrome.
15028	46	M	MK-0518, 400 mg b.i.d.	019	V: Lymphoma D: Lymphoma B: Lymphoma SP: B-cell lymphoma (recurrent)	64	BL: 46 Week 2: 70 Week 4: 91 *Week 8: 33††*	BL: 1170000 Week 2: 2530 Week 4: 2220 *Week 8: <400/110††*	Emtricitabine (+) tenofovir disoproxil fumarate – 1 tablet Enfuvirtide – 180 mg Ritonavir – 200 mg Darunavir – 1200 mg (all meds stopped on Day 62)	Lymphoma, primary of brain; Immunoblastic lymphoma; Non-Hodgkins Lymphoma	Fatal/ Peripheral blood cytometry/ Definitive/ Lymphoma	Recurrent B cell lymphoma

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
15084	63	M	MK-0518, 400 mg b.i.d.	019	V: Rectal Polyp Squamous Cell Carcinoma In Situ D: Rectal carcinoma in situ B: Rectal cancer stage 0 SP: Squamous cell carcinoma --- carcinoma in situ (recurrent)	25	BL: 395 *Week 2: 389††* Week 4: 419 Week 8: 116 Week 12: 40 Week 16: 181 Week 24: 192	BL: 14,700 *Week 2: <400/53††* Week 4: <400 / <50 Week 8: <400 / <50 Week 12: <400 / <50 Week 16: <400 / <50 Week 24: <400 / <50	Enfuvirtide – 180 mg Darunavir – 1200 mg Ritonavir – 200 mg	Squamous cell carcinoma, forehead; Hyperplastic Polyp Colon PCP Bowen's Disease	Non-fatal	Recurrent based on history of Bowen's disease
15090	45	M	MK-0518, 400 mg b.i.d	019	V: squamous cell carcinoma (R) temple with metastasis D: Metastatic squamous cell carcinoma B: Metastatic squamous cell carcinoma SP: Squamous cell Carcinoma (skin/metastatic)	140	BL: 6 Week 2: 7 Week 4: 9 Week 8: Not Done *Week 12: 4††* Week 16: Not Done Week 24: Not Done Week 32: 4	BL: 28,100 Week 2: 655 Week 4: <400/<50 Week 8: Not Done *Week 12: <400/<50††* Week 16: Not Done Week 24: Not Done Week 32: <400/58	Emtricitabine (+) tenofovir disoproxil fumarate – 1 tablet Enfuvirtide – 180 mg Darunavir - 1200 mg Ritonavir – 200 mg Etravirine – 400 mg	Kaposi's Sarcoma CMV retinitis Cryptococcosis (extrapulmonary) Cryptosporidiosis Wasting	Non-fatal	RX: Mohs surgery, radical neck dissection

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
15113	41	M	MK-0518, 400 mg b.i.d.	019	V: mass buttocks D: Mass B: Mass SP: Squamous cell carcinoma — carcinoma in situ	30	Screen: 285 (BL Not Done) *Week 2: 326††* Week 4: 235 Week 8: 281 Week 12: 182 Week 16: 248 Week 24: 254	BL: 36,900 *Week 2: <400 / 62††* Week 4: <400/<50 Week 8: <400/<50 Week 12: <400/<50 Week 16: <400/<50 Week 24: <400/<50	Enfuvirtide – 180 mg Darunavir – 1200 mg Ritonavir – 200 mg emtricitabine (+) tenofovir disoproxil fumarate – 1 tablet	Rectal Lesions	Non-fatal	Per WAES: Carcinoma in situ with evidence of HPV cytopathic effect – entered study with hx of HPV and mass on buttock. Investigator noted that it was possible that the patient's improved immune status on protocol may have contributed to the inflammation and lesions noted.

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
Expanded Access (EAP) Only												
58	52	F	MK-0518, 400 mg b.i.d.	023	B Cell Lymphoma (in CNS)	21	Unknown	Unknown	Didanosine – 250 mg Efavirenz + emtricitabine + tenofovor disoproxil fumarate – 1 tablet (Truvada – 1 tablet and Sustiva – 3 caplets were started on Day 22 in place of efavirenz + emtricitabine + tenofovor disoproxil fumarate	Left sided weakness for 2-3 months prior to entering study	Non-fatal	(Information on spreadsheet based on WAES data as EAP studies not in CTS database)

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
18	50	M	MK-0518, 400 mg b.i.d.	023	Rectal Cancer (Squamous cell carcinoma in situ)	63	Unknown	Unknown	Daruvavir – 1200 mg Ritonavir – 200 mg Emtricitabine + tenofovir disoproxil fumarate – 1 tablet Enfuvirtide – 180 mg	Papilloma viral infection	Non-fatal	Anal squamous cell carcinoma in situ with a background of human papilloma - virus/ condyloma accuminatum at 2 months on study. (Information on spreadsheet based on WAES data as EAP studies not in CTS database)
Pretreatment – Not Randomized/Enrolled												
Non-randomized BL #3005	54	M	NA	019	Lymphoma B-cell type with pericardial involvement/B-cell lymphoma	NA			Prior antiretroviral therapy (per WAES): Emtricitabine + tenofovir disoproxil fumarate Tipranavir	Kaposi's sarcoma Wasting HIV encephalopathy	Non-fatal	

Listing of Neoplasms in MK-0518 Phase II and Phase III Studies - *Cumulative Data*

AN	Age	Gender	Treatment Group (Open Label)	Protocol Number	AE Terms (V, D, B, SP)†	Rel Day of Onset	CD4 (cells/mm^3)	HIV RNA (copies/mL) Amplicor Monitor v 1.5 /Ultrasensitive v1.5	OBT at Onset of AE	Relevant History	Outcome/ Adjudicated Result	Comments
Not enrolled	46	M	NA	023	Non-Hodgkin's lymphoma	NA			Emtricitabine + tenofovir disoproxil fumarate – 1 tablet Abacavir sulfate – 600 mg Ritonavir – 200 mg Darumavir – 120 mg (probably should be 1200 mg) Enfuvirtide – 180 mg		Fatal (patient died due to worsening Non-Hodgkin's lymphoma).	Hepatic function tests were severely elevated. Multiple imaging studies revealed extensive liver lesions consistent with lympho-matous spread of cancer

†V=verbatim; D=dictionary; B=broader;SP=sponsor
††At or prior to onset of AE

[Ref. 5.3.5.1: P004-Define, P005-Define, P018-Define, P019-Define] [Ref. 5.3.6: 460]

It has been noted that the total patient time at risk to MK-0518 and comparators is not balanced for several reasons related to study design: the Phase II studies were dose-ranging studies that randomized patients to MK-0518 versus comparator in 3:1 or 4:1 ratios. The Phase III studies used a 2:1 randomization for MK-0518:comparator. The treatment-experienced population studied in Protocols 005, 018, and 019 had higher attrition in the comparator arm due to virologic failures and such patients were eligible to cross over to open-label MK-0518. Therefore, there is more limited exposure to comparator relative to MK-0518. Both the numbers of highly treatment-experienced patients treated with MK-0518 and the time at risk for these patients is greater than for the aggregate comparator arms. Only the studies of treatment-naïve patients have balanced long-term exposure on the comparator arm; Protocol 004 is the only study in treatment-naïve patients that is complete and included in the Application and Safety Update Report.

Statistical analysis was performed based upon the pooled data from Protocols 004, 005, 018, and 019 for the double-blind portions of the study using the official database frozen file. All analyses were based on the All-Patients-as-Treated (APaT) population, which consisted of all randomized patients who received one or more doses of test drug therapy. As noted previously, the data cutoff date for the 4 individual studies was: [redacted]20[redacted]

See [Table 2.7.4: 50] for a summary of the adverse event terms (sponsor terms) included in the analyses. For each patient, only the first confirmed cancer event was considered in the time-to-event analyses. For example, if a patient had multiple events, either recurrences or events of different types, the first event would be included in the analyses but not the second event. Both events, however, are included in the counts by class of term table (e.g., [Table 2.7.4: 51]).

Time at risk for patients with a certain event was defined as the duration from the randomization date to the first event date; for patients without an event, time at risk was defined as the duration from the date of first dose to the date of the last dose of study therapy; however most patients were still receiving drug since the studies are ongoing. Patients who discontinued study therapy but continued to be followed were censored at 14 days after study therapy discontinuation.

Crude proportions (i.e., crude rates, number of patients with events / number of patients) and patient-year adjusted incidence rates (number of patients with events / patient-years) were provided for the combined analysis, and for each individual protocol. Relative risks of MK-0518 over comparator and associated 95% confidence intervals (CIs) were also provided for the combined analysis. As the number of events is sparse, the ratio of the crude incidence densities was used to calculate the relative risk estimates and associated 95% CIs.

[Table 2.7.4: 51] summarizes the neoplasm events by class of terms and treatment for Protocols 004, 005, 018, and 019 combined for the Cumulative period. There were 13 patients (1.7%) with neoplasms in the MK-0518 group and 1 patient (0.3%) in the comparator group. The corresponding analysis submitted in the Application is found in [Appendix 2.7.4: 75]. There were 2.3-fold more patients in the MK-0518 group compared with the comparator group. There were 3-fold more patient-years of time at risk in the MK-0518 arm relative to comparator. The mean follow-up duration was approximately 43 weeks for the MK-0518 group and 33 weeks for the comparator group.

In the MK-0518 treatment group, the incidence rates of KS, non-Hodgkin's lymphoma as well as non AIDS related cancers observed for the Cumulative period were generally similar to published rates. As noted in the Application, a recent large pooled analysis of 23 international cohorts estimated the incidence of KS and non-Hodgkin's lymphoma during widespread use of Highly Active Anti-Retroviral Therapy (HAART) in the years 1997–1999 to be 0.49/100 person-years and 0.36/100 person years, respectively [Ref. 5.4: 405]. The incidence rate for other cancers (not including KS and non-Hodgkin's lymphoma) was 0.17/100 person-years. These data include patients on HAART but do not specifically focus on cancer rates for highly treatment experienced patients with advanced immunodeficiency, which comprise a majority of the MK-0518-treated population.

Table 2.7.4: 51

Events by Class of Terms
Protocols 004, 005, 018, 019 Combined
(Double Blind Phase, Frozen File) - *Cumulative Data*

	MK-0518 (N = 758) 623 Patient-Years		Control Group (N = 323) 204 Patient-Years	
	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with Endpoint	**13 (1.7)**	**2.1**	**1 (0.3)**	**0.5**
T-cell lymphoma	1 (0.1)	0.2	0 (0.0)	0.0
Squamous cell carcinoma — carcinoma in situ	2 (0.3)	0.3	0 (0.0)	0.0
Squamous cell carcinoma	3 (0.4)	0.5	1 (0.3)	0.5
Rectal cancer	1 (0.1)	0.2	0 (0.0)	0.0
Kaposi's sarcoma	3 (0.4)	0.5	0 (0.0)	0.0
Hepatocellular carcinoma	1 (0.1)	0.2	0 (0.0)	0.0
B-cell lymphoma	2 (0.3)	0.3	0 (0.0)	0.0

Note: Patients with multiple events may be counted more than once in different terms, but only once in one term.

† Crude incidence (100×n/N).

‡ Events per 100 patient-years, with patient-years at risk (PYR) calculated based on the overall endpoint.

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

[Table 2.7.4: 52] summarizes the patient-year-adjusted incidence rates by treatment for Protocols 004, 005, 018, and 019 combined along with the overall estimate of relative risk. The MK-0518 group had 623 patient-years of follow-up and the comparator group had 204 patient-years of follow-up. The patient-year adjusted incidence rates were 2.087 and 0.490 per 100 patient-years for the MK-0518 and comparator arms, respectively, resulting in a relative risk of 4.257. This relative risk has an associated 95% confidence interval of (0.64, 180.90) based upon an exact approach using Binomial conditional distribution. In the Application, the relative risk was 3.328 with 95% CI (0.474, 144.446). For both the Cumulative and Application periods, the confidence intervals are broad due to the small numbers of events, but both cover the 1.0 level of no difference between the groups indicating that an imbalance of this magnitude could be observed by chance.

Table 2.7.4: 52

Events - Relative Risk and Associated 95% CI
Protocol 004, 005, 018, 019 Combined
(Double Blind Phase, Frozen File) - *Cumulative Data*

	MK-0518		Control Group		Relative Risk
	N	Cases/PYR† (Rate‡)	N	Cases/PYR† (Rate‡)	(95% CI)
Total	758	13/623 (2.087)	323	1/204 (0.490)	4.257(0.639, 180.897)
Protocol 004	163	1/228 (0.438)	41	1/53 (1.881)	
Protocol 005	133	0/100 (0.000)	45	0/23 (0.000)	
Protocol 018	232	6/150 (4.001)	118	0/63 (0.000)	
Protocol 019	230	6/145 (4.145)	119	0/64 (0.000)	

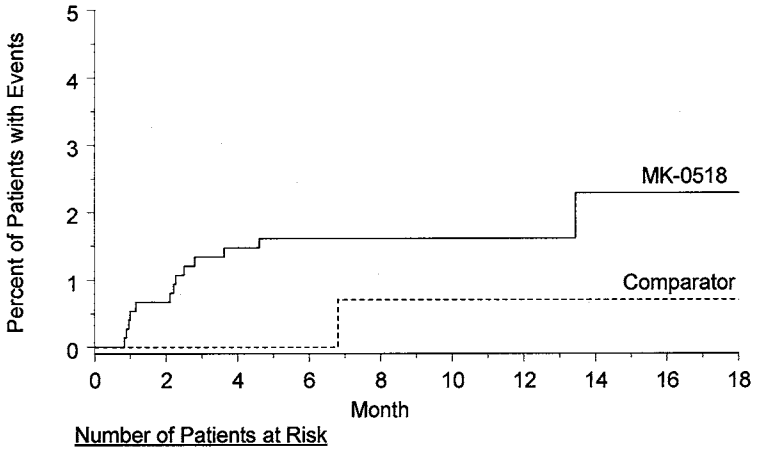
† Patients-years at risk.
‡ Per 100 person-years (PYR).

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

[Figure 2.7.4: 6] displays the Kaplan-Meier estimates of time to malignancies for the double-blind phases of Protocols 004, 005, 018, and 019 combined. A majority of the events occurred by Day 125; only a single event occurred late, after 12 months on MK-0518. The apparent large step in the Kaplan-Meier plot due to the late cancer event is a result of the much smaller number of patients at risk beyond 12 months and the use of a vertical axis that spans 0-5%. However this step indicates only a single new cancer event.

Figure 2.7.4: 6

Kaplan-Meier Plot of Time to Malignancy
(Double-Blind Phase, Frozen File)
(Protocol 004, 005, 018, and 019 Combined)
Cumulative Data



Number of Patients at Risk

MK-0518*	758	740	728	667	459	243	154	144	141	65
Comparator*	323	317	305	191	103	47	34	34	33	15

*: +OBT for P005, P018 and P019; + 3TC+TFV for P004

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

An additional analysis was done including the available follow-up from the open-label parts of the studies.

[Table 2.7.4: 53] summarizes the neoplasm events by class of terms and treatment for Protocols 004, 005, 018, and 019 combined including Open Label phases for the Cumulative Period. The MK-0518 group for this analysis includes 902 patients with 802 patient years time at risk. The numbers of patients and time at risk for the comparator group remains the same as for the Double Blind Phase. There were 4 patients with cancer events from the open-label parts of the combined studies (2 from the Application period and 2 from the SUR period), resulting in 17 patients (1.9%) with neoplasms in the MK-0518 group and 1 patient (0.3%) in the comparator group.

Table 2.7.4: 53

Events by Class of Terms
Protocols 004, 005, 018, 019 Combined
(DB+OL+OLPVF, Frozen File) - *Cumulative Data*

	MK-0518 (N = 902) 802 Patient-Years		Control Group (N = 323) 204 Patient-Years	
	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with Endpoint	**17 (1.9)**	**2.1**	**1 (0.3)**	**0.5**
T-cell lymphoma	1 (0.1)	0.1	0 (0.0)	0.0
Squamous cell carcinoma — carcinoma in situ	2 (0.2)	0.2	0 (0.0)	0.0
Squamous cell carcinoma	4 (0.4)	0.5	1 (0.3)	0.5
Rectal cancer	1 (0.1)	0.1	0 (0.0)	0.0
Kaposi's sarcoma	3 (0.3)	0.4	0 (0.0)	0.0
Hodgkin's lymphoma	2 (0.2)	0.2	0 (0.0)	0.0
Hepatocellular carcinoma	1 (0.1)	0.1	0 (0.0)	0.0
Basal cell carcinoma	1 (0.1)	0.1	0 (0.0)	0.0
B-cell lymphoma	2 (0.2)	0.2	0 (0.0)	0.0
Anal carcinoma	1 (0.1)	0.1	0 (0.0)	0.0

Note: Patients with multiple events may be counted more than once in different terms, but only once in one term.

† Crude incidence (100×n/N).

‡ Events per 100 patient-years, with patient-years at risk (PYR) calculated based on the overall endpoint.

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

[Table 2.7.4: 54] summarizes the patient-adjusted incidence rates by treatment for the combined protocols for the Cumulative period. Since inclusion of the open label phases adds time at risk only to the MK-0518 treated patients, there were no additional events and no additional time at risk in the comparator group in this table. By the end of follow-up, approximately 45% of those patients under follow-up in the comparator group had crossed over to MK-0518 in open-label. This represents an additional 24 patient entering the MK-0518 open-label group above that seen in the Application. Because these patients are represented in both groups, it was not possible to compare independent groups so relative risk estimation was not done.

For the Cumulative period analysis of the double blind plus open label phases, the MK-0518 group had 802 patient-years of follow-up and the patient-year-adjusted incidence rate was 2.121 with a 95% confidence interval of (1.24, 3.40). With increased numbers of patients and increased exposure to MK-0518 during open label phases, the incidence rate was essentially unchanged from the patient-year-adjusted incidence rate of 2.087 for the MK-0518 group during the double-blind parts of the studies for the Cumulative period.

Table 2.7.4: 54

Events - Relative Risk and Associated 95% CI
Protocol 004, 005, 018, 019 Combined
(DB+OL+OLPVF, Frozen File) - *Cumulative Data*

	MK-0518		
	N	Cases/PYR[†] (Rate[‡])	(95% CI)
Total	902	17/802 (2.121)	(1.236, 3.396)
Protocol 004	163	1/228 (0.438)	
Protocol 005	176	2/234 (0.855)	
Protocol 018	285	8/171 (4.671)	
Protocol 019	278	6/168 (3.574)	

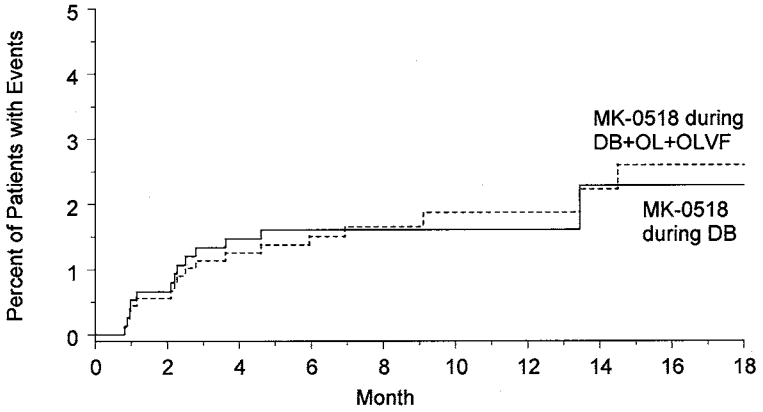
[†] Patients-years at risk.
[‡] Per 100 person-years (PYR).

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

[Figure 2.7.4: 7] displays the Kaplan-Meier estimates of time to malignancies for the double-blind plus open-label phases (including open-label extension and OLPVF) of Protocols 004, 005, 018, and 019 combined for the patients receiving MK-0518. The additional patients receiving MK-0518 in open-label phase with the additional time at risk did not result in an increased rate of malignancies in the Cumulative period.

Figure 2.7.4: 7

Kaplan-Meier Plot of Time to Malignancies
Patients Receiving MK-0518 in Double-Blind Plus Open-Label Extension Plus Open-Label Post Virologic Failure Phases
(Protocols 004, 005, 018, and 019 Combined) - *Cumulative Data*



Number at Risk	Number of Patients at Risk									
DB*	758	740	728	667	459	243	154	144	141	65
DB+OL+OLF*	902	870	819	769	573	347	287	273	242	140

*: on MK-0518

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

A new exploratory analysis was performed, similar to the preceding analyses, but excluding those cancers known to be recurrent, since recurrent cancers are not new events. Cancers were considered as recurrent if reported as recurrent in CTS, or if a cancer diagnosis used a term reported in medical history at the same anatomic site. In one case, AN 15084, the sponsor categorized the AE of rectal cancer stage 0 as recurrent since perianal Bowen's disease, a malignant condition, was recorded as medical history.

[Table 2.7.4: 55] summarizes the neoplasm events by class of terms and treatment for Protocols 004, 005, 018, and 019 combined for the Cumulative period. There were 8 patients (1.1%) with non-recurrent neoplasms in the MK-0518 group and 1 patient (0.3%) in the comparator group.

Table 2.7.4: 55

Events by Class of Terms
Protocols 004, 005, 018, 019 Combined
(Double Blind Phase, Frozen File, Without Recurrence) - *Cumulative Data*

	MK-0518 (N = 758) 625 Patient-Years		Control Group (N = 323) 204 Patient-Years	
	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with Endpoint	**8 (1.1)**	**1.3**	**1 (0.3)**	**0.5**
T-cell lymphoma	1 (0.1)	0.2	0 (0.0)	0.0
Squamous cell carcinoma — carcinoma in situ	1 (0.1)	0.2	0 (0.0)	0.0
Squamous cell carcinoma	2 (0.3)	0.3	1 (0.3)	0.5
Rectal cancer	1 (0.1)	0.2	0 (0.0)	0.0
Kaposi's sarcoma	1 (0.1)	0.2	0 (0.0)	0.0
Hepatocellular carcinoma	1 (0.1)	0.2	0 (0.0)	0.0
B-cell lymphoma	1 (0.1)	0.2	0 (0.0)	0.0

Note: Patients with multiple events may be counted more than once in different terms, but only once in one term.
† Crude incidence (100×n/N).
‡ Events per 100 patient-years, with patient-years at risk (PYR) calculated based on the overall endpoint.

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

[Table 2.7.4: 56] summarizes the patient-year-adjusted incidence rates by treatment for Protocols 004, 005, 018, and 019 combined along with the overall estimate of relative risk. The MK-0518 group had 625 patient-years of follow-up and the comparator group had 204 patient-years of follow-up. The patient-year adjusted incidence rates were 1.279 and 0.490 per 100 patient-years for the MK-0518 and comparator arms, respectively, resulting in a relative risk of 2.61. This relative risk has an associated 95% confidence interval of (0.35, 115.79) based upon an exact approach using Binomial conditional distribution.

Table 2.7.4: 56

Events - Relative Risk and Associated 95% CI
Protocol 004, 005, 018, 019 Combined
(Double Blind Phase, Frozen File, Without Recurrence) - *Cumulative Data*

	MK-0518		Control Group		Relative Risk
	N	Cases/PYR† (Rate‡)	N	Cases/PYR† (Rate‡)	(95% CI)
Total	758	8/625 (1.279)	323	1/204 (0.490)	2.610(0.350, 115.793)
Protocol 004	163	0/229 (0.000)	41	1/53 (1.881)	
Protocol 005	133	0/100 (0.000)	45	0/23 (0.000)	
Protocol 018	232	4/151 (2.649)	118	0/63 (0.000)	
Protocol 019	230	4/145 (2.752)	119	0/64 (0.000)	

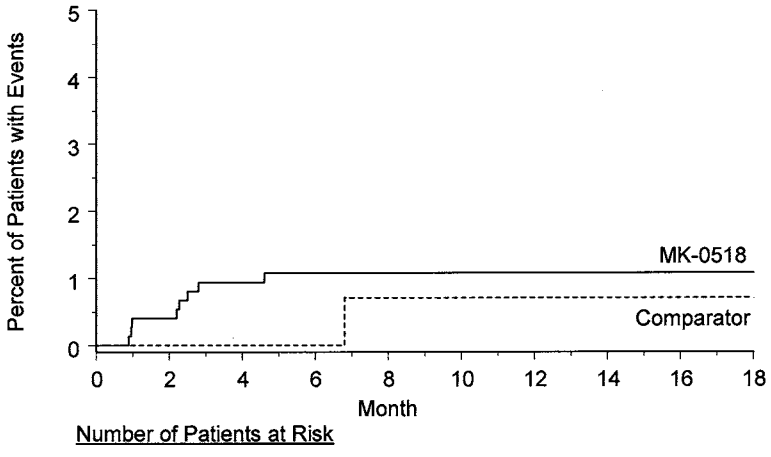
† Patients-years at risk.
‡ Per 100 person-years (PYR).

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

[Figure 2.7.4: 8] displays the Kaplan-Meier estimates of time to non-recurrent malignancies for the double-blind phases of Protocols 004, 005, 018, and 019 combined.

Figure 2.7.4: 8

Kaplan Meier Plot of Time to Non-Recurrent Malignancies
Protocols 004, 005, 018, 019 Combined
(Double Blind Phase, Frozen File, Without Recurrence) - *Cumulative Data*



Number of Patients at Risk

MK-0518*	758	742	731	670	460	243	154	145	142	66
Comparator*	323	317	305	191	103	47	34	34	33	15

*: +OBT for P005, P018 and P019; + 3TC+TFV for P004

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

[Table 2.7.4: 57] summarizes the non-recurrent neoplasm events by class of terms and treatment for Protocols 004, 005, 018, and 019 combined including Open Label phases for the Cumulative Period. The MK-0518 group for this analysis includes 902 patients with 804 patient years time at risk. The numbers of patients and time at risk for the comparator group remains the same as for the Double Blind Phase. There were 10 patients (1.1%) with non-recurrent neoplasms in the MK-0518 group and 1 patient (0.3%) in the comparator group.

Table 2.7.4: 57

Events by Class of Terms
Protocols 004, 005, 018, 019 Combined
(DB+OL+OLPVF, Frozen File, Without Recurrence) - *Cumulative Data*

	MK-0518 (N = 902) 804 Patient-Years		Control Group (N = 323) 204 Patient-Years	
	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with Endpoint	**10 (1.1)**	**1.2**	**1 (0.3)**	**0.5**
T-cell lymphoma	1 (0.1)	0.1	0 (0.0)	0.0
Squamous cell carcinoma — carcinoma in situ	1 (0.1)	0.1	0 (0.0)	0.0
Squamous cell carcinoma	2 (0.2)	0.2	1 (0.3)	0.5
Rectal cancer	1 (0.1)	0.1	0 (0.0)	0.0
Kaposi's sarcoma	1 (0.1)	0.1	0 (0.0)	0.0
Hodgkin's lymphoma	1 (0.1)	0.1	0 (0.0)	0.0
Hepatocellular carcinoma	1 (0.1)	0.1	0 (0.0)	0.0
Basal cell carcinoma	1 (0.1)	0.1	0 (0.0)	0.0
B-cell lymphoma	1 (0.1)	0.1	0 (0.0)	0.0
Anal carcinoma	1 (0.1)	0.1	0 (0.0)	0.0

Note: Patients with multiple events may be counted more than once in different terms, but only once in one term.

† Crude incidence (100×n/N).

‡ Events per 100 patient-years, with patient-years at risk (PYR) calculated based on the overall endpoint.

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

As displayed in [Table 2.7.4: 58], for the Cumulative period analysis of the double blind plus open label phases, the MK-0518 group had 804 patient-years of follow-up and the patient-year-adjusted incidence rate of non-recurrent cancers was 1.244 with a 95% confidence interval of (0.597, 2.288). With increased numbers of patients and increased exposure to MK-0518 during open label phases, the incidence rate of non-recurrent cancers was essentially unchanged from the patient-year-adjusted incidence rate of 1.279 for the MK-0518 group during the double-blind parts of the studies for the Cumulative period.

Table 2.7.4: 58

Events - Relative Risk and Associated 95% CI
Protocol 004, 005, 018, 019 Combined
(DB+OL+OLPVF, Frozen File, Without Recurrence) - *Cumulative Data*

	MK-0518		
	N	Cases/PYR[†] (Rate[‡])	(95% CI)
Total	902	10/804 (1.244)	(0.597, 2.288)
Protocol 004	163	0/229 (0.000)	
Protocol 005	176	1/234 (0.427)	
Protocol 018	285	5/172 (2.910)	
Protocol 019	278	4/168 (2.374)	

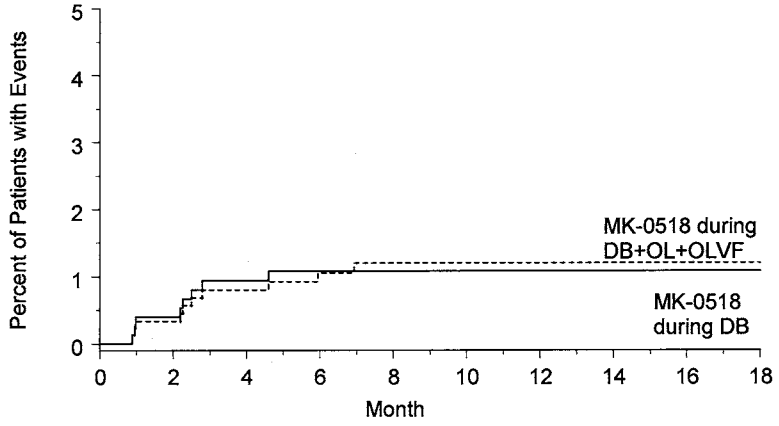
[†] Patients-years at risk.
[‡] Per 100 person-years (PYR).

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

[Figure 2.7.4: 9] displays the Kaplan-Meier estimates of time to non-recurrent malignancies for the double-blind plus open-label phases (including open-label extension and OLPVF) of Protocols 004, 005, 018, and 019 combined for the patients receiving MK-0518.

Figure 2.7.4: 9

Kaplan Meier Plot of Time to Non-Recurrent Malignancies
Protocols 004, 005, 018, 019 Combined
(DB+OL+OLPVF, Frozen File, Without Recurrence) - *Cumulative Data*



Number at Risk	Number of Patients at Risk									
DB*	758	742	731	670	460	243	154	145	142	66
DB+OL+OLF*	902	872	821	771	573	347	287	274	244	141

*: on MK-0518

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

Baseline characteristics, as reported in the Application, indicated that the treatment-experienced population studied in Protocols 005, 018, and 019 had very advanced immunodeficiency (median entry CD4 counts ranged from approximately 200 to 250 cells/mm^3 in Protocol 005, and 120 cells/mm^3. Protocols 018 and 019), and both had median of approximately 10 years of prior ART. More than 90% of patients entered the Phase III studies with a diagnosis of AIDS, and more than 60% had prior AIDS-defining conditions.

The timing of onset of cancer was also reviewed for the MK-0518 groups in the Cumulative period. For this review, onset was considered the date that the serious adverse experience of cancer was reported, but symptoms may have preceded the cancer diagnosis; in the case of recurrence, the onset date may not be relevant since the cancer was pre-existing. Of the new reports of cancers in the SUR period, both were recurrent, one a recurrent KS at day 310 in protocol 004, the other a recurrent SCCa (site unknown at SUR cutoff but later determined to be cutaneous at the scalp) at day 93 of open label MK-0518. Therefore the short time to diagnosis of cancer is similar for the Cumulative and the Application periods.

In summary, while there is an apparent imbalance in the number of malignancies reported for the MK-0518 and comparator groups, there does not appear to be any direct evidence of drug relationship to these events. The study population in which most of these events occurred has highly advanced immunodeficiency and the rates of malignancies observed are within the expected rates for patients with advanced infection. The occurrence of 2 cancers in the screening period further suggests the high background rates of cancer in severely immunodeficient patients with advanced HIV infection. Furthermore, a variety of cancers was reported, and the specific types were expected in this population. Seven (7) of the cancers were recurrent, most were associated with well known risk factors such as AIDS, oncogenic viruses (papillomavirus infection, hepatitis B virus infection), and tobacco, and some had suggestive symptoms and/or signs present prior to or at the time of enrollment (e.g. hoarseness in vocal cord SCCa, anal warts). Most of these cancers were detected within a short period of 3 months of enrollment, and several showed advanced disease state at the time of diagnosis, such as rectal polyp with CIS and stenosing rectal adenocarcinoma indicating an advanced circumferential illness. These findings suggest that these tumors were present but undetected at the time of study entry. Furthermore, a direct comparison of frequencies of cancer between the MK-0518 group and the comparator group are confounded due to the numerical imbalance with the higher numbers of patients on active MK-0518 and the longer duration of treatment compared with the lower numbers on the comparators. The adjustment for patient-time at risk effectively deals with this issue resulting in an apparent 4.3-fold increase in odds of cancer for MK-0518 over comparator. The additional exploratory analysis that counts only new cancers reduces the numerical imbalance substantially and results in a relative risk of 2.61, 95% CI of (0.35, 115.79)

There is another source of potential contributor for bias. Upon virologic failure, patients had the option to switch to open-label treatment with MK-0518. Therefore, some of the sickest patients who are at high risk to develop AIDS associated malignancies crossed over from comparator to MK-0518. The MK-0518 arm is, therefore, a mixture of patients with virologic response continuing on originally allocated MK-0518, patients who had virologic failure on MK-0518 and continuing on MK-0518 in open-label therapy, and patients originally allocated to comparator who had virologic failure and switched over to MK-0518 in open-label therapy. As noted, the patients in the open-label phase are represented in both groups, so it is not possible to compare independent groups using the open-label phase data.

One of the cancers reported in the SUR period occurred in a patient (AN 7024) in the OLPVF phase. Over the first 4 weeks of open label therapy, this patient's CD4 count went from approximately 60 to 250 and viral load from approximately 500,000 to < 10,000 copies/mL; it is possible that immune reconstitution syndrome (IRS) was associated with some of these cancers.

In conclusion, while the data reported here indicate the occurrence of tumors consistent with what is known in AIDS, they do not suggest any specific cancer risk associated with MK-0518 treatment. The profile and time course of the 2 additional recurrent malignancies identified in the SUR period are consistent with the cases observed in the Application. Additional follow-up will be needed as the ongoing studies in both treatment naïve and treatment-experienced patients are completed and further data become available.

Medium-WAES reports for the patients described in this section are included in [Ref. 5.3.6: 460].

Neoplasm tables and figures from the Original Application are in [Appendix 2.7.4: 75] through [Appendix 2.7.4: 80].

Mortality

Analysis of all-cause mortality was again performed in parallel with the analysis of cancers using data in the frozen file for the Cumulative period, both for the double-blind portion of the studies and for the entire study period (including double-blind and open-label portions). As described earlier [Sec. 2.7.4.2.1.2.2] and consistent with the Application data, the adverse experiences that led to death during the Cumulative period were generally serious complications of advanced immunodeficiency.

Statistical analysis was performed based upon the pooled data from Protocols 004, 005, 018 and 019 using the official database frozen file. All safety analyses were based on the All-Patients-as-Treated (APaT) population, which consisted of all randomized patients who received one or more doses of test drug therapy. For all analyses, the period at risk for an adverse event was from the date of first dose to the last dose of study therapy; however most patients were still receiving drug since the studies are ongoing. Time at risk for patients with a certain event was defined as the duration from the randomization date to the event date; for patients without an event, time at risk was defined as the duration from the randomization date to the last dose of study therapy. Event dates were the date that death occurred, rather than the date of onset of the fatal adverse experience. Crude proportions (i.e., crude rates, number of patients with events / number of patients) and patient-year adjusted incidence rates (number of patients with events / patient-years) were provided for the combined analysis, and for each individual protocol. Relative risks of MK-0518 over comparator and associated 95% confidence intervals (CIs) were also provided for the combined analysis. As the number of events is sparse, the ratio of the crude incidence densities were used to calculate the relative risk estimates and associated 95% CIs.

[Table 2.7.4: 59] summarizes the patient-year adjusted incidence rates by treatment for Protocols 004, 005, 018 and 019 combined along with the overall estimate of relative risk for the Cumulative period. There were 9 (1.2%) patients who died in the MK-0518 group and 3 (0.93%) patients in the comparator group. There are 2.3 fold more patients in the MK-0518 group compared to the comparator group. The MK-0518 group had 628 patient years of follow-up and the comparator group had 205 patient years of follow-up. There are 3 fold more patient years of exposure in the MK-0518 arm relative to comparator. The mean follow-up duration is approximately 43 weeks for the MK-0518 group and 33 weeks for the comparator group.

The patient-year adjusted incidence rates for the Cumulative period were 1.433 and 1.465 per 100 patient-years for the MK-0518 and comparator arms, respectively, resulting in a relative risk of 0.978. This relative risk has an associated 95% confidence interval of (0.24, 5.62) based upon an exact approach using Binomial conditional distribution. This confidence interval is broad due to the small numbers of events, but does cover the 1.0 level of no difference between the groups. In the Application, the adjusted incidence rates were 1.568 and 1.771 per 100 patient-years, respectively, with relative risk of 0.885 and 95% CI (0.21, 5.18). The patient year adjusted risk of death remains comparable across the treatment groups in the Cumulative period, and in the MK-0518 group is similar between the Application and Cumulative periods.

Table 2.7.4: 59

All cause of mortality - Relative Risk and Associated 95% CI
Protocol 004, 005, 018, 019 Combined
(Double Blind Phase, Frozen File) - *Cumulative Data*

	MK-0518		Control Group		Relative Risk
	N	Cases/PYR[†](Rate[‡])	N	Cases/PYR[†](Rate[‡])	(95% CI)
Total	758	9/628 (1.433)	323	3/205 (1.465)	0.978(0.244, 5.615)
Protocol 004	163	0/229 (0.000)	41	0/54 (0.000)	
Protocol 005	133	2/100 (2.004)	45	0/23 (0.000)	
Protocol 018	232	3/153 (1.963)	118	3/63 (4.741)	
Protocol 019	230	4/146 (2.733)	119	0/64 (0.000)	

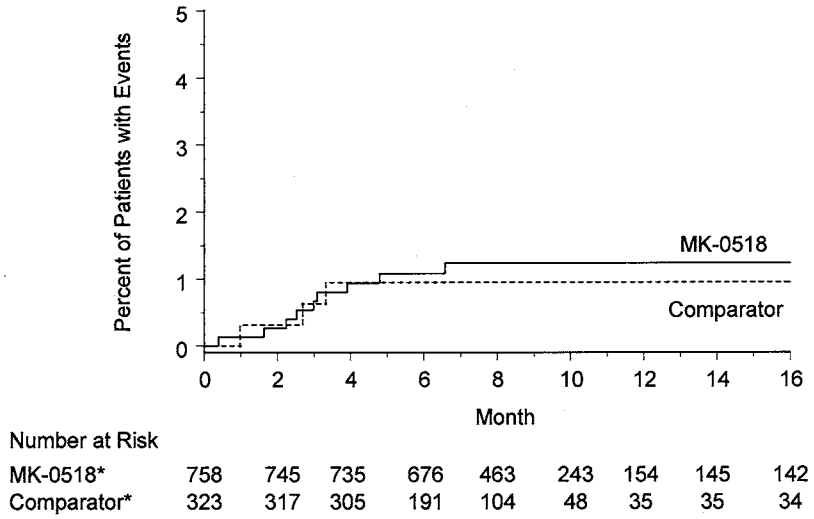
[†] Patients-years at risk.
[‡] Per 100 person-years (PYR).

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

[Figure 2.7.4: 10] displays the Kaplan Meier estimates of time to death for the double-blind phases of Protocol 004, 005, 018, 019 combined. A majority of the events in both groups occurred prior to Week 16 with no events on MK-0518 after Week 20. In the comparator group, the number of patients in the comparator group who remain at risk drop below 100 sometime between month 8 and month 10 of follow-up, and are about 5 fold lower than patients with who remain at risk on MK-0518, leaving relatively few patients at risk beyond 10 months of follow-up.

Figure 2.7.4: 10

Kaplan Meier Plot of All Cause Mortality
(Protocol 004, 005, 018, 019: Combined-
Double-Blind Phase, Frozen File) - *Cumulative Data*



Number at Risk									
MK-0518*	758	745	735	676	463	243	154	145	142
Comparator*	323	317	305	191	104	48	35	35	34

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

An additional analysis was done including the available follow-up from the open-label parts of the studies for the Cumulative period. [Table 2.7.4: 60] summarizes the mortality events by study and overall for those patients receiving MK-0518 in open-label. There were 3 additional patients who died in the open-label phases of the combined studies resulting in 12 (1.3%) patients who died in the MK-0518 group. The crude incidence rate was 1.486 deaths per 100 PYR for the Cumulative period compared with 1.607 per 100 PYR for the Application period.

Table 2.7.4: 60

All cause of mortality - Relative Risk and Associated 95% CI
Protocol 004, 005, 018, 019 Combined
(DB+OL+OLPVF, Frozen File) - *Cumulative Data*

	MK-0518		
	N	Cases/PYR[†](Rate[‡])	(95% CI)
Total	902	12/808 (1.486)	(0.768, 2.596)
Protocol 004	163	0/229 (0.000)	
Protocol 005	176	4/235 (1.703)	
Protocol 018	285	3/174 (1.725)	
Protocol 019	278	5/170 (2.948)	

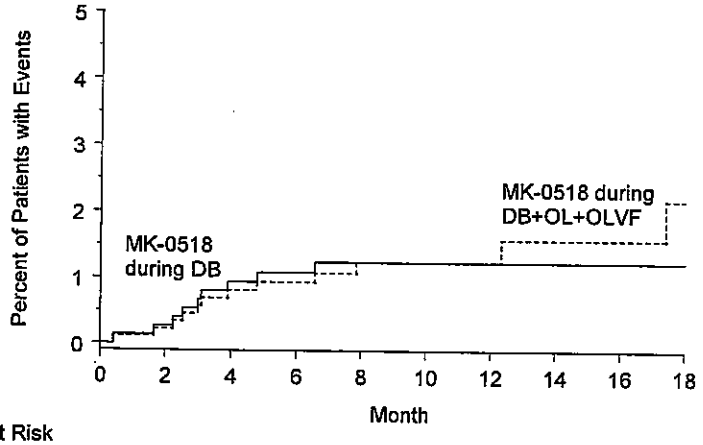
[†] Patients-years at risk.
[‡] Per 100 person-years (PYR).

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

[Figure 2.7.4: 11] displays the Kaplan Meier estimates of time to death for the double-blind plus open-label phases of Protocols 004, 005, 018, 019 combined for the patients receiving MK-0518 for the Cumulative period. The additional patients receiving MK-0518 in open-label phase with the additional time at risk does not result in meaningful increases in risk of mortality.

Figure 2.7.4: 11

Kaplan Meier Plot of All Cause Mortality
(Protocols 004, 005, 018, 019 Combined)
(Double-Blind + Open-Label + Open-Label Post Virologic Failure, Frozen File) -
Cumulative Data



Number at Risk

DB*	758	745	735	676	463	243	154	145	142	66
DB+OL+OLF*	902	875	825	778	578	348	288	275	245	140

*: on MK-0518

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

In order for this mortality review to be as complete as possible with multiple ongoing studies, data from the WAES system as of the [redacted]20[redacted] cutoff for cases with insufficient data in the CTS database are summarized here but are not included in the statistical analysis because of insufficient data in the CTS database to enable determination of patient-year adjusted incidence rates. In addition to the 15 deaths in the frozen file, there were 2 additional deaths reported in the WAES system, one in the MK-0518 group and one while receiving open label MK-0518 but originally randomized to the placebo group, and none were considered by the investigator to be related to study therapy, both occurred during the open-label phase. AN 7005 was reported in the Application: this patient was in the MK-0518 group in Protocol 018 and died due to end stage AIDS after discontinuing from the open-label post virologic failure phase

This case is also included in the prior section on neoplasms. AN 3264 died during the SUR period due to gastroenteritis after approximately 18 months in Protocol 005, initially randomized to placebo, then at about 4 months on study switched to open-label MK-0518 600 mg b.i.d. post virologic failure, then at about 12 months on study switched to MK-0518 400 mg b.i.d. in the study extension. Inclusion of these additional deaths in the mortality analyses would not be expected to change the conclusion.

In summary, review of all cause mortality indicates that the mortality rates were low and generally comparable in the two treatment groups during the double-blind phase, and remained similar for the MK-0518 group in the Cumulative and Application periods. The causes of death were generally diagnoses expected in a population with advanced immunodeficiency. In addition, based upon available data, the mortality rate on MK-0518 was similar between the double-blind portion and the entire study period. Medium-WAES reports for patients described in this section are included in [Ref. 5.3.6: 461].

Mortality tables and figures from the Original Application are in [Appendix 2.7.4: 81] through [Appendix 2.7.4: 84].

2.7.4.2.2 Narratives

Narratives summarizing the details of all deaths during the SUR period are presented in [Appendix 2.7.4: 40]. Narratives for all other serious adverse experiences reported during the SUR period are presented in [Appendix 2.7.4: 43].

2.7.4.3 Clinical Laboratory Evaluations

Predefined Limits of Change (PDLC) tables are provided in this section. The PDLCs were derived using DAIDS toxicity criteria for the tests of interest, or based on the fold-change from baseline. A patient could be counted only once within the DAIDS criteria grades, but could also be counted once based on the fold-change from baseline, if appropriate. The order of presentation for the PDLC tables with respect to the analysis populations is similar to that utilized in the presentation of adverse experience data in [Sec. 2.7.4.2.1.2].

2.7.4.3.1 Phase II Dose-Ranging PDLC Data

As reported in the Original Application, in Protocols 004 and 005, there were no clinically meaningful differences between treatment groups for any of the PDLC comparisons [Ref. 5.3.5.1: P004, P005]. PDLC tables for the Cumulative Periods of Protocol 004 and Protocol 005 are presented in [Table 2.7.4: 61] and [Table 2.7.4: 62], respectively, representing the entire study periods for both protocols. Other than hyperbilirubinemia, seen primarily in Protocol 005 in association with atazanavir use in OBT, Grade 3 and 4 abnormalities remained uncommon in the Cumulative period. There were no Grade 3 or 4 serum glucose increases seen in the Phase II studies. Overall the PDLC data for MK-0518 during the Cumulative Period for the Phase II studies were consistent with data from the Application Period.

Table 2.7.4: 61

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Protocol 004: Cohort I and II Combined; Combination Therapy Phase, Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC				
			MK-0518 100 mg b.i.d. (N=39) n/m (%)	MK-0518 200 mg b.i.d. (N=40) n/m (%)	MK-0518 400 mg b.i.d. (N=41) n/m (%)	MK-0518 600 mg b.i.d. (N=40) n/m (%)	Efavirenz 600 mg q.d. (N=38) n/m (%)
hematology laboratory test							
absolute neutrophil count (10[3]/microL)	1.00 - 1.30	Grade 1	2/39 (5.1)	5/40 (12.5)	3/41 (7.3)	1/40 (2.5)	1/38 (2.6)
	0.75 - 0.999	Grade 2	1/39 (2.6)	1/40 (2.5)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	0.50 - 0.749	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	<0.50	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	1/40 (2.5)	0/38 (0.0)
hemoglobin (gm/dL)	8.5 - 10.0	Grade 1	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	1/40 (2.5)	0/38 (0.0)
	7.5 - 8.4	Grade 2	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	6.5 - 7.4	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	< 6.5	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
platelet count (10[3]/microL)	100 - 124.999	Grade 1	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	2/38 (5.3)
	50 - 99.999	Grade 2	0/39 (0.0)	1/40 (2.5)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	25 - 49.999	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	<25	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Protocol 004: Cohort I and II Combined; Combination Therapy Phase, Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC				
			MK-0518 100 mg b.i.d. (N=39) n/m (%)	MK-0518 200 mg b.i.d. (N=40) n/m (%)	MK-0518 400 mg b.i.d. (N=41) n/m (%)	MK-0518 600 mg b.i.d. (N=40) n/m (%)	Efavirenz 600 mg q.d. (N=38) n/m (%)
blood chemistry test							
fasting(non-random) serum LDL-C (mg/dL)	130 - 159	Grade 1	8/39 (20.5)	5/40 (12.5)	8/41 (19.5)	6/40 (15.0)	10/38 (26.3)
	160 - 189	Grade 2	1/39 (2.6)	0/40 (0.0)	1/41 (2.4)	0/40 (0.0)	2/38 (5.3)
	≥190	Grade 3	0/39 (0.0)	1/40 (2.5)	0/41 (0.0)	0/40 (0.0)	2/38 (5.3)
fasting(non-random) serum cholesterol (mg/dL)	200 - 239	Grade 1	9/39 (23.1)	5/40 (12.5)	5/41 (12.2)	6/40 (15.0)	13/38 (34.2)
	240 - 300	Grade 2	1/39 (2.6)	1/40 (2.5)	2/41 (4.9)	0/40 (0.0)	5/38 (13.2)
	>300	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	2/38 (5.3)
fasting(non-random) serum triglyceride (mg/dL)	500 - 750	Grade 2	2/39 (5.1)	0/40 (0.0)	1/41 (2.4)	0/40 (0.0)	0/38 (0.0)
	751 - 1200	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	3/38 (7.9)
	>1200	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
fasting(non-random) serum glucose test (mg/dL)	110 -125	Grade 1	1/39 (2.6)	5/40 (12.5)	3/41 (7.3)	3/40 (7.5)	5/38 (13.2)
	126 - 250	Grade 2	4/39 (10.3)	0/40 (0.0)	4/41 (9.8)	1/40 (2.5)	0/38 (0.0)
	251 - 500	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>500	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
total serum bilirubin (mg/dL)	1.1 - 1.5 x ULN	Grade 1	6/39 (15.4)	3/40 (7.5)	3/41 (7.3)	3/40 (7.5)	1/38 (2.6)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Protocol 004: Cohort I and II Combined; Combination Therapy Phase, Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC				
			MK-0518 100 mg b.i.d. (N=39) n/m (%)	MK-0518 200 mg b.i.d. (N=40) n/m (%)	MK-0518 400 mg b.i.d. (N=41) n/m (%)	MK-0518 600 mg b.i.d. (N=40) n/m (%)	Efavirenz 600 mg q.d. (N=38) n/m (%)
	1.6 - 2.5 x ULN	Grade 2	2/39 (5.1)	0/40 (0.0)	1/41 (2.4)	1/40 (2.5)	0/38 (0.0)
	2.6 - 5.0 x ULN	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>5.0 x ULN	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>2.5 - 5.0 x Baseline[‡]		2/39 (5.1)	0/40 (0.0)	0/41 (0.0)	1/40 (2.5)	1/38 (2.6)
	>5.0 -10.0 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>10.0 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
serum direct bilirubin (mg/dL)	>2.5 - 5.0 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>5.0 - 10.0 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>10.0 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
serum indirect bilirubin (mg/dL)	>2.5 - 5.0 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	1/40 (2.5)	0/38 (0.0)
	>5.0 - 10.0 x Baseline[‡]		1/39 (2.6)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>10.0 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
serum creatinine (mg/dL)	1.1 - 1.3 x ULN	Grade 1	1/39 (2.6)	1/40 (2.5)	2/41 (4.9)	1/40 (2.5)	0/38 (0.0)
	1.4 - 1.8 x ULN	Grade 2	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	1.9 - 3.4 x ULN	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	≥3.5 x ULN	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Protocol 004: Cohort I and II Combined; Combination Therapy Phase, Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC				
			MK-0518 100 mg b.i.d. (N=39) n/m (%)	MK-0518 200 mg b.i.d. (N=40) n/m (%)	MK-0518 400 mg b.i.d. (N=41) n/m (%)	MK-0518 600 mg b.i.d. (N=40) n/m (%)	Efavirenz 600 mg q.d. (N=38) n/m (%)
	>2.5 x Baseline[‡]		0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
serum aspartate aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	10/39 (25.6)	10/40 (25.0)	8/41 (19.5)	11/40 (27.5)	10/38 (26.3)
	2.6 - 5.0 x ULN	Grade 2	0/39 (0.0)	4/40 (10.0)	0/41 (0.0)	0/40 (0.0)	6/38 (15.8)
	5.1 - 10.0 x ULN	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	1/38 (2.6)
	>10.0 x ULN	Grade 4	2/39 (5.1)	0/40 (0.0)	1/41 (2.4)	1/40 (2.5)	0/38 (0.0)
	>2.5 - 5.0 x Baseline[‡]		1/39 (2.6)	8/40 (20.0)	1/41 (2.4)	1/40 (2.5)	7/38 (18.4)
	>5.0 x Baseline[‡]		2/39 (5.1)	1/40 (2.5)	1/41 (2.4)	1/40 (2.5)	2/38 (5.3)
serum alanine aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	10/39 (25.6)	6/40 (15.0)	13/41 (31.7)	11/40 (27.5)	15/38 (39.5)
	2.6 - 5.0 x ULN	Grade 2	1/39 (2.6)	6/40 (15.0)	1/41 (2.4)	1/40 (2.5)	3/38 (7.9)
	5.1 - 10.0 x ULN	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	1/40 (2.5)	2/38 (5.3)
	>10.0 x ULN	Grade 4	1/39 (2.6)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>2.5 - 5.0 x Baseline[‡]		2/39 (5.1)	3/40 (7.5)	5/41 (12.2)	3/40 (7.5)	8/38 (21.1)
	>5.0 x Baseline[‡]		2/39 (5.1)	3/40 (7.5)	3/41 (7.3)	2/40 (5.0)	4/38 (10.5)
serum alkaline phosphatase (IU(alk phos)/L)	1.25 - 2.5 x ULN	Grade 1	5/39 (12.8)	7/40 (17.5)	0/41 (0.0)	1/40 (2.5)	7/38 (18.4)
	2.6 - 5.0 x ULN	Grade 2	0/39 (0.0)	1/40 (2.5)	0/41 (0.0)	1/40 (2.5)	0/38 (0.0)
	5.1 - 10.0 x ULN	Grade 3	0/39 (0.0)	1/40 (2.5)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Protocol 004: Cohort I and II Combined; Combination Therapy Phase, Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC				
			MK-0518 100 mg b.i.d. (N=39) n/m (%)	MK-0518 200 mg b.i.d. (N=40) n/m (%)	MK-0518 400 mg b.i.d. (N=41) n/m (%)	MK-0518 600 mg b.i.d. (N=40) n/m (%)	Efavirenz 600 mg q.d. (N=38) n/m (%)
	>10.0 x ULN	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>2.5 - 5.0 x Baseline[‡]		0/39 (0.0)	2/40 (5.0)	0/41 (0.0)	0/40 (0.0)	1/38 (2.6)
	>5.0 x Baseline[‡]		0/39 (0.0)	1/40 (2.5)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
serum pancreatic amylase test (IU(amylase)/L)[§]	1.1 - 1.5 x ULN	Grade 1	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	1.6 - 2.0 x ULN	Grade 2	0/39 (0.0)	3/40 (7.5)	0/41 (0.0)	0/40 (0.0)	2/38 (5.3)
	2.1 - 5.0 x ULN	Grade 3	2/39 (5.1)	0/40 (0.0)	2/41 (4.9)	0/40 (0.0)	0/38 (0.0)
	>5.0 x ULN	Grade 4	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
serum lipase test (IU(lipase)/L)	1.1 - 1.5 x ULN	Grade 1	2/39 (5.1)	4/40 (10.0)	4/41 (9.8)	4/40 (10.0)	1/38 (2.6)
	1.6 - 3.0 x ULN	Grade 2	0/39 (0.0)	1/40 (2.5)	4/41 (9.8)	0/40 (0.0)	1/38 (2.6)
	3.1 - 5.0 x ULN	Grade 3	1/39 (2.6)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)
	>5.0 x ULN	Grade 4	1/39 (2.6)	0/40 (0.0)	0/41 (0.0)	0/40 (0.0)	0/38 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Protocol 004: Cohort I and II Combined; Combination Therapy Phase, Entire Study Period) - *Cumulative Data*

[†] For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. A patient was included as a Grade X event if his/her highest grade during treatment was X and the laboratory value was worse than baseline.

[‡] A patient was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal (ULNA).

[§] Defined as (the number of patients meeting the specific serum pancreatic amylase criteria) / (the number of patients with serum amylase test result).

Note: MK-0518 and efavirenz (EFV) were administered with tenofovir (TFV) and lamivudine (3TC).

N = total number of patients randomized in the treatment group.

n/m = number of patients with PDLC/number of patients with laboratory test. For the criteria using baseline, m=number of patients with baseline values for that laboratory test.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

[Ref. 5.3.5.1: P004-Define]

Table 2.7.4: 62

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
Protocol 005 (Studies A and B Combined; Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC			
			MK-0518 200 mg b.i.d. (N=43) n/m (%)	MK-0518 400 mg b.i.d. (N=45) n/m (%)	MK-0518 600 mg b.i.d. (N=45) n/m (%)	Placebo (N=45) n/m (%)
hematology laboratory test						
absolute neutrophil count (10[3]/microL)	1.00 - 1.30	Grade 1	2/43 (4.7)	2/45 (4.4)	5/45 (11.1)	4/45 (8.9)
	0.75 - 0.999	Grade 2	0/43 (0.0)	1/45 (2.2)	1/45 (2.2)	2/45 (4.4)
	0.50 - 0.749	Grade 3	0/43 (0.0)	0/45 (0.0)	1/45 (2.2)	0/45 (0.0)
	<0.50	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	1/45 (2.2)
hemoglobin (gm/dL)	8.5 - 10.0	Grade 1	2/43 (4.7)	1/45 (2.2)	2/45 (4.4)	2/45 (4.4)
	7.5 - 8.4	Grade 2	0/43 (0.0)	0/45 (0.0)	1/45 (2.2)	1/45 (2.2)
	6.5 - 7.4	Grade 3	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	< 6.5	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
platelet count (10[3]/microL)	100 - 124.999	Grade 1	1/43 (2.3)	1/45 (2.2)	2/45 (4.4)	4/45 (8.9)
	50 - 99.999	Grade 2	4/43 (9.3)	1/45 (2.2)	1/45 (2.2)	0/45 (0.0)
	25 - 49.999	Grade 3	0/43 (0.0)	0/45 (0.0)	1/45 (2.2)	0/45 (0.0)
	<25	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group
Protocol 005 (Studies A and B Combined; Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC			
			MK-0518 200 mg b.i.d. (N=43) n/m (%)	MK-0518 400 mg b.i.d. (N=45) n/m (%)	MK-0518 600 mg b.i.d. (N=45) n/m (%)	Placebo (N=45) n/m (%)
blood chemistry test						
fasting(non-random) serum LDL-C (mg/dL)	130 - 159	Grade 1	4/39 (10.3)	10/41 (24.4)	11/43 (25.6)	3/37 (8.1)
	160 - 189	Grade 2	2/39 (5.1)	2/41 (4.9)	5/43 (11.6)	3/37 (8.1)
	≥190	Grade 3	3/39 (7.7)	2/41 (4.9)	1/43 (2.3)	3/37 (8.1)
fasting(non-random) serum cholesterol (mg/dL)	200 - 239	Grade 1	11/41 (26.8)	9/44 (20.5)	13/45 (28.9)	8/40 (20.0)
	240 - 300	Grade 2	5/41 (12.2)	7/44 (15.9)	9/45 (20.0)	4/40 (10.0)
	>300	Grade 3	3/41 (7.3)	3/44 (6.8)	0/45 (0.0)	3/40 (7.5)
fasting(non-random) serum triglyceride (mg/dL)	500 - 750	Grade 2	1/41 (2.4)	6/44 (13.6)	4/45 (8.9)	3/40 (7.5)
	751 - 1200	Grade 3	5/41 (12.2)	1/44 (2.3)	3/45 (6.7)	0/40 (0.0)
	>1200	Grade 4	1/41 (2.4)	0/44 (0.0)	0/45 (0.0)	1/40 (2.5)
fasting(non-random) serum glucose test (mg/dL)	110 -125	Grade 1	4/41 (9.8)	4/45 (8.9)	4/44 (9.1)	6/44 (13.6)
	126 - 250	Grade 2	4/41 (9.8)	7/45 (15.6)	6/44 (13.6)	2/44 (4.5)
	251 - 500	Grade 3	0/41 (0.0)	0/45 (0.0)	0/44 (0.0)	0/44 (0.0)
	>500	Grade 4	0/41 (0.0)	0/45 (0.0)	0/44 (0.0)	0/44 (0.0)
total serum bilirubin (mg/dL)	1.1 - 1.5 x ULN	Grade 1	2/43 (4.7)	5/45 (11.1)	4/45 (8.9)	1/45 (2.2)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
Protocol 005 (Studies A and B Combined; Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC			
			MK-0518 200 mg b.i.d. (N=43) n/m (%)	MK-0518 400 mg b.i.d. (N=45) n/m (%)	MK-0518 600 mg b.i.d. (N=45) n/m (%)	Placebo (N=45) n/m (%)
	1.6 - 2.5 x ULN	Grade 2	6/43 (14.0)	6/45 (13.3)	6/45 (13.3)	8/45 (17.8)
	2.6 - 5.0 x ULN	Grade 3	4/43 (9.3)	5/45 (11.1)	8/45 (17.8)	3/45 (6.7)
	>5.0 x ULN	Grade 4	2/43 (4.7)	2/45 (4.4)	0/45 (0.0)	0/45 (0.0)
	>2.5 - 5.0 x Baseline[‡]		2/43 (4.7)	4/45 (8.9)	4/45 (8.9)	5/45 (11.1)
	>5.0 -10.0 x Baseline[‡]		6/43 (14.0)	9/45 (20.0)	6/45 (13.3)	4/45 (8.9)
	>10.0 x Baseline[‡]		2/43 (4.7)	1/45 (2.2)	3/45 (6.7)	2/45 (4.4)
serum direct bilirubin (mg/dL)	>2.5 - 5.0 x Baseline[‡]		1/43 (2.3)	5/45 (11.1)	5/45 (11.1)	2/45 (4.4)
	>5.0 - 10.0 x Baseline[‡]		0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	>10.0 x Baseline[‡]		0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
serum indirect bilirubin (mg/dL)	>2.5 - 5.0 x Baseline[‡]		1/43 (2.3)	5/45 (11.1)	4/45 (8.9)	6/45 (13.3)
	>5.0 - 10.0 x Baseline[‡]		7/43 (16.3)	2/45 (4.4)	5/45 (11.1)	2/45 (4.4)
	>10.0 x Baseline[‡]		1/43 (2.3)	7/45 (15.6)	4/45 (8.9)	2/45 (4.4)
serum creatinine (mg/dL)	1.1 - 1.3 x ULN	Grade 1	3/43 (7.0)	0/45 (0.0)	4/45 (8.9)	4/45 (8.9)
	1.4 - 1.8 x ULN	Grade 2	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	1.9 - 3.4 x ULN	Grade 3	1/43 (2.3)	1/45 (2.2)	0/45 (0.0)	0/45 (0.0)
	≥3.5 x ULN	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
Protocol 005 (Studies A and B Combined; Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC			
			MK-0518 200 mg b.i.d. (N=43) n/m (%)	MK-0518 400 mg b.i.d. (N=45) n/m (%)	MK-0518 600 mg b.i.d. (N=45) n/m (%)	Placebo (N=45) n/m (%)
	>2.5 x Baseline[‡]		1/43 (2.3)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
serum aspartate aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	6/43 (14.0)	11/45 (24.4)	5/45 (11.1)	14/45 (31.1)
	2.6 - 5.0 x ULN	Grade 2	3/43 (7.0)	4/45 (8.9)	3/45 (6.7)	1/45 (2.2)
	5.1 - 10.0 x ULN	Grade 3	0/43 (0.0)	2/45 (4.4)	0/45 (0.0)	0/45 (0.0)
	>10.0 x ULN	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	>2.5 - 5.0 x Baseline[‡]		3/43 (7.0)	7/45 (15.6)	2/45 (4.4)	2/45 (4.4)
	>5.0 x Baseline[‡]		0/43 (0.0)	1/45 (2.2)	1/45 (2.2)	0/45 (0.0)
serum alanine aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	5/43 (11.6)	11/45 (24.4)	4/45 (8.9)	10/45 (22.2)
	2.6 - 5.0 x ULN	Grade 2	4/43 (9.3)	3/45 (6.7)	1/45 (2.2)	1/45 (2.2)
	5.1 - 10.0 x ULN	Grade 3	1/43 (2.3)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	>10.0 x ULN	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	>2.5 - 5.0 x Baseline[‡]		5/43 (11.6)	4/45 (8.9)	4/45 (8.9)	1/45 (2.2)
	>5.0 x Baseline[‡]		0/43 (0.0)	1/45 (2.2)	0/45 (0.0)	0/45 (0.0)
serum alkaline phosphatase (IU(alk phos)/L)	1.25 - 2.5 x ULN	Grade 1	7/43 (16.3)	5/45 (11.1)	0/45 (0.0)	2/45 (4.4)
	2.6 - 5.0 x ULN	Grade 2	0/43 (0.0)	0/45 (0.0)	1/45 (2.2)	0/45 (0.0)
	5.1 - 10.0 x ULN	Grade 3	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
Protocol 005 (Studies A and B Combined; Entire Study Period) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC			
			MK-0518 200 mg b.i.d. (N=43) n/m (%)	MK-0518 400 mg b.i.d. (N=45) n/m (%)	MK-0518 600 mg b.i.d. (N=45) n/m (%)	Placebo (N=45) n/m (%)
	>10.0 x ULN	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	>2.5 - 5.0 x Baseline[‡]		0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	1/45 (2.2)
	>5.0 x Baseline[‡]		0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
serum pancreatic amylase test (IU(amylase)/L)[§]	1.1 - 1.5 x ULN	Grade 1	1/43 (2.3)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	1.6 - 2.0 x ULN	Grade 2	1/43 (2.3)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
	2.1 - 5.0 x ULN	Grade 3	0/43 (0.0)	2/45 (4.4)	1/45 (2.2)	1/45 (2.2)
	>5.0 x ULN	Grade 4	0/43 (0.0)	0/45 (0.0)	0/45 (0.0)	0/45 (0.0)
serum lipase test (IU(lipase)/L)	1.1 - 1.5 x ULN	Grade 1	4/43 (9.3)	5/45 (11.1)	3/45 (6.7)	2/45 (4.4)
	1.6 - 3.0 x ULN	Grade 2	0/43 (0.0)	4/45 (8.9)	1/45 (2.2)	0/45 (0.0)
	3.1 - 5.0 x ULN	Grade 3	0/43 (0.0)	0/45 (0.0)	1/45 (2.2)	0/45 (0.0)
	>5.0 x ULN	Grade 4	0/43 (0.0)	1/45 (2.2)	0/45 (0.0)	0/45 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
Protocol 005 (Studies A and B Combined; Entire Study Period) - *Cumulative Data*

[†] For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. A patient was included as a Grade X event if his/her highest grade during treatment was X and the laboratory value was worse than baseline.

[‡] A patient was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal (ULNA).

[§] Defined as (the number of patients meeting the specific serum pancreatic amylase criteria) / (the number of patients with serum amylase test result).

Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).

N = total number of patients randomized in the treatment group.

n/m = number of patients with PDLC/number of patients with laboratory test. For the criteria using baseline, m=number of patients with baseline values for that laboratory test.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

[Ref. 5.3.5.1: P005-Define]

2.7.4.3.2 Phase II and Phase III Treatment-Experienced MK-0518 400 mg b.i.d. Double-Blind Cohort PDLC Data

A summary of the number and percent of patients with values outside the predefined limits of change meeting Grade 1 or higher criteria in the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort for selected parameters are presented for the cumulative period in [Table 2.7.4: 63] and for the Original Application period in [Table 2.7.4: 64]. There were no clinically meaningful differences between treatment groups for any of the comparisons. In general, Grade 3 and Grade 4 abnormalities were somewhat more common overall in the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort in Phase III studies than in MK-0518 treatment groups in the Phase II studies, as may be expected given the advanced disease, less stringent laboratory inclusion criteria, enrollment of patients with hepatitis B or C co-infection, and the extent of other co-morbidities of the patients enrolled in Protocols 018 and 019, who make up the majority of this cohort. The percentages shown are not adjusted for duration of exposure.

Overall, the rates of PDLC abnormalities were similar for the MK-0518 groups for the Cumulative period compared to the Application period Specifically, Grades 3 and 4 serum AST and ALT abnormalities remained similar and Grades 3 and 4 hyperglycemia remained uncommon for the MK-0518 group in the Cumulative and Application periods [Sec. 2.7.4.2.1.2.5].

Table 2.7.4: 63

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
hematology laboratory test				
absolute neutrophil count (10[3]/microL)	1.00 - 1.30	Grade 1	36/507 (7.1)	33/282 (11.7)
	0.75 - 0.999	Grade 2	19/507 (3.7)	21/282 (7.4)
	0.50 - 0.749	Grade 3	12/507 (2.4)	7/282 (2.5)
	<0.50	Grade 4	5/507 (1.0)	3/282 (1.1)
hemoglobin (gm/dL)	8.5 - 10.0	Grade 1	22/507 (4.3)	19/282 (6.7)
	7.5 - 8.4	Grade 2	5/507 (1.0)	8/282 (2.8)
	6.5 - 7.4	Grade 3	5/507 (1.0)	1/282 (0.4)
	< 6.5	Grade 4	0/507 (0.0)	0/282 (0.0)
platelet count (10[3]/microL)	100 - 124.999	Grade 1	18/507 (3.6)	20/282 (7.1)
	50 - 99.999	Grade 2	19/507 (3.7)	16/282 (5.7)
	25 - 49.999	Grade 3	2/507 (0.4)	1/282 (0.4)
	<25	Grade 4	4/507 (0.8)	1/282 (0.4)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
blood chemistry test				
fasting(non-random) serum LDL-C (mg/dL)	130 - 159	Grade 1	78/474 (16.5)	32/254 (12.6)
	160 - 189	Grade 2	41/474 (8.6)	15/254 (5.9)
	≥190	Grade 3	20/474 (4.2)	8/254 (3.1)
fasting(non-random) serum cholesterol (mg/dL)	200 - 239	Grade 1	121/506 (23.9)	57/277 (20.6)
	240 - 300	Grade 2	79/506 (15.6)	35/277 (12.6)
	>300	Grade 3	29/506 (5.7)	12/277 (4.3)
fasting(non-random) serum triglyceride (mg/dL)	500 - 750	Grade 2	29/506 (5.7)	21/277 (7.6)
	751 - 1200	Grade 3	19/506 (3.8)	9/277 (3.2)
	>1200	Grade 4	9/506 (1.8)	5/277 (1.8)
fasting(non-random) serum glucose test (mg/dL)	110 -125	Grade 1	45/507 (8.9)	24/281 (8.5)
	126 - 250	Grade 2	47/507 (9.3)	19/281 (6.8)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	251 - 500	Grade 3	7/507 (1.4)	4/281 (1.4)
	>500	Grade 4	0/507 (0.0)	0/281 (0.0)
total serum bilirubin (mg/dL)	1.1 - 1.5 x ULN	Grade 1	26/507 (5.1)	9/282 (3.2)
	1.6 - 2.5 x ULN	Grade 2	27/507 (5.3)	19/282 (6.7)
	2.6 - 5.0 x ULN	Grade 3	16/507 (3.2)	7/282 (2.5)
	>5.0 x ULN	Grade 4	4/507 (0.8)	0/282 (0.0)
	>2.5 - 5.0 x Baseline[‡]		22/507 (4.3)	14/282 (5.0)
	>5.0 -10.0 x Baseline[‡]		19/507 (3.7)	10/282 (3.5)
	>10.0 x Baseline[‡]		9/507 (1.8)	2/282 (0.7)
serum direct bilirubin (mg/dL)	>2.5 - 5.0 x Baseline[‡]		12/507 (2.4)	5/282 (1.8)
	>5.0 - 10.0 x Baseline[‡]		0/507 (0.0)	2/282 (0.7)
	>10.0 x Baseline[‡]		4/507 (0.8)	0/282 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
serum indirect bilirubin (mg/dL)	>2.5 - 5.0 x Baseline[‡]		11/507 (2.2)	8/282 (2.8)
	>5.0 - 10.0 x Baseline[‡]		15/507 (3.0)	9/282 (3.2)
	>10.0 x Baseline[‡]		13/507 (2.6)	2/282 (0.7)
serum creatinine (mg/dL)	1.1 - 1.3 x ULN	Grade 1	38/507 (7.5)	21/282 (7.4)
	1.4 - 1.8 x ULN	Grade 2	14/507 (2.8)	4/282 (1.4)
	1.9 - 3.4 x ULN	Grade 3	6/507 (1.2)	4/282 (1.4)
	≥3.5 x ULN	Grade 4	0/507 (0.0)	0/282 (0.0)
	>2.5 x Baseline[‡]		2/507 (0.4)	0/282 (0.0)
serum aspartate aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	98/507 (19.3)	74/282 (26.2)
	2.6 - 5.0 x ULN	Grade 2	46/507 (9.1)	16/282 (5.7)
	5.1 - 10.0 x ULN	Grade 3	11/507 (2.2)	6/282 (2.1)
	>10.0 x ULN	Grade 4	2/507 (0.4)	2/282 (0.7)
	>2.5 - 5.0 x Baseline[‡]		31/507 (6.1)	12/282 (4.3)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	>5.0 x Baseline[‡]		11/507 (2.2)	9/282 (3.2)
serum alanine aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	103/507 (20.3)	61/282 (21.6)
	2.6 - 5.0 x ULN	Grade 2	35/507 (6.9)	22/282 (7.8)
	5.1 - 10.0 x ULN	Grade 3	15/507 (3.0)	4/282 (1.4)
	>10.0 x ULN	Grade 4	3/507 (0.6)	3/282 (1.1)
	>2.5 - 5.0 x Baseline[‡]		37/507 (7.3)	22/282 (7.8)
	>5.0 x Baseline[‡]		18/507 (3.6)	8/282 (2.8)
serum alkaline phosphatase (IU(alk phos)/L)	1.25 - 2.5 x ULN	Grade 1	52/507 (10.3)	26/282 (9.2)
	2.6 - 5.0 x ULN	Grade 2	10/507 (2.0)	1/282 (0.4)
	5.1 - 10.0 x ULN	Grade 3	2/507 (0.4)	3/282 (1.1)
	>10.0 x ULN	Grade 4	2/507 (0.4)	1/282 (0.4)
	>2.5 - 5.0 x Baseline[‡]		7/507 (1.4)	3/282 (1.1)
	>5.0 x Baseline[‡]		1/507 (0.2)	1/282 (0.4)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Cumulative Data*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
serum pancreatic amylase test (IU(amylase)/L)[§]	1.1 - 1.5 x ULN	Grade 1	8/507 (1.6)	4/282 (1.4)
	1.6 - 2.0 x ULN	Grade 2	7/507 (1.4)	2/282 (0.7)
	2.1 - 5.0 x ULN	Grade 3	18/507 (3.6)	6/282 (2.1)
	>5.0 x ULN	Grade 4	1/507 (0.2)	0/282 (0.0)
serum lipase test (IU(lipase)/L)	1.1 - 1.5 x ULN	Grade 1	32/507 (6.3)	18/282 (6.4)
	1.6 - 3.0 x ULN	Grade 2	17/507 (3.4)	5/282 (1.8)
	3.1 - 5.0 x ULN	Grade 3	3/507 (0.6)	1/282 (0.4)
	>5.0 x ULN	Grade 4	1/507 (0.2)	0/282 (0.0)

[†] For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. A patient was included as a Grade X event if his/her highest grade during treatment was X and the laboratory value was worse than baseline.

[‡] A patient was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal (ULNA).

[§] Defined as (the number of patients meeting the specific serum pancreatic amylase criteria) / (the number of patients with serum amylase test result).

Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).

N = total number of patients randomized in the treatment group.

n/m = number of patients with PDLC/number of patients with laboratory test. For the criteria using baseline, m=number of patients with baseline values for that laboratory test.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

[Ref. 5.3.5.1: P005-Define, P018-Define, P019-Define]

Table 2.7.4: 64

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Original Application*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
hematology laboratory test				
absolute neutrophil count (10[3]/microL)	1.00 - 1.30	Grade 1	34/507 (6.7)	33/282 (11.7)
	0.75 - 0.999	Grade 2	17/507 (3.4)	22/282 (7.8)
	0.50 - 0.749	Grade 3	12/507 (2.4)	6/282 (2.1)
	<0.50	Grade 4	5/507 (1.0)	3/282 (1.1)
hemoglobin (gm/dL)	8.5 - 10.0	Grade 1	23/507 (4.5)	19/282 (6.7)
	7.5 - 8.4	Grade 2	5/507 (1.0)	7/282 (2.5)
	6.5 - 7.4	Grade 3	4/507 (0.8)	1/282 (0.4)
	< 6.5	Grade 4	0/507 (0.0)	0/282 (0.0)
platelet count (10[3]/microL)	100 - 124.999	Grade 1	17/507 (3.4)	21/282 (7.4)
	50 - 99.999	Grade 2	18/507 (3.6)	14/282 (5.0)
	25 - 49.999	Grade 3	2/507 (0.4)	1/282 (0.4)
	<25	Grade 4	4/507 (0.8)	1/282 (0.4)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Original Application*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
blood chemistry test				
fasting(non-random) serum LDL-C (mg/dL)	130 - 159	Grade 1	68/471 (14.4)	28/249 (11.2)
	160 - 189	Grade 2	36/471 (7.6)	12/249 (4.8)
	≥190	Grade 3	18/471 (3.8)	6/249 (2.4)
fasting(non-random) serum cholesterol (mg/dL)	200 - 239	Grade 1	114/506 (22.5)	49/276 (17.8)
	240 - 300	Grade 2	74/506 (14.6)	35/276 (12.7)
	>300	Grade 3	23/506 (4.5)	10/276 (3.6)
fasting(non-random) serum triglyceride (mg/dL)	500 - 750	Grade 2	24/506 (4.7)	21/276 (7.6)
	751 - 1200	Grade 3	16/506 (3.2)	8/276 (2.9)
	>1200	Grade 4	7/506 (1.4)	5/276 (1.8)
fasting(non-random) serum glucose test (mg/dL)	110 -125	Grade 1	44/507 (8.7)	23/280 (8.2)
	126 - 250	Grade 2	42/507 (8.3)	17/280 (6.1)
	251 - 500	Grade 3	5/507 (1.0)	4/280 (1.4)
	>500	Grade 4	0/507 (0.0)	0/280 (0.0)
total serum bilirubin (mg/dL)	1.1 - 1.5 x ULN	Grade 1	22/507 (4.3)	10/282 (3.5)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Original Application*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	1.6 - 2.5 x ULN	Grade 2	28/507 (5.5)	18/282 (6.4)
	2.6 - 5.0 x ULN	Grade 3	15/507 (3.0)	7/282 (2.5)
	>5.0 x ULN	Grade 4	3/507 (0.6)	0/282 (0.0)
	>2.5 - 5.0 x Baseline‡		21/507 (4.1)	16/282 (5.7)
	>5.0 -10.0 x Baseline‡		19/507 (3.7)	8/282 (2.8)
	>10.0 x Baseline‡		6/507 (1.2)	2/282 (0.7)
serum direct bilirubin (mg/dL)	>2.5 - 5.0 x Baseline‡		11/507 (2.2)	4/282 (1.4)
	>5.0 - 10.0 x Baseline‡		0/507 (0.0)	2/282 (0.7)
	>10.0 x Baseline‡		4/507 (0.8)	0/282 (0.0)
serum indirect bilirubin (mg/dL)	>2.5 - 5.0 x Baseline‡		13/507 (2.6)	9/282 (3.2)
	>5.0 - 10.0 x Baseline‡		15/507 (3.0)	8/282 (2.8)
	>10.0 x Baseline‡		10/507 (2.0)	2/282 (0.7)
serum creatinine (mg/dL)	1.1 - 1.3 x ULN	Grade 1	37/507 (7.3)	21/282 (7.4)
	1.4 - 1.8 x ULN	Grade 2	11/507 (2.2)	4/282 (1.4)
	1.9 - 3.4 x ULN	Grade 3	4/507 (0.8)	3/282 (1.1)
	≥3.5 x ULN	Grade 4	0/507 (0.0)	0/282 (0.0)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Original Application*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	>2.5 x Baseline‡		1/507 (0.2)	0/282 (0.0)
serum aspartate aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	91/507 (17.9)	74/282 (26.2)
	2.6 - 5.0 x ULN	Grade 2	45/507 (8.9)	13/282 (4.6)
	5.1 - 10.0 x ULN	Grade 3	10/507 (2.0)	6/282 (2.1)
	>10.0 x ULN	Grade 4	2/507 (0.4)	1/282 (0.4)
	>2.5 - 5.0 x Baseline‡		29/507 (5.7)	13/282 (4.6)
	>5.0 x Baseline‡		10/507 (2.0)	7/282 (2.5)
serum alanine aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	94/507 (18.5)	57/282 (20.2)
	2.6 - 5.0 x ULN	Grade 2	34/507 (6.7)	22/282 (7.8)
	5.1 - 10.0 x ULN	Grade 3	13/507 (2.6)	4/282 (1.4)
	>10.0 x ULN	Grade 4	3/507 (0.6)	1/282 (0.4)
	>2.5 - 5.0 x Baseline‡		38/507 (7.5)	19/282 (6.7)
	>5.0 x Baseline‡		16/507 (3.2)	7/282 (2.5)
serum alkaline phosphatase (IU(alk phos)/L)	1.25 - 2.5 x ULN	Grade 1	47/507 (9.3)	25/282 (8.9)
	2.6 - 5.0 x ULN	Grade 2	9/507 (1.8)	1/282 (0.4)
	5.1 - 10.0 x ULN	Grade 3	2/507 (0.4)	3/282 (1.1)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019) - *Original Application*

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			MK-0518 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	>10.0 x ULN	Grade 4	2/507 (0.4)	1/282 (0.4)
	>2.5 - 5.0 x Baseline‡		7/507 (1.4)	3/282 (1.1)
	>5.0 x Baseline‡		1/507 (0.2)	1/282 (0.4)
serum pancreatic amylase test (IU(amylase)/L)§	1.1 - 1.5 x ULN	Grade 1	8/507 (1.6)	3/282 (1.1)
	1.6 - 2.0 x ULN	Grade 2	7/507 (1.4)	2/282 (0.7)
	2.1 - 5.0 x ULN	Grade 3	16/507 (3.2)	6/282 (2.1)
	>5.0 x ULN	Grade 4	1/507 (0.2)	0/282 (0.0)
serum lipase test (IU(lipase)/L)	1.1 - 1.5 x ULN	Grade 1	26/507 (5.1)	19/282 (6.7)
	1.6 - 3.0 x ULN	Grade 2	15/507 (3.0)	4/282 (1.4)
	3.1 - 5.0 x ULN	Grade 3	3/507 (0.6)	0/282 (0.0)
	>5.0 x ULN	Grade 4	1/507 (0.2)	0/282 (0.0)

† For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. A patient was included as a Grade X event if his/her highest grade during treatment was X and the laboratory value was worse than baseline.

‡ A patient was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal (ULNA).

§ Defined as (the number of patients meeting the specific serum pancreatic amylase criteria) / (the number of patients with serum amylase test result).

Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).

N = total number of patients randomized in the treatment group.

n/m = number of patients with PDLC/number of patients with laboratory test. For the criteria using baseline, m=number of patients with baseline values for that laboratory test.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

[Ref. 5.3.5.1: P005, P018, P019]

2.7.4.3.3 Open-Label Post Virologic Failure (OLPVF) Phase PDLC Data

A summary of the number and percent of patients exceeding the predefined limits of change meeting Grade 1 or higher criteria in the OLPVF phase for selected parameters are presented for the cumulative period in [Appendix 2.7.4: 85] and for the Original Application period in [Appendix 2.7.4: 86]. In general, PDLC data seen in the OLPVF phase during the Cumulative Period was similar to that seen in the Application period.

2.7.4.3.4 Laboratory Changes From Baseline

For the treatment-experienced MK-0518 400 mg b.i.d. double-blind cohort, summary statistics (baseline and change from baseline) for protocol-specified laboratory tests within each of the categories of laboratory measurements (serum chemistry, hematology, and urinalysis) are in [Appendix 2.7.4: 87] for the Cumulative period and in [Appendix 2.7.4: 88] for the Original Application. There were no clinically meaningful differences in the changes from baseline in specific laboratory tests among treatment groups seen in the Cumulative period.

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

No update

2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Intrinsic Factors

No update provided, since the overall adverse experience profiles were similar in the Cumulative and Application Periods.

2.7.4.5.2 Extrinsic Factors

No update provided, since the overall adverse experience profiles were similar in the Cumulative and Application Periods.

2.7.4.5.3 Drug Interactions

No update

2.7.4.5.4 Use in Pregnancy and Lactation

Although not considered an adverse experience, all pregnancies occurring throughout the entire study period were to be reported and followed for outcome whenever possible.

There were 2 pregnancies reported and described in the Original Application. There were no pregnancies reported during the SUR period.

The use of MK-0518 in pregnancy and lactation is not recommended.

2.7.4.5.5 Overdose

There were 9 overdoses of MK-0518 reported and described in the Original Application. There was 1 overdose of MK-0518 reported during the SUR period as described below.

In Protocol 019, 1 patient (AN 15607) in the MK-0518 group, reported an accidental overdose with no associated adverse experiences. The patient incorrectly took 2 tablets in the AM and 2 tablets in the PM from Study Day 233 to Study Day 268, for total daily dosage of 1600 mg per day during that period.

2.7.4.5.6 Drug Abuse

No reports of drug abuse of study medication occurred in any patients participating in the studies summarized in this SUR. Based upon the activity profile of this compound and relative lack of CNS toxicity, the abuse potential of this compound is considered low.

2.7.4.5.7 Withdrawal and Rebound

In the development program for MK-0518, no specific studies have been conducted to assess the response to withdrawal and rebound. No withdrawal or rebound effects were observed in MK-0518 clinical trials to date. MK-0518 is not targeted to elicit a change in human physiology or biochemistry, but rather is an anti-infective with activity against HIV. Therefore, the terms withdrawal and rebound are not applicable to this compound.

2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Although no studies on the effects on the ability to drive and use machines have been performed, there is no information to suggest that MK-0518 affects a person's ability to drive and use machines. However, individual responses to MK-0518 may vary.

2.7.4.6 Postmarketing Data

Not applicable

2.7.4.7 Discussion and Conclusions Regarding the Safety of MK-0518

The safety of MK-0518 in both treatment-naïve and treatment-experienced patients with HIV infection has been reviewed in 899 patients (758 patients initially randomized to MK-0518) the majority of whom were treated with MK-0518 for at least 24 weeks and up to approximately 90 weeks (633 days) in combination regimens in the 2 Phase II studies and 2 Phase III studies, which are the basis for this Safety Update Report. Some of this treatment was under open-label conditions. The main focus of the Safety Update Report remains the majority of patients studied who were highly treatment experienced and had advanced immunodeficiency. The design of the studies resulted in imbalance of exposure to MK-0518 vs. comparator due to randomization ratios weighted in favor of MK-0518 (ratios were 2:1, 3:1, or 4:1) and the option of open-label MK-0518 for all treatment-experienced patients who had virologic failure, resulting in substantial

crossover from the placebo group. Consequently, the overall extent of exposure to MK-0518 was substantially greater than that of the comparator regimens, particularly in the treatment-experienced population due to the open-label option: median durations of double blind treatment were 35.1 and 27.0 weeks for MK-0518 and placebo, respectively, in the Cumulative period, compared with 26.4 and 21.4 weeks, respectively, in the Application period. Time at risk during double-blind treatment was 332.2 patient-years in the MK-0518 400 mg b.i.d. group and 150.2 patient-years in the placebo group in the Cumulative period, compared with 260.8 and 126.6 patient-years respectively, in the Application period. Time at risk in the OLPVF phase was 106.8 patient-years in the Cumulative period.

The increasing imbalance in double blind and total MK-0518 exposure for the Cumulative Period compared with the Application Period also reflects a greater number of patients from the Phase III studies who have left the placebo arm due to virologic failure and entered open label treatment.

Phase I study results are essentially unchanged, as all new studies are ongoing or have only preliminary data. Phase II studies were examined over the Entire Study Period for this SUR, and were compared with double blind dose ranging phase data from the Application Period. Phase II studies showed generally similar safety profiles for MK-0518 in the Cumulative Period and the Application Period in both treatment naïve and treatment experienced patients. The overall safety profile for the primary safety population, the treatment experienced 400 mg double blind cohort, in the Cumulative period is essentially unchanged as compared with the Application Period.

As noted in the Original Application, across the entire MK-0518 development program, a greater number of malignancies were reported for the MK-0518 group than the comparator group, in the SUR period, 2 additional cancers were reported in patients receiving MK-0518 in the double blind period. The updated analysis of cancer based upon crude rates adjusted for exposure, showed a relative risk of 4.26 and 95% confidence interval (0.64, 180.90). When the cancers were analyzed excluding recurrences, the relative risk of cancer was 2.61 with 95% CI of (0.35, 115.79). Using either approach the cancer event rate did not increase with additional open label exposure. The general characteristics of the new cases reported in the SUR period resembled those reported in the Application. There does not appear to be any direct evidence of drug relationship to these events.

Review of all cause mortality indicates that mortality rates were low and remained generally comparable in the two treatment groups and between the Cumulative and Application Periods. The causes of death were generally diagnoses expected in a population with advanced immunodeficiency. In addition, based upon data in the Cumulative period, the mortality rate on MK-0518 adjusted for exposure was similar between the double-blind portion and the entire study period.

Conclusions regarding Safety:

1. In treatment-experienced patients failing antiretroviral therapy with triple-class resistant HIV, MK-0518 400 mg b.i.d. administered in combination with Optimized Background Therapy (OBT), as compared to placebo in combination with OBT:
    - is generally well tolerated.
    - is not associated with fasting hyperglycemia
    - does not appear to be associated with lipodystrophy or lipoatrophy
    - is generally well tolerated irrespective of gender and race
    - is generally well tolerated in patients with active hepatitis B and/or hepatitis C coinfection
2. In antiretroviral treatment-naïve patients, MK-0518 when administered with tenofovir and lamivudine, as compared with efavirenz plus tenofovir and lamivudine:
    - has a generally similar safety profile
    - has no adverse effect on fasting lipids
3. In dose-ranging Phase II studies, and in patients using tenofovir and/or atazanavir in OBT, there is no evidence that higher doses or higher exposure due to drug-drug interactions lead to increased drug toxicity.
4. The higher number of cancers observed in the MK-0518 group compared with the comparator group warrants further follow-up, but based on the data currently available, no specific cancer risk attributable to MK-0518 is apparent.

2.7.4.8 Appendix

Appendix 2.7.4: 1

Number (%) of Patients With Specific Concomitant Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category— Treatment-Experienced MK-0518 400 mg b.i.d. Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Patients with one or more concomitant therapies	507	(100.0)	282	(100.0)	789	(100.0)
Patients with no concomitant therapy	0	(0.0)	0	(0.0)	0	(0.0)
Antiinfectives For Systemic Use						
Antivirals For Systemic Use	507	(100.0)	282	(100.0)	789	(100.0)
Abacavir Sulfate	51	(10.1)	24	(8.5)	75	(9.5)
Abacavir Sulfate (+) Lamivudine	42	(8.3)	32	(11.3)	74	(9.4)
Abacavir Sulfate (+) Lamivudine (+) Zidovudine	27	(5.3)	22	(7.8)	49	(6.2)
Amprenavir	15	(3.0)	8	(2.8)	23	(2.9)
Atazanavir Sulfate	52	(10.3)	38	(13.5)	90	(11.4)
Darunavir	194	(38.3)	103	(36.5)	297	(37.6)
Delavirdine Mesylate	3	(0.6)	5	(1.8)	8	(1.0)
Didanosine	87	(17.2)	45	(16.0)	132	(16.7)
Efavirenz	26	(5.1)	17	(6.0)	43	(5.4)
Efavirenz (+) Emtricitabine (+) Tenofovir Disoproxil Fumarate	2	(0.4)	1	(0.4)	3	(0.4)
Emtricitabine	14	(2.8)	12	(4.3)	26	(3.3)
Emtricitabine (+) Tenofovir Disoproxil Fumarate	212	(41.8)	104	(36.9)	316	(40.1)
Enfuvirtide	195	(38.5)	106	(37.6)	301	(38.1)
Etravirine	1	(0.2)	0	(0.0)	1	(0.1)
Fosamprenavir Calcium	35	(6.9)	33	(11.7)	68	(8.6)
Indinavir Sulfate	15	(3.0)	3	(1.1)	18	(2.3)
Lamivudine	92	(18.1)	51	(18.1)	143	(18.1)

Number (%) of Patients With Specific Concomitant Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category— Treatment-Experienced MK-0518 400 mg b.i.d. Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Lamivudine (+) Zidovudine	58	(11.4)	43	(15.2)	101	(12.8)
Lopinavir (+) Ritonavir	95	(18.7)	47	(16.7)	142	(18.0)
Nelfinavir Mesylate	0	(0.0)	2	(0.7)	2	(0.3)
Nevirapine	3	(0.6)	2	(0.7)	5	(0.6)
Ritonavir	376	(74.2)	216	(76.6)	592	(75.0)
Saquinavir	51	(10.1)	34	(12.1)	85	(10.8)
Stavudine	50	(9.9)	24	(8.5)	74	(9.4)
Tenofovir Disoproxil Fumarate	175	(34.5)	116	(41.1)	291	(36.9)
Tipranavir	102	(20.1)	47	(16.7)	149	(18.9)
Zalcitabine	0	(0.0)	1	(0.4)	1	(0.1)
Zidovudine	44	(8.7)	28	(9.9)	72	(9.1)
Although a patient may have had two or more concomitant optimized background therapies, the patient is counted only once within a category. The same patient may appear in different categories.						
Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).						

[Ref. 5.3.5.1: P005-Define, P018-Define, P019-Define]

Appendix 2.7.4: 2
Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Patients with one or more concomitant therapies	466	(91.9)	263	(93.3)	729	(92.4)
Patients with no concomitant therapy	41	(8.1)	19	(6.7)	60	(7.6)
Alimentary Tract And Metabolism						
Anabolic Agents For Systemic Use	21	(4.1)	8	(2.8)	29	(3.7)
Nandrolone Decanoate	12	(2.4)	3	(1.1)	15	(1.9)
Oxandrolone	11	(2.2)	5	(1.8)	16	(2.0)
Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	100	(19.7)	50	(17.7)	150	(19.0)
Albumin Tannate	1	(0.2)	0	(0.0)	1	(0.1)
Attapulgite, Activated	1	(0.2)	1	(0.4)	2	(0.3)
Benzoic Acid (+) Glycerin (+) Opium	1	(0.2)	0	(0.0)	1	(0.1)
Bifidobacterium Lactis (+) Lactobacillus Acidophilus (+) Lactobacillus Paracasei (+) Streptococcus Thermophilus	1	(0.2)	0	(0.0)	1	(0.1)
Bismuth Subsalicylate	3	(0.6)	1	(0.4)	4	(0.5)
Charcoal, Activated	2	(0.4)	0	(0.0)	2	(0.3)
Diphenoxylate	1	(0.2)	1	(0.4)	2	(0.3)
Diphenoxylate Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Lactobacillus Acidophilus	1	(0.2)	0	(0.0)	1	(0.1)
Lactobacillus Acidophilus, Tyndallized	1	(0.2)	0	(0.0)	1	(0.1)
Loperamide Hydrochloride	84	(16.6)	47	(16.7)	131	(16.6)
Loperamide Oxide	1	(0.2)	0	(0.0)	1	(0.1)
Mesalamine	2	(0.4)	0	(0.0)	2	(0.3)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Paromomycin	0	(0.0)	1	(0.4)	1	(0.1)
Racecadotril	3	(0.6)	0	(0.0)	3	(0.4)
Rifaximin	2	(0.4)	0	(0.0)	2	(0.3)
Saccharomyces Boulardii	0	(0.0)	2	(0.7)	2	(0.3)
Smectite	2	(0.4)	0	(0.0)	2	(0.3)
Antiemetics And Antinauseants	23	(4.5)	12	(4.3)	35	(4.4)
Chlorobutanol	1	(0.2)	0	(0.0)	1	(0.1)
Dronabinol	11	(2.2)	8	(2.8)	19	(2.4)
Granisetron	5	(1.0)	0	(0.0)	5	(0.6)
Metopimazine	2	(0.4)	0	(0.0)	2	(0.3)
Nabilone	1	(0.2)	0	(0.0)	1	(0.1)
Ondansetron	5	(1.0)	3	(1.1)	8	(1.0)
Scopolamine	1	(0.2)	2	(0.7)	3	(0.4)
Tropisetron	0	(0.0)	1	(0.4)	1	(0.1)
Bile And Liver Therapy	1	(0.2)	0	(0.0)	1	(0.1)
Ursodiol	1	(0.2)	0	(0.0)	1	(0.1)
Digestives, Incl. Enzymes	6	(1.2)	3	(1.1)	9	(1.1)
Amylase (+) Lipase (+) Proteases (Unspecified)	1	(0.2)	2	(0.7)	3	(0.4)
Aspergillus Oryzae Extract (+) Pancreatin	1	(0.2)	0	(0.0)	1	(0.1)
Pancreatin	2	(0.4)	0	(0.0)	2	(0.3)
Pancrelipase	2	(0.4)	1	(0.4)	3	(0.4)
Drugs For Acid Related Disorders	90	(17.8)	61	(21.6)	151	(19.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Almagate	0	(0.0)	1	(0.4)	1	(0.1)
Aluminum Hydroxide	1	(0.2)	0	(0.0)	1	(0.1)
Aluminum Hydroxide (+) Magnesium Hydroxide	5	(1.0)	0	(0.0)	5	(0.6)
Amoxicillin (+) Clarithromycin (+) Omeprazole	1	(0.2)	0	(0.0)	1	(0.1)
Calcium Carbonate	5	(1.0)	1	(0.4)	6	(0.8)
Calcium Carbonate (+) Magnesium Hydroxide	1	(0.2)	0	(0.0)	1	(0.1)
Cimetidine	3	(0.6)	2	(0.7)	5	(0.6)
Esomeprazole	10	(2.0)	8	(2.8)	18	(2.3)
Famotidine	6	(1.2)	4	(1.4)	10	(1.3)
Hydrotalcite	1	(0.2)	0	(0.0)	1	(0.1)
Lansoprazole	9	(1.8)	3	(1.1)	12	(1.5)
Magnesia [Milk Of]	1	(0.2)	1	(0.4)	2	(0.3)
Magnesium Oxide	4	(0.8)	0	(0.0)	4	(0.5)
Misoprostol	1	(0.2)	0	(0.0)	1	(0.1)
Omeprazole	31	(6.1)	19	(6.7)	50	(6.3)
Pantoprazole	12	(2.4)	13	(4.6)	25	(3.2)
Rabeprazole Sodium	2	(0.4)	1	(0.4)	3	(0.4)
Ranitidine	19	(3.7)	13	(4.6)	32	(4.1)
Sodium Alginate (+) Sodium Bicarbonate	0	(0.0)	1	(0.4)	1	(0.1)
Sucralfate	1	(0.2)	0	(0.0)	1	(0.1)
Drugs For Functional Gastrointestinal Disorders	51	(10.1)	31	(11.0)	82	(10.4)
Alizapride	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Atropine	1	(0.2)	0	(0.0)	1	(0.1)
Atropine Sulfate (+) Diphenoxylate Hydrochloride	28	(5.5)	9	(3.2)	37	(4.7)
Belladonna	1	(0.2)	0	(0.0)	1	(0.1)
Bromopride	0	(0.0)	1	(0.4)	1	(0.1)
Butylscopolamine Bromide	3	(0.6)	3	(1.1)	6	(0.8)
Butylscopolamine Bromide (+) Dipyrone	1	(0.2)	0	(0.0)	1	(0.1)
Caffeine (+) Dipyrone (+) Isometheptene Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Charcoal, Activated (+) Dimethicone	0	(0.0)	1	(0.4)	1	(0.1)
Clonixin Lysine (+) Pargeverine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Dicyclomine Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Dimethicone	0	(0.0)	2	(0.7)	2	(0.3)
Dimethicone (+) Pancreatin	1	(0.2)	0	(0.0)	1	(0.1)
Dipenine Bromide	0	(0.0)	1	(0.4)	1	(0.1)
Dipyrone Magnesium (+) Pargeverine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Domperidone	2	(0.4)	3	(1.1)	5	(0.6)
Glycopyrrolate	0	(0.0)	1	(0.4)	1	(0.1)
Hyoscyamine	3	(0.6)	1	(0.4)	4	(0.5)
Metoclopramide	10	(2.0)	14	(5.0)	24	(3.0)
Pargeverine	1	(0.2)	0	(0.0)	1	(0.1)
Phloroglucinol	0	(0.0)	1	(0.4)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Phloroglucinol (+) Trimethylphloroglucinol	1	(0.2)	0	(0.0)	1	(0.1)
Propantheline Bromide	0	(0.0)	1	(0.4)	1	(0.1)
Simethicone	1	(0.2)	3	(1.1)	4	(0.5)
Trimebutine	0	(0.0)	1	(0.4)	1	(0.1)
Drugs Used In Diabetes	43	(8.5)	23	(8.2)	66	(8.4)
Gliclazide	1	(0.2)	0	(0.0)	1	(0.1)
Glimepiride	1	(0.2)	1	(0.4)	2	(0.3)
Glipizide	4	(0.8)	2	(0.7)	6	(0.8)
Glyburide	10	(2.0)	3	(1.1)	13	(1.6)
Insulin	8	(1.6)	8	(2.8)	16	(2.0)
Insulin Glargine	7	(1.4)	3	(1.1)	10	(1.3)
Insulin, Biphasic Isophane [Injection]	2	(0.4)	1	(0.4)	3	(0.4)
Insulin, Isophane	1	(0.2)	1	(0.4)	2	(0.3)
Metformin	18	(3.6)	9	(3.2)	27	(3.4)
Metformin Hydrochloride (+) Rosiglitazone Maleate	1	(0.2)	0	(0.0)	1	(0.1)
Pioglitazone Hydrochloride	3	(0.6)	1	(0.4)	4	(0.5)
Repaglinide	1	(0.2)	0	(0.0)	1	(0.1)
Rosiglitazone Maleate	7	(1.4)	3	(1.1)	10	(1.3)
Tolbutamide	1	(0.2)	0	(0.0)	1	(0.1)
Laxatives	21	(4.1)	13	(4.6)	34	(4.3)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Acacia (+) Barley (+) Dandelion (+) Ginger (+) Oat (+) Pectin (+) Psyllium Husk (+) Senna (+) Red Clover	0	(0.0)	1	(0.4)	1	(0.1)
Bisacodyl	1	(0.2)	0	(0.0)	1	(0.1)
Calcium Polycarbophil	1	(0.2)	1	(0.4)	2	(0.3)
Docusate Sodium	4	(0.8)	2	(0.7)	6	(0.8)
Docusate Sodium (+) Senna	0	(0.0)	3	(1.1)	3	(0.4)
Flaxseed	6	(1.2)	1	(0.4)	7	(0.9)
Lactulose	1	(0.2)	2	(0.7)	3	(0.4)
Mineral Oil	0	(0.0)	1	(0.4)	1	(0.1)
Plantago Seed	1	(0.2)	0	(0.0)	1	(0.1)
Polyethylene Glycol 3350	1	(0.2)	0	(0.0)	1	(0.1)
Polyethylene Glycol 3350 (+) Potassium Chloride (+) Sodium Bicarbonate (+) Sodium Chloride	0	(0.0)	1	(0.4)	1	(0.1)
Psyllium Husk	2	(0.4)	4	(1.4)	6	(0.8)
Senna	2	(0.4)	0	(0.0)	2	(0.3)
Senna (+) Tamarind	1	(0.2)	0	(0.0)	1	(0.1)
Sodium Phosphate, Dibasic (+) Sodium Phosphate, Monobasic	1	(0.2)	0	(0.0)	1	(0.1)
Sodium Picosulfate	1	(0.2)	0	(0.0)	1	(0.1)
Sorbitol	1	(0.2)	0	(0.0)	1	(0.1)
Sterculia	0	(0.0)	1	(0.4)	1	(0.1)

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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Mineral Supplements	39	(7.7)	14	(5.0)	53	(6.7)
Calcium (Unspecified)	13	(2.6)	4	(1.4)	17	(2.2)
Calcium (Unspecified) (+) Magnesium (Unspecified)	1	(0.2)	1	(0.4)	2	(0.3)
Calcium (Unspecified) (+) Magnesium (Unspecified) (+) Zinc (Unspecified)	0	(0.0)	1	(0.4)	1	(0.1)
Calcium Carbonate (+) Calcium Glubionate	1	(0.2)	0	(0.0)	1	(0.1)
Calcium Carbonate (+) Cholecalciferol	1	(0.2)	0	(0.0)	1	(0.1)
Calcium Carbonate (+) Vitamin D (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Chromic Chloride	1	(0.2)	0	(0.0)	1	(0.1)
Magnesium (Unspecified)	3	(0.6)	2	(0.7)	5	(0.6)
Potassium (Unspecified)	15	(3.0)	5	(1.8)	20	(2.5)
Potassium Bicarbonate (+) Potassium Chloride	1	(0.2)	0	(0.0)	1	(0.1)
Selenium (Unspecified)	3	(0.6)	1	(0.4)	4	(0.5)
Sodium Chloride	6	(1.2)	2	(0.7)	8	(1.0)
Zinc (Unspecified)	4	(0.8)	1	(0.4)	5	(0.6)
Other Alimentary Tract And Metabolism Products	10	(2.0)	5	(1.8)	15	(1.9)
Alpha Galactosidase A	0	(0.0)	1	(0.4)	1	(0.1)
Anethole Trithione	1	(0.2)	0	(0.0)	1	(0.1)
Arginine (+) Beta-Hydroxyisovaleric Acid (+) Levoglutamide	3	(0.6)	0	(0.0)	3	(0.4)
Gastrointestinal Preparations (Unspecified)	0	(0.0)	1	(0.4)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Levocarnitine	4	(0.8)	1	(0.4)	5	(0.6)
Levoglutamide	2	(0.4)	2	(0.7)	4	(0.5)
Lysine	1	(0.2)	0	(0.0)	1	(0.1)
Stomatological Preparations	4	(0.8)	1	(0.4)	5	(0.6)
Aluminum Hydroxide (+) Diphenhydramine Hydrochloride (+) Lidocaine (+) Magnesium Hydroxide (+) Nystatin	1	(0.2)	0	(0.0)	1	(0.1)
Chlorhexidine Gluconate (+) Chlorobutanol (+) Chloroform (+) Docusate Sodium	1	(0.2)	0	(0.0)	1	(0.1)
Chlorhexidine Gluconate (+) Tixocortol Pivalate	1	(0.2)	0	(0.0)	1	(0.1)
Chlorobutanol (+) Choline Salicylate (+) Hexetidine	1	(0.2)	0	(0.0)	1	(0.1)
Copovidone (+) Cetylpyridinium Chloride (+) Methylparaben (+) Sodium Benzoate (+) Sodium Phosphate, Dibasic (+) Sorbitol	0	(0.0)	1	(0.4)	1	(0.1)
Hexetidine	1	(0.2)	0	(0.0)	1	(0.1)
Vitamins	99	(19.5)	50	(17.7)	149	(18.9)
Amino Acids (Unspecified) (+) Bilberry (+) Folic Acid (+) Ginkgo (+) Horsetail (+) Minerals (Unspecified) (+) Quercetin (+) Thioctic Acid (+) Vitamins (Unspecified) (+) Xanthophyll (+) Zeaxanthin	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Amino Acids (Unspecified) (+) Minerals (Unspecified) (+) Vitamins (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Aminobenzoic Acid (+) Biotin (+) Choline (+) Folic Acid (+) Inositol (+) Pantothenic Acid (+) Taurine (+) Vitamin B Complex	1	(0.2)	0	(0.0)	1	(0.1)
Antioxidants (Unspecified) (+) Bioflavonoids (+) Minerals (Unspecified) (+) Vitamins (Unspecified)	1	(0.2)	1	(0.4)	2	(0.3)
Antioxidants (Unspecified) (+) Digestive Enzymes (+) Minerals (Unspecified) (+) Vitamins (Unspecified)	2	(0.4)	0	(0.0)	2	(0.3)
Ascorbic Acid	14	(2.8)	11	(3.9)	25	(3.2)
Ascorbic Acid (+) Betaine Hydrochloride (+) Calcium (Unspecified) (+) Cholecalciferol (+) Folic Acid (+) Minerals (Unspecified) (+) Phytonadione (+) Silicon (+) Strontium Chloride (+) Vitamin B Complex	1	(0.2)	0	(0.0)	1	(0.1)
Ascorbic Acid (+) Calcium Phosphate, Tribasic (+) Cholecalciferol (+) Copper Sulfate (+) Iron (Unspecified) (+) Magnesium Sulfate (+) Vitamin A Palmitate (+) Vitamin B Complex (+) Vitamin E (+) Zinc Sulfate	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Ascorbic Acid (+) Folic Acid (+) Vitamin B Complex	0	(0.0)	2	(0.7)	2	(0.3)
Ascorbic Acid (+) Ginseng (Unspecified) (+) Hawthorn (+) Kola (+) Lemon (+) Pyridoxine (+) Sodium Chloride (+) Thiamine	1	(0.2)	0	(0.0)	1	(0.1)
Ascorbic Acid (+) Vitamin A Palmitate (+) Vitamin E Acetate	0	(0.0)	1	(0.4)	1	(0.1)
Calcium (Unspecified) (+) Vitamins (Unspecified)	0	(0.0)	1	(0.4)	1	(0.1)
Calcium Ascorbate	0	(0.0)	1	(0.4)	1	(0.1)
Cholecalciferol (+) Vitamin A	1	(0.2)	0	(0.0)	1	(0.1)
Cod Liver Oil	1	(0.2)	0	(0.0)	1	(0.1)
Cyanocobalamin (+) Pyridoxine (+) Thiamine	2	(0.4)	0	(0.0)	2	(0.3)
Cyanocobalamin (+) Pyridoxine Hydrochloride (+) Thiamine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Dexpanthenol	2	(0.4)	1	(0.4)	3	(0.4)
Minerals (Unspecified) (+) Vitamins (Unspecified)	5	(1.0)	4	(1.4)	9	(1.1)
Pyridoxine	4	(0.8)	0	(0.0)	4	(0.5)
Thiamine	4	(0.8)	1	(0.4)	5	(0.6)
Vitamin A	1	(0.2)	0	(0.0)	1	(0.1)
Vitamin B (Unspecified)	2	(0.4)	2	(0.7)	4	(0.5)
Vitamin B Complex	11	(2.2)	4	(1.4)	15	(1.9)
Vitamin D (Unspecified)	7	(1.4)	1	(0.4)	8	(1.0)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Vitamin E	5	(1.0)	3	(1.1)	8	(1.0)
Vitamins (Unspecified)	65	(12.8)	29	(10.3)	94	(11.9)
Antiinfectives For Systemic Use						
Antibacterials For Systemic Use	315	(62.1)	182	(64.5)	497	(63.0)
Amdinocillin	0	(0.0)	1	(0.4)	1	(0.1)
Amikacin	3	(0.6)	0	(0.0)	3	(0.4)
Amoxicillin	18	(3.6)	10	(3.5)	28	(3.5)
Amoxicillin (+) Clavulanate Potassium	31	(6.1)	10	(3.5)	41	(5.2)
Ampicillin	1	(0.2)	0	(0.0)	1	(0.1)
Ampicillin Sodium (+) Sulbactam Sodium	3	(0.6)	0	(0.0)	3	(0.4)
Antimicrobial (Unspecified)	0	(0.0)	1	(0.4)	1	(0.1)
Azithromycin	103	(20.3)	55	(19.5)	158	(20.0)
Cefaclor	1	(0.2)	0	(0.0)	1	(0.1)
Cefadroxil	1	(0.2)	1	(0.4)	2	(0.3)
Cefazolin	1	(0.2)	3	(1.1)	4	(0.5)
Cefepime	2	(0.4)	1	(0.4)	3	(0.4)
Cefixime	2	(0.4)	0	(0.0)	2	(0.3)
Ceftazidime	1	(0.2)	1	(0.4)	2	(0.3)
Ceftriaxone Sodium	11	(2.2)	2	(0.7)	13	(1.6)
Cefuroxime	6	(1.2)	4	(1.4)	10	(1.3)
Cephalexin	13	(2.6)	6	(2.1)	19	(2.4)
Chloramphenicol	2	(0.4)	1	(0.4)	3	(0.4)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Ciprofloxacin	30	(5.9)	14	(5.0)	44	(5.6)
Clarithromycin	15	(3.0)	9	(3.2)	24	(3.0)
Clemizole Penicillin	0	(0.0)	1	(0.4)	1	(0.1)
Clindamycin	14	(2.8)	5	(1.8)	19	(2.4)
Daptomycin	1	(0.2)	0	(0.0)	1	(0.1)
Dicloxacillin	5	(1.0)	5	(1.8)	10	(1.3)
Doxycycline	12	(2.4)	7	(2.5)	19	(2.4)
Erythromycin	5	(1.0)	2	(0.7)	7	(0.9)
Fosfomycin	2	(0.4)	0	(0.0)	2	(0.3)
Fusidate Sodium	4	(0.8)	2	(0.7)	6	(0.8)
Gentamicin	2	(0.4)	1	(0.4)	3	(0.4)
Levofloxacin	22	(4.3)	11	(3.9)	33	(4.2)
Linezolid	1	(0.2)	0	(0.0)	1	(0.1)
Meropenem	1	(0.2)	0	(0.0)	1	(0.1)
Metronidazole	17	(3.4)	10	(3.5)	27	(3.4)
Minocycline	3	(0.6)	1	(0.4)	4	(0.5)
Moxifloxacin Hydrochloride	14	(2.8)	13	(4.6)	27	(3.4)
Netilmicin Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Nifurtoinol	1	(0.2)	0	(0.0)	1	(0.1)
Nitrofurantoin	0	(0.0)	1	(0.4)	1	(0.1)
Norfloxacin	0	(0.0)	6	(2.1)	6	(0.8)
Ofloxacin	5	(1.0)	1	(0.4)	6	(0.8)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Oxytetracycline	1	(0.2)	0	(0.0)	1	(0.1)
Penicillin (Unspecified)	7	(1.4)	2	(0.7)	9	(1.1)
Penicillin G	1	(0.2)	1	(0.4)	2	(0.3)
Penicillin V	2	(0.4)	1	(0.4)	3	(0.4)
Penicillin V Potassium	1	(0.2)	0	(0.0)	1	(0.1)
Piperacillin	1	(0.2)	0	(0.0)	1	(0.1)
Piperacillin Sodium (+) Tazobactam Sodium	5	(1.0)	0	(0.0)	5	(0.6)
Pivampicillin	1	(0.2)	0	(0.0)	1	(0.1)
Pristinamycin	2	(0.4)	0	(0.0)	2	(0.3)
Roxithromycin	2	(0.4)	3	(1.1)	5	(0.6)
Sulfadiazine	5	(1.0)	2	(0.7)	7	(0.9)
Sulfamethazone (+) Trimethoprim	0	(0.0)	1	(0.4)	1	(0.1)
Sulfamethoxazole	0	(0.0)	1	(0.4)	1	(0.1)
Sulfamethoxazole (+) Trimethoprim	181	(35.7)	115	(40.8)	296	(37.5)
Sultamicillin	1	(0.2)	0	(0.0)	1	(0.1)
Telithromycin	4	(0.8)	0	(0.0)	4	(0.5)
Tetracycline	3	(0.6)	0	(0.0)	3	(0.4)
Tigecycline	1	(0.2)	0	(0.0)	1	(0.1)
Tinidazole	0	(0.0)	1	(0.4)	1	(0.1)
Tobramycin	2	(0.4)	1	(0.4)	3	(0.4)
Trimethoprim	1	(0.2)	1	(0.4)	2	(0.3)
Vancomycin	7	(1.4)	1	(0.4)	8	(1.0)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category—Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Antimycobacterials	44	(8.7)	24	(8.5)	68	(8.6)
Dapsone	30	(5.9)	16	(5.7)	46	(5.8)
Ethambutol Hydrochloride	14	(2.8)	7	(2.5)	21	(2.7)
Isoniazid	4	(0.8)	1	(0.4)	5	(0.6)
Pyrazinamide	2	(0.4)	0	(0.0)	2	(0.3)
Rifabutin	4	(0.8)	1	(0.4)	5	(0.6)
Rifampin	2	(0.4)	0	(0.0)	2	(0.3)
Rifamycin	0	(0.0)	1	(0.4)	1	(0.1)
Antimycotics For Systemic Use	103	(20.3)	78	(27.7)	181	(22.9)
Amphotericin B	7	(1.4)	5	(1.8)	12	(1.5)
Amphotericin B (+) L-(Alpha)-Dimyristoylphosphatidylcholine (+) L-(Alpha)-Dimyristoylphosphatidylglycerol	1	(0.2)	0	(0.0)	1	(0.1)
Caspofungin Acetate	3	(0.6)	4	(1.4)	7	(0.9)
Fluconazole	87	(17.2)	69	(24.5)	156	(19.8)
Itraconazole	8	(1.6)	2	(0.7)	10	(1.3)
Micafungin Sodium	1	(0.2)	0	(0.0)	1	(0.1)
Posaconazole	0	(0.0)	1	(0.4)	1	(0.1)
Voriconazole	4	(0.8)	3	(1.1)	7	(0.9)
Antivirals For Systemic Use	140	(27.6)	75	(26.6)	215	(27.2)
Acyclovir	67	(13.2)	33	(11.7)	100	(12.7)
Brivudine	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Cidofovir	1	(0.2)	2	(0.7)	3	(0.4)
Famciclovir	6	(1.2)	6	(2.1)	12	(1.5)
Foscarnet Sodium	5	(1.0)	3	(1.1)	8	(1.0)
Ganciclovir	5	(1.0)	3	(1.1)	8	(1.0)
Ganciclovir Sodium	0	(0.0)	1	(0.4)	1	(0.1)
Penciclovir	1	(0.2)	0	(0.0)	1	(0.1)
Valacyclovir Hydrochloride	59	(11.6)	28	(9.9)	87	(11.0)
Valganciclovir Hydrochloride	18	(3.6)	7	(2.5)	25	(3.2)
Immune Sera And Immunoglobulins	5	(1.0)	2	(0.7)	7	(0.9)
Globulin, Immune	5	(1.0)	2	(0.7)	7	(0.9)
Vaccines	46	(9.1)	24	(8.5)	70	(8.9)
Diphtheria Toxoid (+) Pertussis Vaccine (Unspecified) (+) Tetanus Toxoid	1	(0.2)	0	(0.0)	1	(0.1)
Diphtheria Toxoid (+) Poliovirus Vaccine Inactivated (Unspecified) (+) Tetanus Toxoid	0	(0.0)	1	(0.4)	1	(0.1)
Diphtheria Toxoid (+) Tetanus Toxoid	1	(0.2)	0	(0.0)	1	(0.1)
Hepatitis A Virus Vaccine (Unspecified)	2	(0.4)	0	(0.0)	2	(0.3)
Hepatitis A Virus Vaccine Inactivated	2	(0.4)	0	(0.0)	2	(0.3)
Hepatitis A Virus Vaccine Inactivated (+) Hepatitis B Virus Vaccine Rhbsag (Yeast)	1	(0.2)	0	(0.0)	1	(0.1)
Hepatitis B Virus Vaccine (Unspecified)	2	(0.4)	0	(0.0)	2	(0.3)
Hepatitis B Virus Vaccine Rhbsag (Yeast)	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Influenza Virus Sag 3v Vaccine Inactivated	1	(0.2)	1	(0.4)	2	(0.3)
Influenza Virus Sag 3v Virosome Vaccine Inactivated	1	(0.2)	0	(0.0)	1	(0.1)
Influenza Virus Split Virion 3v Vaccine Inactivated	8	(1.6)	5	(1.8)	13	(1.6)
Influenza Virus Vaccine (Unspecified)	26	(5.1)	15	(5.3)	41	(5.2)
Influenza Virus Whole Virion 3v Vaccine Inactivated	2	(0.4)	1	(0.4)	3	(0.4)
Pneumococcal 23v Polysaccharide Vaccine	1	(0.2)	2	(0.7)	3	(0.4)
Pneumococcal Vaccine (Unspecified)	1	(0.2)	1	(0.4)	2	(0.3)
Tetanus Toxoid	3	(0.6)	1	(0.4)	4	(0.5)
Tick-Borne Encephalitis Virus Vaccine	1	(0.2)	0	(0.0)	1	(0.1)
Antineoplastic And Immunomodulating Agents						
Antineoplastic Agents	7	(1.4)	2	(0.7)	9	(1.1)
Capecitabine	1	(0.2)	0	(0.0)	1	(0.1)
Cyclophosphamide (+) Doxorubicin (+) Prednisone (+) Rituximab (+) Vincristine Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Cytarabine	1	(0.2)	0	(0.0)	1	(0.1)
Doxorubicin	1	(0.2)	0	(0.0)	1	(0.1)
Fluorouracil	4	(0.8)	2	(0.7)	6	(0.8)
Methotrexate	1	(0.2)	0	(0.0)	1	(0.1)
Mitomycin	1	(0.2)	0	(0.0)	1	(0.1)
Oxaliplatin	2	(0.4)	0	(0.0)	2	(0.3)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Endocrine Therapy	6	(1.2)	5	(1.8)	11	(1.4)
Megestrol Acetate	6	(1.2)	5	(1.8)	11	(1.4)
Immunomodulators/-Stimulants	15	(3.0)	10	(3.5)	25	(3.2)
Filgrastim	11	(2.2)	9	(3.2)	20	(2.5)
Granulocyte Colony Stimulating Factor (Unspecified)	4	(0.8)	0	(0.0)	4	(0.5)
Lenograstim	1	(0.2)	0	(0.0)	1	(0.1)
Pegfilgrastim	1	(0.2)	1	(0.4)	2	(0.3)
Immunomodulators/-Suppressants	2	(0.4)	0	(0.0)	2	(0.3)
Thalidomide	2	(0.4)	0	(0.0)	2	(0.3)
Antiparasitic Products, Insecticides, And Repellents						
Anthelmintics	3	(0.6)	2	(0.7)	5	(0.6)
Albendazole	2	(0.4)	1	(0.4)	3	(0.4)
Ivermectin	1	(0.2)	1	(0.4)	2	(0.3)
Antiprotozoals	48	(9.5)	31	(11.0)	79	(10.0)
Atovaquone	17	(3.4)	7	(2.5)	24	(3.0)
Dapsone (+) Pyrimethamine	1	(0.2)	0	(0.0)	1	(0.1)
Hydroxychloroquine Sulfate	0	(0.0)	1	(0.4)	1	(0.1)
Nitazoxanide	0	(0.0)	2	(0.7)	2	(0.3)
Nitromide	1	(0.2)	0	(0.0)	1	(0.1)
Pentamidine Isetionate	19	(3.7)	8	(2.8)	27	(3.4)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Primaquine Phosphate	1	(0.2)	0	(0.0)	1	(0.1)
Pyrimethamine	11	(2.2)	9	(3.2)	20	(2.5)
Pyrimethamine (+) Sulfadoxine	1	(0.2)	0	(0.0)	1	(0.1)
Quinfamide	1	(0.2)	0	(0.0)	1	(0.1)
Quinine	1	(0.2)	2	(0.7)	3	(0.4)
Secnidazole	0	(0.0)	2	(0.7)	2	(0.3)
Ectoparasticides, Incl. Scabicides, Insecticides And Repellents	3	(0.6)	1	(0.4)	4	(0.5)
Lindane	1	(0.2)	0	(0.0)	1	(0.1)
Permethrin	2	(0.4)	1	(0.4)	3	(0.4)
Blood And Blood Forming Organs						
Antianemic Preparations	48	(9.5)	29	(10.3)	77	(9.8)
Ascorbic Acid (+) Ferrous Gluconate	1	(0.2)	0	(0.0)	1	(0.1)
Ascorbic Acid (+) Ferrous Sulfate (+) Folic Acid (+) Vitamin B Complex	1	(0.2)	0	(0.0)	1	(0.1)
Calcium L-Methylfolate	0	(0.0)	1	(0.4)	1	(0.1)
Carbonyl Iron	1	(0.2)	0	(0.0)	1	(0.1)
Cyanocobalamin	14	(2.8)	10	(3.5)	24	(3.0)
Cyanocobalamin (+) Folic Acid (+) Pyridoxine Hydrochloride	1	(0.2)	2	(0.7)	3	(0.4)
Darbepoetin Alfa	1	(0.2)	2	(0.7)	3	(0.4)
Epoetin	2	(0.4)	0	(0.0)	2	(0.3)
Epoetin Alfa	7	(1.4)	2	(0.7)	9	(1.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Epoetin Beta	0	(0.0)	1	(0.4)	1	(0.1)
Ferrous Fumarate	1	(0.2)	0	(0.0)	1	(0.1)
Ferrous Glycine Sulfate	2	(0.4)	2	(0.7)	4	(0.5)
Ferrous Sulfate	9	(1.8)	2	(0.7)	11	(1.4)
Folic Acid	12	(2.4)	12	(4.3)	24	(3.0)
Hydroxocobalamin	1	(0.2)	1	(0.4)	2	(0.3)
Iron (Unspecified)	2	(0.4)	2	(0.7)	4	(0.5)
Iron (Unspecified) (+) Vitamins (Unspecified)	2	(0.4)	0	(0.0)	2	(0.3)
Antihemorrhagics	5	(1.0)	1	(0.4)	6	(0.8)
Collagen	1	(0.2)	0	(0.0)	1	(0.1)
Factor Ix	1	(0.2)	0	(0.0)	1	(0.1)
Factor Viii	2	(0.4)	0	(0.0)	2	(0.3)
Platelet Concentrate	1	(0.2)	1	(0.4)	2	(0.3)
Antithrombotic Agents	24	(4.7)	14	(5.0)	38	(4.8)
Acenocoumarol	1	(0.2)	0	(0.0)	1	(0.1)
Aspirin (+) Dipyridamole	0	(0.0)	1	(0.4)	1	(0.1)
Clopidogrel Bisulfate	3	(0.6)	7	(2.5)	10	(1.3)
Dipyridamole	1	(0.2)	0	(0.0)	1	(0.1)
Enoxaparin Sodium	9	(1.8)	4	(1.4)	13	(1.6)
Eptifibatide	0	(0.0)	1	(0.4)	1	(0.1)
Heparin	1	(0.2)	2	(0.7)	3	(0.4)
Heparinoid	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Nadroparin	1	(0.2)	0	(0.0)	1	(0.1)
Phenprocoumon	1	(0.2)	0	(0.0)	1	(0.1)
Tenecteplase	1	(0.2)	0	(0.0)	1	(0.1)
Ticlopidine Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Tinzaparin Sodium	1	(0.2)	0	(0.0)	1	(0.1)
Warfarin	7	(1.4)	2	(0.7)	9	(1.1)
Blood Substitutes And Perfusion Solutions	14	(2.8)	3	(1.1)	17	(2.2)
Amino Acids (Unspecified) (+) Carbohydrates (Unspecified) (+) Electrolytes (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Ammonium Lactate	1	(0.2)	1	(0.4)	2	(0.3)
Blood Cells, Red	4	(0.8)	0	(0.0)	4	(0.5)
Dextrose (+) Electrolytes (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Dextrose (+) Sodium Chloride	1	(0.2)	0	(0.0)	1	(0.1)
Electrolytes (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Glucose-1-Phosphate Disodium	1	(0.2)	0	(0.0)	1	(0.1)
Nitrofurazone	0	(0.0)	1	(0.4)	1	(0.1)
Potassium Bicarbonate (+) Sodium Bicarbonate (+) Sodium Phosphate, Monobasic	1	(0.2)	0	(0.0)	1	(0.1)
Potassium Phosphate, Dibasic (+) Potassium Phosphate, Monobasic (+) Sodium Phosphate, Dibasic (+) Sodium Phosphate, Monobasic	2	(0.4)	0	(0.0)	2	(0.3)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Potassium Phosphate, Monobasic (+) Sodium Phosphate, Dibasic (+) Sodium Phosphate, Monobasic	0	(0.0)	1	(0.4)	1	(0.1)
Sodium Bicarbonate	1	(0.2)	0	(0.0)	1	(0.1)
Sodium Phosphate, Monobasic	1	(0.2)	0	(0.0)	1	(0.1)
Other Hematological Agents	1	(0.2)	0	(0.0)	1	(0.1)
Hyaluronidase (Ovine)	1	(0.2)	0	(0.0)	1	(0.1)
Cardiovascular System						
Agents Acting On The Renin-Angiotensin System	63	(12.4)	32	(11.3)	95	(12.0)
Benazepril Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Candesartan	1	(0.2)	1	(0.4)	2	(0.3)
Captopril	4	(0.8)	0	(0.0)	4	(0.5)
Enalapril Maleate	10	(2.0)	4	(1.4)	14	(1.8)
Enalapril Maleate (+) Hydrochlorothiazide	1	(0.2)	0	(0.0)	1	(0.1)
Fosinopril Sodium	0	(0.0)	1	(0.4)	1	(0.1)
Hydrochlorothiazide (+) Irbesartan	1	(0.2)	3	(1.1)	4	(0.5)
Hydrochlorothiazide (+) Ramipril	1	(0.2)	0	(0.0)	1	(0.1)
Hydrochlorothiazide (+) Valsartan	1	(0.2)	0	(0.0)	1	(0.1)
Irbesartan	1	(0.2)	3	(1.1)	4	(0.5)
Lisinopril	27	(5.3)	10	(3.5)	37	(4.7)
Losartan Potassium	1	(0.2)	0	(0.0)	1	(0.1)
Olmesartan Medoxomil	0	(0.0)	1	(0.4)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Perindopril	6	(1.2)	3	(1.1)	9	(1.1)
Quinapril Hydrochloride	0	(0.0)	2	(0.7)	2	(0.3)
Ramipril	8	(1.6)	1	(0.4)	9	(1.1)
Telmisartan	0	(0.0)	1	(0.4)	1	(0.1)
Trandolapril	0	(0.0)	1	(0.4)	1	(0.1)
Valsartan	1	(0.2)	3	(1.1)	4	(0.5)
Antihypertensives	4	(0.8)	1	(0.4)	5	(0.6)
Clonidine	1	(0.2)	1	(0.4)	2	(0.3)
Hydralazine	1	(0.2)	0	(0.0)	1	(0.1)
Hydrochlorothiazide (+) Reserpine	1	(0.2)	0	(0.0)	1	(0.1)
Terazosin Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Beta Blocking Agents	42	(8.3)	19	(6.7)	61	(7.7)
Atenolol	10	(2.0)	8	(2.8)	18	(2.3)
Bisoprolol	6	(1.2)	2	(0.7)	8	(1.0)
Carvedilol	3	(0.6)	1	(0.4)	4	(0.5)
Metoprolol	16	(3.2)	6	(2.1)	22	(2.8)
Propranolol Hydrochloride	6	(1.2)	1	(0.4)	7	(0.9)
Sotalol Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Timolol	2	(0.4)	0	(0.0)	2	(0.3)
Calcium Channel Blockers	11	(2.2)	5	(1.8)	16	(2.0)
Amlodipine Besylate	8	(1.6)	3	(1.1)	11	(1.4)
Diltiazem Hydrochloride	1	(0.2)	1	(0.4)	2	(0.3)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Felodipine	1	(0.2)	0	(0.0)	1	(0.1)
Nicardipine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Nifedipine	2	(0.4)	1	(0.4)	3	(0.4)
Cardiac Therapy	7	(1.4)	8	(2.8)	15	(1.9)
Alprostadil	1	(0.2)	2	(0.7)	3	(0.4)
Calcium Lactate (+) Hawthorn (+) Lemon Balm (+) Magnesium Thiosulfate	0	(0.0)	1	(0.4)	1	(0.1)
Digoxin	0	(0.0)	1	(0.4)	1	(0.1)
Dopamine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Isosorbide Dinitrate	1	(0.2)	1	(0.4)	2	(0.3)
Isosorbide Mononitrate	1	(0.2)	0	(0.0)	1	(0.1)
Nitroglycerin	2	(0.4)	1	(0.4)	3	(0.4)
Ubidecarenone	3	(0.6)	1	(0.4)	4	(0.5)
Diuretics	20	(3.9)	14	(5.0)	34	(4.3)
Bendroflumethiazide (+) Potassium Chloride	1	(0.2)	1	(0.4)	2	(0.3)
Furosemide	3	(0.6)	5	(1.8)	8	(1.0)
Hydrochlorothiazide	12	(2.4)	6	(2.1)	18	(2.3)
Hydrochlorothiazide (+) Triamterene	4	(0.8)	0	(0.0)	4	(0.5)
Indapamide	1	(0.2)	2	(0.7)	3	(0.4)
Metolazone	1	(0.2)	0	(0.0)	1	(0.1)
Spironolactone	1	(0.2)	0	(0.0)	1	(0.1)
Torsemide	0	(0.0)	1	(0.4)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Lipid Modifying Agents	119	(23.5)	68	(24.1)	187	(23.7)
Atorvastatin Calcium	32	(6.3)	18	(6.4)	50	(6.3)
Bezafibrate	9	(1.8)	3	(1.1)	12	(1.5)
Cholestyramine Resin	1	(0.2)	0	(0.0)	1	(0.1)
Ciprofibrate	0	(0.0)	1	(0.4)	1	(0.1)
Docosahexaenoic Acid (+) Eicosapentaenoic Acid	1	(0.2)	0	(0.0)	1	(0.1)
Ezetimibe	3	(0.6)	4	(1.4)	7	(0.9)
Fenofibrate	34	(6.7)	23	(8.2)	57	(7.2)
Fluvastatin Sodium	0	(0.0)	3	(1.1)	3	(0.4)
Gemfibrozil	16	(3.2)	10	(3.5)	26	(3.3)
Niacin	4	(0.8)	3	(1.1)	7	(0.9)
Omega-3 Acid Ethyl Esters	4	(0.8)	1	(0.4)	5	(0.6)
Omega-3 Marine Triglycerides	15	(3.0)	9	(3.2)	24	(3.0)
Pravastatin Sodium	23	(4.5)	15	(5.3)	38	(4.8)
Rosuvastatin Calcium	14	(2.8)	4	(1.4)	18	(2.3)
Simvastatin	1	(0.2)	1	(0.4)	2	(0.3)
Perpheral Vasodilators	3	(0.6)	1	(0.4)	4	(0.5)
Buflomedil	1	(0.2)	1	(0.4)	2	(0.3)
Nafronyl Oxalate	1	(0.2)	0	(0.0)	1	(0.1)
Pentoxifylline	1	(0.2)	0	(0.0)	1	(0.1)
Vasoprotectives	3	(0.6)	3	(1.1)	6	(0.8)
Bioflavonoids	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Bismuth Subgallate (+) Bufexamac (+) Lidocaine Hydrochloride (+) Titanium Dioxide	0	(0.0)	1	(0.4)	1	(0.1)
Clemizole Undecanoate (+) Dibucaine Hydrochloride (+) Prednisolone Hexanoate	1	(0.2)	0	(0.0)	1	(0.1)
Diosmin	0	(0.0)	2	(0.7)	2	(0.3)
Ruscogenin (+) Trimebutine	1	(0.2)	0	(0.0)	1	(0.1)
Rutin	1	(0.2)	0	(0.0)	1	(0.1)
Dermatologicals						
Anti-Acne Preparations	2	(0.4)	1	(0.4)	3	(0.4)
Isotretinoin	1	(0.2)	0	(0.0)	1	(0.1)
Tretinoin	1	(0.2)	1	(0.4)	2	(0.3)
Antibiotics And Chemotherapeutics For Dermatological Use	29	(5.7)	7	(2.5)	36	(4.6)
Bacitracin Zinc (+) Neomycin Sulfate (+) Polymyxin B Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Imiquimod	17	(3.4)	5	(1.8)	22	(2.8)
Mupirocin	6	(1.2)	1	(0.4)	7	(0.9)
Mupirocin Calcium	0	(0.0)	1	(0.4)	1	(0.1)
Podofilox	2	(0.4)	1	(0.4)	3	(0.4)
Podophyllum	4	(0.8)	0	(0.0)	4	(0.5)
Sulfadiazine, Silver	0	(0.0)	1	(0.4)	1	(0.1)
Antifungals For Dermatological Use	57	(11.2)	28	(9.9)	85	(10.8)
Amorolfine	0	(0.0)	1	(0.4)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Betamethasone Dipropionate (+) Clotrimazole	5	(1.0)	2	(0.7)	7	(0.9)
Butenafine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Ciclopirox	3	(0.6)	1	(0.4)	4	(0.5)
Clotrimazole	9	(1.8)	8	(2.8)	17	(2.2)
Clotrimazole (+) Hydrocortisone	1	(0.2)	0	(0.0)	1	(0.1)
Econazole	2	(0.4)	1	(0.4)	3	(0.4)
Econazole Nitrate (+) Triamcinolone Acetonide	1	(0.2)	0	(0.0)	1	(0.1)
Flucytosine	0	(0.0)	1	(0.4)	1	(0.1)
Ketoconazole	12	(2.4)	4	(1.4)	16	(2.0)
Miconazole	5	(1.0)	4	(1.4)	9	(1.1)
Nystatin	15	(3.0)	4	(1.4)	19	(2.4)
Selenium Sulfide	1	(0.2)	0	(0.0)	1	(0.1)
Sertaconazole Nitrate	0	(0.0)	1	(0.4)	1	(0.1)
Terbinafine	5	(1.0)	2	(0.7)	7	(0.9)
Tolnaftate	0	(0.0)	1	(0.4)	1	(0.1)
Antipruritics, Incl. Antihistamines, Anesthetics, Etc.	5	(1.0)	2	(0.7)	7	(0.9)
Calamine	1	(0.2)	0	(0.0)	1	(0.1)
Calamine (+) Camphor (+) Pramoxine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Calamine (+) Lanolin (+) Menthol (+) Zinc Oxide	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Camphor (+) Chlorpheniramine Maleate (+) Hexachlorophene (+) Lidocaine Hydrochloride (+) Menthol (+) Methyl Salicylate	0	(0.0)	1	(0.4)	1	(0.1)
Crotamiton	1	(0.2)	0	(0.0)	1	(0.1)
Dibucaine	0	(0.0)	1	(0.4)	1	(0.1)
Menthol (+) Polidocanol	1	(0.2)	0	(0.0)	1	(0.1)
Antiseptics And Disinfectants	11	(2.2)	2	(0.7)	13	(1.6)
Benzalkonium Chloride	2	(0.4)	0	(0.0)	2	(0.3)
Camphor (+) Menthol (+) Phenol	1	(0.2)	0	(0.0)	1	(0.1)
Carbamide Peroxide	1	(0.2)	0	(0.0)	1	(0.1)
Chlorhexidine Gluconate	6	(1.2)	2	(0.7)	8	(1.0)
Povidone-Iodine	1	(0.2)	0	(0.0)	1	(0.1)
Corticosteroids, Dermatological Preparations	38	(7.5)	9	(3.2)	47	(6.0)
Bacitracin Zinc (+) Hydrocortisone (+) Neomycin Sulfate (+) Polymyxin B Sulfate	1	(0.2)	1	(0.4)	2	(0.3)
Betamethasone Dipropionate	1	(0.2)	0	(0.0)	1	(0.1)
Betamethasone Dipropionate (+) Gentamicin Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Betamethasone Valerate	4	(0.8)	0	(0.0)	4	(0.5)
Clobetasol Propionate	3	(0.6)	0	(0.0)	3	(0.4)
Desonide	1	(0.2)	1	(0.4)	2	(0.3)
Desoximetasone	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Fluocinolone Acetonide	2	(0.4)	0	(0.0)	2	(0.3)
Fluocinonide	1	(0.2)	0	(0.0)	1	(0.1)
Gramicidin (+) Neomycin Sulfate (+) Nystatin (+) Triamcinolone Acetonide	0	(0.0)	1	(0.4)	1	(0.1)
Hydrocortisone (+) Iodoquinol	1	(0.2)	0	(0.0)	1	(0.1)
Hydrocortisone Acetate	4	(0.8)	3	(1.1)	7	(0.9)
Hydrocortisone Acetate (+) Pramoxine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Hydrocortisone Butyrate	3	(0.6)	0	(0.0)	3	(0.4)
Hydrocortisone Valerate	2	(0.4)	0	(0.0)	2	(0.3)
Mometasone Furoate	18	(3.6)	3	(1.1)	21	(2.7)
Prednicarbate	1	(0.2)	2	(0.7)	3	(0.4)
Emollients And Protectives	13	(2.6)	5	(1.8)	18	(2.3)
Beta Carotene	4	(0.8)	1	(0.4)	5	(0.6)
Ceteareth-20 (+) Cetostearyl Alcohol (+) Chlorocresol (+) Mineral Oil (+) Petrolatum, White	0	(0.0)	1	(0.4)	1	(0.1)
Copper Sulfate (+) Oat (+) Zinc Oxide (+) Zinc Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Glycerin (+) Mineral Oil (+) Petrolatum, White	2	(0.4)	1	(0.4)	3	(0.4)
Mineral Oil (+) Petrolatum	2	(0.4)	0	(0.0)	2	(0.3)
Mineral Oil (+) Wax, White	1	(0.2)	0	(0.0)	1	(0.1)
Petrolatum, White	0	(0.0)	1	(0.4)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Silicone	1	(0.2)	0	(0.0)	1	(0.1)
Urea	2	(0.4)	1	(0.4)	3	(0.4)
Other Dermatological Preparations	11	(2.2)	1	(0.4)	12	(1.5)
Alcohol (+) Carbomer (+) Cetyl Alcohol (+) Diazolidinyl Urea (+) Glycerin (+) Hypromellose (+) Polysorbate 20 (+) Trolamine	1	(0.2)	0	(0.0)	1	(0.1)
Coal Tar	1	(0.2)	0	(0.0)	1	(0.1)
Dermatologic (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Dichloroacetic Acid	2	(0.4)	0	(0.0)	2	(0.3)
Keluamid (+) Piroctone Olamine	1	(0.2)	0	(0.0)	1	(0.1)
Mequinol (+) Tretinoin	1	(0.2)	0	(0.0)	1	(0.1)
Minoxidil	0	(0.0)	1	(0.4)	1	(0.1)
Petrolatum, White (+) Salicylic Acid	1	(0.2)	0	(0.0)	1	(0.1)
Pimecrolimus	1	(0.2)	0	(0.0)	1	(0.1)
Salicylic Acid	1	(0.2)	0	(0.0)	1	(0.1)
Squaric Acid Dibutylester	1	(0.2)	0	(0.0)	1	(0.1)
Genitourinary System And Sex Hormones						
Gynecological Antiinfectives And Antiseptics	1	(0.2)	1	(0.4)	2	(0.3)
Betamethasone (+) Ketoconazole	0	(0.0)	1	(0.4)	1	(0.1)
Furazolidone	1	(0.2)	0	(0.0)	1	(0.1)
Sex Hormones And Modulators Of The Genital System	72	(14.2)	36	(12.8)	108	(13.7)
Desogestrel (+) Ethinyl Estradiol	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Estradiol	1	(0.2)	1	(0.4)	2	(0.3)
Estriol	0	(0.0)	1	(0.4)	1	(0.1)
Estrogens, Conjugated	0	(0.0)	2	(0.7)	2	(0.3)
Medroxyprogesterone Acetate	1	(0.2)	1	(0.4)	2	(0.3)
Testosterone	67	(13.2)	27	(9.6)	94	(11.9)
Testosterone Decanoate (+) Testosterone Isocaproate (+) Testosterone Phenylpropionate (+) Testosterone Propionate	2	(0.4)	4	(1.4)	6	(0.8)
Testosterone Isocaproate (+) Testosterone Phenylpropionate (+) Testosterone Propionate (+) Testosterone Undecanoate	1	(0.2)	1	(0.4)	2	(0.3)
Tibolone	0	(0.0)	1	(0.4)	1	(0.1)
Urologicals	40	(7.9)	30	(10.6)	70	(8.9)
Alfuzosin Hydrochloride	3	(0.6)	2	(0.7)	5	(0.6)
Atropine Sulfate (+) Benzoic Acid (+) Hyoscyamine Sulfate (+) Methenamine (+) Methylene Blue (+) Phenyl Salicylate	1	(0.2)	0	(0.0)	1	(0.1)
Dutasteride	1	(0.2)	0	(0.0)	1	(0.1)
Finasteride	2	(0.4)	4	(1.4)	6	(0.8)
Oxybutynin	3	(0.6)	0	(0.0)	3	(0.4)
Phenazopyridine Hydrochloride	2	(0.4)	1	(0.4)	3	(0.4)
Sildenafil Citrate	20	(3.9)	14	(5.0)	34	(4.3)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Tadalafil	5	(1.0)	8	(2.8)	13	(1.6)
Tamsulosin Hydrochloride	5	(1.0)	3	(1.1)	8	(1.0)
Tolterodine	1	(0.2)	0	(0.0)	1	(0.1)
Vardenafil Dihydrochloride	3	(0.6)	1	(0.4)	4	(0.5)
Musculoskeletal System						
Antigout Preparations	4	(0.8)	4	(1.4)	8	(1.0)
Allopurinol	1	(0.2)	4	(1.4)	5	(0.6)
Colchicine	2	(0.4)	1	(0.4)	3	(0.4)
Colchicine (+) Opium, Powdered (+) Tiemonium Methylsulfate	1	(0.2)	0	(0.0)	1	(0.1)
Antiinflammatory And Antirheumatic Products	86	(17.0)	58	(20.6)	144	(18.3)
Celecoxib	4	(0.8)	2	(0.7)	6	(0.8)
Cyanocobalamin (+) Diclofenac Sodium (+) Pyridoxine Hydrochloride (+) Thiamine Mononitrate	1	(0.2)	0	(0.0)	1	(0.1)
Dexibuprofen	1	(0.2)	0	(0.0)	1	(0.1)
Dexketoprofen	0	(0.0)	1	(0.4)	1	(0.1)
Diclofenac	11	(2.2)	11	(3.9)	22	(2.8)
Flurbiprofen	1	(0.2)	0	(0.0)	1	(0.1)
Ibuprofen	50	(9.9)	34	(12.1)	84	(10.6)
Ibuprofen (+) Pseudoephedrine Hydrochloride	2	(0.4)	1	(0.4)	3	(0.4)
Indomethacin	4	(0.8)	2	(0.7)	6	(0.8)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Ketoprofen	1	(0.2)	0	(0.0)	1	(0.1)
Ketorolac Tromethamine	1	(0.2)	1	(0.4)	2	(0.3)
Loxoprofen	0	(0.0)	1	(0.4)	1	(0.1)
Lumiracoxib	1	(0.2)	1	(0.4)	2	(0.3)
Mefenamic Acid	2	(0.4)	1	(0.4)	3	(0.4)
Meloxicam	1	(0.2)	0	(0.0)	1	(0.1)
Morniflumate	1	(0.2)	0	(0.0)	1	(0.1)
Mucopolysaccharide Polysulfate	2	(0.4)	1	(0.4)	3	(0.4)
Nabumetone	1	(0.2)	1	(0.4)	2	(0.3)
Naproxen	10	(2.0)	3	(1.1)	13	(1.6)
Niflumic Acid	2	(0.4)	1	(0.4)	3	(0.4)
Nimesulide	4	(0.8)	2	(0.7)	6	(0.8)
Piroxicam	2	(0.4)	0	(0.0)	2	(0.3)
Sulindac	1	(0.2)	0	(0.0)	1	(0.1)
Suprofen	0	(0.0)	1	(0.4)	1	(0.1)
Tenoxicam	0	(0.0)	1	(0.4)	1	(0.1)
Drugs For Treatment Of Bone Diseases	9	(1.8)	2	(0.7)	11	(1.4)
Alendronic Acid	5	(1.0)	0	(0.0)	5	(0.6)
Ibandronic Acid	0	(0.0)	1	(0.4)	1	(0.1)
Pamidronic Acid	1	(0.2)	0	(0.0)	1	(0.1)
Risedronate Sodium	2	(0.4)	0	(0.0)	2	(0.3)
Teriparatide	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Zoledronic Acid	0	(0.0)	1	(0.4)	1	(0.1)
Muscle Relaxants	6	(1.2)	4	(1.4)	10	(1.3)
Acetaminophen (+) Methocarbamol	1	(0.2)	0	(0.0)	1	(0.1)
Caffeine (+) Dipyrone (+) Orphenadrine Citrate	0	(0.0)	1	(0.4)	1	(0.1)
Carisoprodol	0	(0.0)	1	(0.4)	1	(0.1)
Chlormezanone	0	(0.0)	1	(0.4)	1	(0.1)
Cyclobenzaprine Hydrochloride	2	(0.4)	1	(0.4)	3	(0.4)
Metaxalone	1	(0.2)	0	(0.0)	1	(0.1)
Tetrazepam	2	(0.4)	0	(0.0)	2	(0.3)
Other Drugs For Disorders Of Musculo-Skeletal System	1	(0.2)	0	(0.0)	1	(0.1)
Hyaluronic Acid	1	(0.2)	0	(0.0)	1	(0.1)
Topical Products For Joint And Muscular Pain	2	(0.4)	0	(0.0)	2	(0.3)
Capsicum	1	(0.2)	0	(0.0)	1	(0.1)
Dexamethasone (+) Glycol Salicylate (+) Methyl Nicotinate (+) Salicylamide	1	(0.2)	0	(0.0)	1	(0.1)
Nervous System						
Analgesics	174	(34.3)	91	(32.3)	265	(33.6)
Acetaminophen	63	(12.4)	28	(9.9)	91	(11.5)
Acetaminophen (+) Amantadine Hydrochloride (+) Chlorpheniramine Maleate	1	(0.2)	0	(0.0)	1	(0.1)
Acetaminophen (+) Ascorbic Acid	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Acetaminophen (+) Ascorbic Acid (+) Caffeine (+) Chlorpheniramine Maleate	0	(0.0)	1	(0.4)	1	(0.1)
Acetaminophen (+) Caffeine (+) Cresotamide	1	(0.2)	0	(0.0)	1	(0.1)
Acetaminophen (+) Caffeine (+) Opium	1	(0.2)	0	(0.0)	1	(0.1)
Acetaminophen (+) Chlorpheniramine Maleate (+) Dextromethorphan Hydrobromide (+) Pseudoephedrine Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Acetaminophen (+) Chlorpheniramine Maleate (+) Phenylephrine Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Acetaminophen (+) Chlorpheniramine Maleate (+) Pseudoephedrine Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Acetaminophen (+) Codeine	15	(3.0)	4	(1.4)	19	(2.4)
Acetaminophen (+) Dextromethorphan Hydrobromide (+) Doxylamine Succinate (+) Pseudoephedrine Hydrochloride	2	(0.4)	4	(1.4)	6	(0.8)
Acetaminophen (+) Dextromethorphan Hydrobromide (+) Pseudoephedrine Hydrochloride	2	(0.4)	1	(0.4)	3	(0.4)
Acetaminophen (+) Diclofenac	1	(0.2)	0	(0.0)	1	(0.1)
Acetaminophen (+) Diphenhydramine Citrate (+) Diphenhydramine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Acetaminophen (+) Diphenhydramine Hydrochloride (+) Pseudoephedrine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)

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	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Acetaminophen (+) Hydrocodone Bitartrate	16	(3.2)	8	(2.8)	24	(3.0)
Acetaminophen (+) Loratadine (+) Pseudoephedrine Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Acetaminophen (+) Oxycodone Hydrochloride	10	(2.0)	5	(1.8)	15	(1.9)
Acetaminophen (+) Phenyltoloxamine Citrate	1	(0.2)	0	(0.0)	1	(0.1)
Acetaminophen (+) Propoxyphene Hydrochloride	3	(0.6)	0	(0.0)	3	(0.4)
Acetaminophen (+) Propoxyphene Napsylate	4	(0.8)	0	(0.0)	4	(0.5)
Acetaminophen (+) Pseudoephedrine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Acetaminophen (+) Pseudoephedrine Hydrochloride (+) Triprolidine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Acetaminophen (+) Tramadol Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Adiphenine Hydrochloride (+) Dipyrone (+) Promethazine	1	(0.2)	1	(0.4)	2	(0.3)
Analgesic Or Anesthetic (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Ascorbic Acid (+) Aspirin (+) Caffeine	1	(0.2)	0	(0.0)	1	(0.1)
Ascorbic Acid (+) Caffeine (+) Chlorpheniramine Maleate (+) Salicylamide	1	(0.2)	0	(0.0)	1	(0.1)
Aspirin	44	(8.7)	28	(9.9)	72	(9.1)
Aspirin (+) Caffeine	1	(0.2)	0	(0.0)	1	(0.1)
Aspirin (+) Oxycodone Hydrochloride (+) Oxycodone Terephthalate	0	(0.0)	1	(0.4)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Brompheniramine Maleate (+) Caffeine (+) Calcium Ascorbate (+) Propyphenazone (+) Quinine Hydrochloride (+) Salicylamide	1	(0.2)	0	(0.0)	1	(0.1)
Buprenorphine	2	(0.4)	1	(0.4)	3	(0.4)
Buprenorphine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Choline Magnesium Trisalicylate	1	(0.2)	0	(0.0)	1	(0.1)
Codeine Phosphate (+) Diclofenac Sodium	0	(0.0)	1	(0.4)	1	(0.1)
Dipyrone	7	(1.4)	7	(2.5)	14	(1.8)
Eletriptan Hydrobromide	0	(0.0)	1	(0.4)	1	(0.1)
Fentanyl	11	(2.2)	4	(1.4)	15	(1.9)
Hydromorphone Hydrochloride	5	(1.0)	1	(0.4)	6	(0.8)
Meperidine Hydrochloride	2	(0.4)	2	(0.7)	4	(0.5)
Morphine	17	(3.4)	7	(2.5)	24	(3.0)
Nefopam Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Opium	1	(0.2)	4	(1.4)	5	(0.6)
Oxycodone	10	(2.0)	10	(3.5)	20	(2.5)
Sumatriptan	2	(0.4)	5	(1.8)	7	(0.9)
Tramadol Hydrochloride	7	(1.4)	6	(2.1)	13	(1.6)
Anesthetics	13	(2.6)	4	(1.4)	17	(2.2)
Bupivacaine Hydrochloride (+) Epinephrine Bitartrate	1	(0.2)	0	(0.0)	1	(0.1)
Cocaine	3	(0.6)	0	(0.0)	3	(0.4)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Epinephrine (+) Lidocaine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Lidocaine	7	(1.4)	2	(0.7)	9	(1.1)
Lidocaine (+) Prilocaine	1	(0.2)	0	(0.0)	1	(0.1)
Prilocaine	1	(0.2)	0	(0.0)	1	(0.1)
Procaine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Propofol	1	(0.2)	1	(0.4)	2	(0.3)
Anti-Parkinson Drugs	3	(0.6)	3	(1.1)	6	(0.8)
Amantadine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Benztropine Mesylate	0	(0.0)	2	(0.7)	2	(0.3)
Orphenadrine	1	(0.2)	0	(0.0)	1	(0.1)
Pramipexole	1	(0.2)	0	(0.0)	1	(0.1)
Ropinirole Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Antiepileptics	66	(13.0)	26	(9.2)	92	(11.7)
Carbamazepine	3	(0.6)	1	(0.4)	4	(0.5)
Clonazepam	17	(3.4)	7	(2.5)	24	(3.0)
Gabapentin	32	(6.3)	16	(5.7)	48	(6.1)
Lamotrigine	7	(1.4)	0	(0.0)	7	(0.9)
Levetiracetam	0	(0.0)	1	(0.4)	1	(0.1)
Phenobarbital	1	(0.2)	0	(0.0)	1	(0.1)
Phenytoin	1	(0.2)	0	(0.0)	1	(0.1)
Pregabalin	8	(1.6)	1	(0.4)	9	(1.1)
Primidone	0	(0.0)	1	(0.4)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Tiagabine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Topiramate	1	(0.2)	0	(0.0)	1	(0.1)
Valproate Sodium	0	(0.0)	1	(0.4)	1	(0.1)
Valproic Acid	3	(0.6)	2	(0.7)	5	(0.6)
Other Nervous System Drugs	4	(0.8)	4	(1.4)	8	(1.0)
Bethanechol Chloride	0	(0.0)	1	(0.4)	1	(0.1)
Cinnarizine	0	(0.0)	1	(0.4)	1	(0.1)
Methadone Hydrochloride	3	(0.6)	2	(0.7)	5	(0.6)
Nicotine	1	(0.2)	0	(0.0)	1	(0.1)
Psychoanaleptics	96	(18.9)	59	(20.9)	155	(19.6)
Acetylcarnitine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Amitriptyline Hydrochloride	11	(2.2)	10	(3.5)	21	(2.7)
Amphetamine	1	(0.2)	0	(0.0)	1	(0.1)
Amphetamine Aspartate (+) Amphetamine Sulfate (+) Dextroamphetamine Saccharate (+) Dextroamphetamine Sulfate	2	(0.4)	0	(0.0)	2	(0.3)
Asian Ginseng (+) Deanol Tartrate (+) Minerals (Unspecified) (+) Rutin (+) Vitamins (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Bupropion Hydrochloride	17	(3.4)	9	(3.2)	26	(3.3)
Citalopram	13	(2.6)	10	(3.5)	23	(2.9)
Clomipramine Hydrochloride	2	(0.4)	1	(0.4)	3	(0.4)
Donepezil Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Doxepin Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Duloxetine Hydrochloride	5	(1.0)	1	(0.4)	6	(0.8)
Escitalopram	3	(0.6)	0	(0.0)	3	(0.4)
Escitalopram Oxalate	13	(2.6)	5	(1.8)	18	(2.3)
Fluoxetine	6	(1.2)	3	(1.1)	9	(1.1)
Flupentixol Hydrochloride (+) Melitracen Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Fluvoxamine Maleate	1	(0.2)	0	(0.0)	1	(0.1)
Galantamine Hydrobromide	1	(0.2)	0	(0.0)	1	(0.1)
Imipramine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Methylphenidate	6	(1.2)	4	(1.4)	10	(1.3)
Mianserin Hydrochloride	1	(0.2)	1	(0.4)	2	(0.3)
Mirtazapine	5	(1.0)	7	(2.5)	12	(1.5)
Moclobemide	0	(0.0)	1	(0.4)	1	(0.1)
Nortriptyline	4	(0.8)	0	(0.0)	4	(0.5)
Paroxetine	5	(1.0)	4	(1.4)	9	(1.1)
Paroxetine Mesylate	1	(0.2)	0	(0.0)	1	(0.1)
Sertraline Hydrochloride	10	(2.0)	9	(3.2)	19	(2.4)
Trazodone Hydrochloride	14	(2.8)	4	(1.4)	18	(2.3)
Venlafaxine Hydrochloride	6	(1.2)	5	(1.8)	11	(1.4)
Psycholeptics	110	(21.7)	72	(25.5)	182	(23.1)
Alprazolam	15	(3.0)	7	(2.5)	22	(2.8)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Aspirin (+) Butalbital (+) Caffeine	1	(0.2)	0	(0.0)	1	(0.1)
Bromazepam	4	(0.8)	4	(1.4)	8	(1.0)
Buspirone Hydrochloride	3	(0.6)	0	(0.0)	3	(0.4)
Butalbital	1	(0.2)	0	(0.0)	1	(0.1)
Chlorpromazine	0	(0.0)	1	(0.4)	1	(0.1)
Clorazepate Dipotassium	0	(0.0)	1	(0.4)	1	(0.1)
Cyamemazine	1	(0.2)	0	(0.0)	1	(0.1)
Diazepam	13	(2.6)	8	(2.8)	21	(2.7)
Estazolam	1	(0.2)	0	(0.0)	1	(0.1)
Eszopiclone	4	(0.8)	2	(0.7)	6	(0.8)
Flunitrazepam	1	(0.2)	0	(0.0)	1	(0.1)
Flupentixol	1	(0.2)	0	(0.0)	1	(0.1)
Fluphenazine	0	(0.0)	1	(0.4)	1	(0.1)
Flurazepam	1	(0.2)	0	(0.0)	1	(0.1)
Haloperidol	2	(0.4)	4	(1.4)	6	(0.8)
Hydroxyzine Hydrochloride	11	(2.2)	6	(2.1)	17	(2.2)
Lithium Carbonate	3	(0.6)	0	(0.0)	3	(0.4)
Loprazolam Mesylate	1	(0.2)	0	(0.0)	1	(0.1)
Lorazepam	24	(4.7)	13	(4.6)	37	(4.7)
Lormetazepam	2	(0.4)	0	(0.0)	2	(0.3)
Midazolam	4	(0.8)	6	(2.1)	10	(1.3)
Olanzapine	3	(0.6)	3	(1.1)	6	(0.8)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Oxazepam	1	(0.2)	0	(0.0)	1	(0.1)
Prochlorperazine	0	(0.0)	5	(1.8)	5	(0.6)
Quetiapine Fumarate	6	(1.2)	3	(1.1)	9	(1.1)
Ramelteon	1	(0.2)	1	(0.4)	2	(0.3)
Risperidone	1	(0.2)	3	(1.1)	4	(0.5)
Sulpiride	1	(0.2)	0	(0.0)	1	(0.1)
Temazepam	13	(2.6)	7	(2.5)	20	(2.5)
Triazolam	1	(0.2)	1	(0.4)	2	(0.3)
Zolpidem Tartrate	21	(4.1)	17	(6.0)	38	(4.8)
Zopiclone	10	(2.0)	5	(1.8)	15	(1.9)
Respiratory System						
Antihistamines For Systemic Use	82	(16.2)	40	(14.2)	122	(15.5)
Azelastine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Bamipine	0	(0.0)	1	(0.4)	1	(0.1)
Cetirizine Hydrochloride	15	(3.0)	7	(2.5)	22	(2.8)
Chlorpheniramine Maleate	7	(1.4)	4	(1.4)	11	(1.4)
Cyproheptadine Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Desloratadine	2	(0.4)	4	(1.4)	6	(0.8)
Dexchlorpheniramine Maleate	4	(0.8)	3	(1.1)	7	(0.9)
Dimenhydrinate	4	(0.8)	1	(0.4)	5	(0.6)
Dimethindene Maleate	1	(0.2)	0	(0.0)	1	(0.1)
Diphenhydramine Hydrochloride	12	(2.4)	7	(2.5)	19	(2.4)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Doxylamine Succinate	1	(0.2)	0	(0.0)	1	(0.1)
Ebastine	1	(0.2)	0	(0.0)	1	(0.1)
Fexofenadine Hydrochloride	12	(2.4)	3	(1.1)	15	(1.9)
Levocetirizine	3	(0.6)	1	(0.4)	4	(0.5)
Levocetirizine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Loratadine	18	(3.6)	10	(3.5)	28	(3.5)
Meclizine	1	(0.2)	1	(0.4)	2	(0.3)
Oxatomide	3	(0.6)	0	(0.0)	3	(0.4)
Promethazine	7	(1.4)	2	(0.7)	9	(1.1)
Trimethobenzamide Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Cough And Cold Preparations	54	(10.7)	15	(5.3)	69	(8.7)
Acetylcysteine	18	(3.6)	5	(1.8)	23	(2.9)
Ambroxol	5	(1.0)	0	(0.0)	5	(0.6)
Benzonatate	4	(0.8)	2	(0.7)	6	(0.8)
Brompheniramine Maleate (+) Dextromethorphan Hydrobromide (+) Guaifenesin	1	(0.2)	0	(0.0)	1	(0.1)
Carbocysteine	3	(0.6)	1	(0.4)	4	(0.5)
Clobutinol	2	(0.4)	0	(0.0)	2	(0.3)
Codeine	4	(0.8)	2	(0.7)	6	(0.8)
Codeine (+) Hedge Mustard	1	(0.2)	0	(0.0)	1	(0.1)
Codeine Phosphate (+) Guaifenesin	2	(0.4)	0	(0.0)	2	(0.3)
Cough, Cold, And Flu Therapies (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Dextromethorphan	6	(1.2)	1	(0.4)	7	(0.9)
Dextromethorphan Hydrobromide (+) Guaifenesin	2	(0.4)	1	(0.4)	3	(0.4)
Dextromethorphan Hydrobromide (+) Guaifenesin (+) Phenylephrine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Dextromethorphan Hydrobromide (+) Guaifenesin (+) Pseudoephedrine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Guaifenesin	9	(1.8)	3	(1.1)	12	(1.5)
Guaifenesin (+) Hydrocodone Bitartrate (+) Pseudoephedrine Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Guaifenesin (+) Phenylephrine Hydrochloride	2	(0.4)	0	(0.0)	2	(0.3)
Hydrocodone Bitartrate	3	(0.6)	0	(0.0)	3	(0.4)
Pholcodine (+) Thenoic Acid	1	(0.2)	0	(0.0)	1	(0.1)
Thebacon	2	(0.4)	0	(0.0)	2	(0.3)
Drugs For Obstructive Airway Diseases	53	(10.5)	31	(11.0)	84	(10.6)
Albuterol	26	(5.1)	17	(6.0)	43	(5.4)
Albuterol Sulfate (+) Ipratropium Bromide	3	(0.6)	1	(0.4)	4	(0.5)
Beclomethasone Dipropionate	4	(0.8)	1	(0.4)	5	(0.6)
Budesonide	3	(0.6)	3	(1.1)	6	(0.8)
Budesonide (+) Formoterol Fumarate	0	(0.0)	1	(0.4)	1	(0.1)
Ciclesonide	1	(0.2)	1	(0.4)	2	(0.3)
Cromolyn Sodium	1	(0.2)	1	(0.4)	2	(0.3)
Epinephrine	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Fenoterol	2	(0.4)	1	(0.4)	3	(0.4)
Fenspiride Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Flunisolide	8	(1.6)	2	(0.7)	10	(1.3)
Fluticasone Propionate	6	(1.2)	5	(1.8)	11	(1.4)
Fluticasone Propionate (+) Salmeterol Xinafoate	7	(1.4)	3	(1.1)	10	(1.3)
Formoterol Fumarate	3	(0.6)	0	(0.0)	3	(0.4)
Ipratropium Bromide	3	(0.6)	2	(0.7)	5	(0.6)
Levalbuterol Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Montelukast Sodium	4	(0.8)	1	(0.4)	5	(0.6)
Salmeterol	3	(0.6)	0	(0.0)	3	(0.4)
Terbutaline Sulfate	2	(0.4)	0	(0.0)	2	(0.3)
Tiotropium Bromide	6	(1.2)	2	(0.7)	8	(1.0)
Nasal Preparations	22	(4.3)	12	(4.3)	34	(4.3)
Acetylcysteine (+) Benzalkonium Chloride (+) Tuaminoheptane Sulfate	1	(0.2)	1	(0.4)	2	(0.3)
Cetirizine Hydrochloride (+) Pseudoephedrine Hydrochloride	0	(0.0)	2	(0.7)	2	(0.3)
Chlorpheniramine Maleate (+) Pseudoephedrine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Chlorpheniramine Maleate (+) Pseudoephedrine Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Cromolyn Sodium (+) Reproterol Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Dexamethasone (+) Neomycin Sulfate (+) Tramazoline Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Fexofenadine Hydrochloride (+) Pseudoephedrine Hydrochloride	4	(0.8)	3	(1.1)	7	(0.9)
Framycetin Sulfate (+) Naphazoline Nitrate (+) Prednisolone Acetate	0	(0.0)	1	(0.4)	1	(0.1)
Loratadine (+) Pseudoephedrine Sulfate	2	(0.4)	2	(0.7)	4	(0.5)
Naphazoline Hydrochloride (+) Phenylephrine Hydrochloride (+) Pyrilamine Maleate	1	(0.2)	0	(0.0)	1	(0.1)
Oxymetazoline Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Phenylephrine	1	(0.2)	0	(0.0)	1	(0.1)
Pseudoephedrine	6	(1.2)	4	(1.4)	10	(1.3)
Pseudoephedrine Hydrochloride (+) Triprolidine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Tetrahydrozoline Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Tixocortol Pivalate	2	(0.4)	0	(0.0)	2	(0.3)
Xylometazoline Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Throat Preparations	2	(0.4)	1	(0.4)	3	(0.4)
Cetylpyridinium Chloride (+) Chlorobutanol (+) Eugenol	1	(0.2)	1	(0.4)	2	(0.3)
Fusafungine	1	(0.2)	0	(0.0)	1	(0.1)
Sensory Organs						

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
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Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Ophthalmological And Otological Preparations	2	(0.4)	1	(0.4)	3	(0.4)
Dexamethasone Sodium Phosphate (+) Neomycin Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Hydrocortisone (+) Neomycin Sulfate (+) Polymyxin B Sulfate	1	(0.2)	1	(0.4)	2	(0.3)
Ophthalmologicals	10	(2.0)	7	(2.5)	17	(2.2)
Carbomer	0	(0.0)	1	(0.4)	1	(0.1)
Carbomer (+) Glycerin (+) Hyaluronate Sodium	1	(0.2)	0	(0.0)	1	(0.1)
Carboxymethylcellulose Sodium	1	(0.2)	1	(0.4)	2	(0.3)
Ciprofloxacin Hydrochloride (+) Dexamethasone	0	(0.0)	1	(0.4)	1	(0.1)
Ciprofloxacin Hydrochloride (+) Hydrocortisone	1	(0.2)	0	(0.0)	1	(0.1)
Dexamethasone (+) Oxytetracycline	1	(0.2)	0	(0.0)	1	(0.1)
Dexamethasone (+) Tobramycin	1	(0.2)	0	(0.0)	1	(0.1)
Dextran 70 (+) Hypromellose	1	(0.2)	0	(0.0)	1	(0.1)
Dorzolamide Hydrochloride (+) Timolol Maleate	1	(0.2)	0	(0.0)	1	(0.1)
Hypromellose	1	(0.2)	0	(0.0)	1	(0.1)
Latanoprost	1	(0.2)	0	(0.0)	1	(0.1)
Loteprednol Etabonate (+) Tobramycin	1	(0.2)	0	(0.0)	1	(0.1)
Nepafenac	0	(0.0)	1	(0.4)	1	(0.1)
Olopatadine Hydrochloride	1	(0.2)	2	(0.7)	3	(0.4)
Polyvinyl Alcohol	0	(0.0)	1	(0.4)	1	(0.1)
Travoprost	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins						
Corticosteroids For Systemic Use	61	(12.0)	22	(7.8)	83	(10.5)
Betamethasone	7	(1.4)	1	(0.4)	8	(1.0)
Cortisone	3	(0.6)	1	(0.4)	4	(0.5)
Dexamethasone	14	(2.8)	3	(1.1)	17	(2.2)
Hydrocortisone	8	(1.6)	6	(2.1)	14	(1.8)
Methylprednisolone	9	(1.8)	2	(0.7)	11	(1.4)
Prednisolone	4	(0.8)	3	(1.1)	7	(0.9)
Prednisone	18	(3.6)	5	(1.8)	23	(2.9)
Triamcinolone	7	(1.4)	3	(1.1)	10	(1.3)
Pituitary And Hypothalamic Hormones And Analogues	4	(0.8)	3	(1.1)	7	(0.9)
Octreotide	2	(0.4)	0	(0.0)	2	(0.3)
Somatropin	2	(0.4)	3	(1.1)	5	(0.6)
Thyroid Therapy	17	(3.4)	8	(2.8)	25	(3.2)
Levothyroxine Sodium	15	(3.0)	8	(2.8)	23	(2.9)
Liothyronine Sodium	1	(0.2)	0	(0.0)	1	(0.1)
Methimazole	1	(0.2)	0	(0.0)	1	(0.1)
Propylthiouracil	1	(0.2)	0	(0.0)	1	(0.1)
Various						
All Other Therapeutic Products	55	(10.8)	28	(9.9)	83	(10.5)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category—Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Acerola (+) Alfalfa (+) Amaranth (+) Barley (+) Buckwheat (+) Chenopodium Quinoa (+) Chia (+) Flaxseed (+) Kelp (+) Millet (+) Oat (+) Pumpkin Seed (+) Sesame (+) Spirulina (+) Sunflower (+) Vegetables (Unspecified) (+) Wheat Grass	0	(0.0)	1	(0.4)	1	(0.1)
Acerola (+) Astragalus (+) Bee Pollen (+) Betaine (+) Choline (+) Cysteine (+) Echinacea (+) Eleuthero (+) Ginkgo (+) Inositol (+) Kelp (+) Methionine (+) Minerals (+) Papaya (+) Royal Jelly (+) Spirulina (+) Vitamins (+) Yeast, Dried	0	(0.0)	1	(0.4)	1	(0.1)
Amyl Nitrite	0	(0.0)	1	(0.4)	1	(0.1)
Antioxidants (Unspecified)	3	(0.6)	0	(0.0)	3	(0.4)
Arginine (+) Arginine Ketoglutarate (+) Arginine Ethyl Ester Hydrochloride (+) Aspartic Acid (+) Asian Ginseng (+) Citrulline (+) Dicreatine Malate (+) Picamilon Hydrochloride (+) Scotch Pine	1	(0.2)	0	(0.0)	1	(0.1)
Bilberry	1	(0.2)	0	(0.0)	1	(0.1)
Calcium Polystyrene Sulfonate	0	(0.0)	1	(0.4)	1	(0.1)
Cetylated Fatty Acids	1	(0.2)	0	(0.0)	1	(0.1)
Chondroitin Sulfate Sodium (+) Dimethyl Sulfone (+) Glucosamine	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Chondroitin Sulfate Sodium (+) Glucosamine Hydrochloride	0	(0.0)	1	(0.4)	1	(0.1)
Chondroitin Sulfate Sodium (+) Glucosamine Sulfate	1	(0.2)	0	(0.0)	1	(0.1)
Colloidal Silver	1	(0.2)	0	(0.0)	1	(0.1)
Comfrey	1	(0.2)	0	(0.0)	1	(0.1)
Dimethyl Sulfone (+) Glucosamine	0	(0.0)	1	(0.4)	1	(0.1)
Echinacea (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Epimedium	1	(0.2)	0	(0.0)	1	(0.1)
Eucalyptol (+) Pumillo Pine Oil (+) Rosemary (+) Terpineol (+) Thyme Oil	1	(0.2)	0	(0.0)	1	(0.1)
Evening Primrose Oil	1	(0.2)	0	(0.0)	1	(0.1)
Folinic Acid	8	(1.6)	4	(1.4)	12	(1.5)
Garlic	1	(0.2)	1	(0.4)	2	(0.3)
Ginkgo	1	(0.2)	0	(0.0)	1	(0.1)
Glucosamine	6	(1.2)	1	(0.4)	7	(0.9)
Hemp	0	(0.0)	3	(1.1)	3	(0.4)
Herbs (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Leucovorin Calcium	12	(2.4)	7	(2.5)	19	(2.4)
Melatonin	1	(0.2)	1	(0.4)	2	(0.3)
Myrtle	1	(0.2)	0	(0.0)	1	(0.1)
Naloxone Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Niaouli Oil	1	(0.2)	0	(0.0)	1	(0.1)
Nitrogen	2	(0.4)	2	(0.7)	4	(0.5)
Oat	1	(0.2)	0	(0.0)	1	(0.1)
Olive	0	(0.0)	1	(0.4)	1	(0.1)
Peppermint	0	(0.0)	1	(0.4)	1	(0.1)
Phosphorus (Unspecified)	0	(0.0)	1	(0.4)	1	(0.1)
Poly-L-Lactic Acid	5	(1.0)	0	(0.0)	5	(0.6)
Potasssium R-Lipoate	1	(0.2)	0	(0.0)	1	(0.1)
Prasterone	2	(0.4)	0	(0.0)	2	(0.3)
Pregnenolone	0	(0.0)	1	(0.4)	1	(0.1)
Sevelamer Hydrochloride	1	(0.2)	0	(0.0)	1	(0.1)
Silk Tree	1	(0.2)	0	(0.0)	1	(0.1)
Spirulina	1	(0.2)	0	(0.0)	1	(0.1)
Sugarcane	1	(0.2)	0	(0.0)	1	(0.1)
Thioctic Acid	3	(0.6)	0	(0.0)	3	(0.4)
Turmeric	1	(0.2)	0	(0.0)	1	(0.1)
Ubiquinones (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
[Composition Unspecified]	1	(0.2)	0	(0.0)	1	(0.1)
Contrast Media	0	(0.0)	1	(0.4)	1	(0.1)
Iohexol	0	(0.0)	1	(0.4)	1	(0.1)
Diagnostic Agents	0	(0.0)	2	(0.7)	2	(0.3)
Tuberculin Purified Protein Derivative	0	(0.0)	2	(0.7)	2	(0.3)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies (Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Diagnostic Radiopharmaceuticals	0	(0.0)	1	(0.4)	1	(0.1)
Technetium Tc 99m Tetrofosmin	0	(0.0)	1	(0.4)	1	(0.1)
General Nutrients	19	(3.7)	4	(1.4)	23	(2.9)
Amino Acids (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Amino Acids (Unspecified) (+) Carbohydrates (Unspecified) (+) Fat (Unspecified) (+) Minerals (Unspecified) (+) Protein (Unspecified) (+) Vitamins (Unspecified)	0	(0.0)	1	(0.4)	1	(0.1)
Amino Acids (Unspecified) (+) Fat (Unspecified) (+) Lecithin (+) Medium-Chain Triglycerides (+) Minerals (Unspecified) (+) Protein (Unspecified) (+) Vitamins (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Amino Acids (Unspecified) (+) Protein (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Benziphos Sodium	1	(0.2)	0	(0.0)	1	(0.1)
Carbohydrates (Unspecified) (+) Fat (Unspecified) (+) Minerals (Unspecified) (+) Protein (Unspecified) (+) Vitamins (Unspecified)	5	(1.0)	0	(0.0)	5	(0.6)
Carbohydrates (Unspecified) (+) Protein (Unspecified)	1	(0.2)	0	(0.0)	1	(0.1)
Creatine	2	(0.4)	0	(0.0)	2	(0.3)
Dextrose	1	(0.2)	1	(0.4)	2	(0.3)

Number (%) of Patients With Specific Concomitant Non-Optimized Background Therapies
(Incidence >0% in One or More Treatment Groups) by Drug Category—
Treatment-Experienced Double-Blind Cohort (Protocols 005, 018, and 019) - *Cumulative Data*

	MK-0518 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Lecithin	1	(0.2)	0	(0.0)	1	(0.1)
Minerals (Unspecified) (+) Protein (Unspecified) (+) Vitamins (Unspecified)	2	(0.4)	1	(0.4)	3	(0.4)
Nutritional Supplements	2	(0.4)	1	(0.4)	3	(0.4)
Protein (Unspecified)	5	(1.0)	1	(0.4)	6	(0.8)
Although a patient may have had two or more concomitant optimized background therapies, the patient is counted only once within a category. The same patient may appear in different categories.						
Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT).						

[Ref. 5.3.5.1: P005-Define, P018-Define, P019-Define]