Table 7.2.3: Clinical testing to elicit AEs, vital signs, and laboratory parameters in the golimumab studies

Studies[1]	Evaluation	Frequency
All 13 golimumab studies	For each AE, the investigator noted whether the AE was or was not an infection. For each infection, the investigator noted whether the AE was treated with or without oral or parental antibiotics.	For each reported AE
Major Evaluations		
5 Phase 3 Trials[2]	AE review prior to and 30 minutes after SC agent administration	Every visit which occurred at least every 4 weeks
	Tuberculosis evaluations	Every visits which occurred at least every 4 weeks
	Vital signs	Every visits which occurred at least every 4 weeks. Vital signs were not entered into the database; however, any significant changes were reported as AEs.
	Routine chemistry (chemistry 7 panel, hepatic panel, phosphorus, and total protein), routine hematology (CBC with differential)	At least every 4 to 8 weeks
	Physical exam	At Weeks 24 and 52
	ANA and anti-dsDNA antibodies[3]	At Weeks 14, 24, and/or 52
Additional Evaluations		
Studies 5 & 6	Fasting lipid profiles, fasting glucose, and other cardiovascular biomarkers	At Weeks 24 and 52
Study 8	Response to the 23-valent pneumococcal vaccine administered at Week 12	Immune response titers measured 4 weeks after antigen challenge
Studies 466-1 & 466-2	Response to delayed-type hypersensitivity antigens (C. albicans skin test antigen and mumps skin test antigen). Inoculated with the antigens 24 hours after the last study agent administration.	Skin tests read 48 hours after antigen inoculation.
	Urine analysis	Frequent measurements
	INR and PTT	Frequent measurements
	Response to the 23-valent pneumococcal vaccine administered 3 days after the initial dose of the study agent	Immune response titers measured 4 weeks after antigen challenge
Studies 466-1, 466-2, 13, & 23	ECG	Frequent measurements
Studies 466-1, 466-2, 1, 3, 13, 23, 24	Vital Signs	Frequent measurements

1 The 13 golimumab studies included the 5 Phase 3 trials (Studies 5, 6, 11, 8, and 9), the 1 Phase 2 RA trial (Study 2), the 1 Phase 2 asthma study (Study 3), the 2 RA Phase 1 studies (Studies 466-1 and 466-2), the 1 Phase 1 [redacted] study (Study 1), and the 3 studies in healthy subjects (Studies 13, 23, and 24). b(4)

2 The 5 Phase 3 trials included Studies 5, 6, 11, 8, and 9. Safety evaluations in the 5 Phase 3 trials up to Week 52. Safety evaluations during the long-term extension portions of the ongoing 5 Phase 3 trials are not included in this table.

3 ANA and anti-dsDNA were performed to assess the impact of golimumab treatment on the appearance of biomarkers of autoimmune disorders (the TNF inhibitors have been associated with auto-immune disorders). Anti-dsDNA tests were only performed if ANA was positive (≥ 1:160 titer). All 5 Phase 3 trials had testing at Week 52 and at the primary efficacy endpoint measure (Week 14 for Studies 6, 11, 8, and 9 and Week 24 for Study 5). In addition Study 11 had testing at Week 24.

Table 7.2.4 describes the eligibility criteria and baseline testing regarding tuberculosis in the Phase 2 and Phase 3 trials of SC golimumab. The baseline TB testing in the Phase 2 and Phase 3 trials were adequate to assess for the presence of latent or active TB.

Table 7.2.4: Eligibility criteria and baseline testing for tuberculosis in the Phase 2 and Phase 3 trials of SC golimumab

	Eligibility Criteria	Baseline Testing
5 Phase 3 trials	**1. No history of latent or active TB prior to screening.[1] 2. No signs or symptoms suggestive of active TB upon medical history and/or physical examination. 3. No recent close contact with a person with active TB. 4. Within 4-6 weeks prior to administration of study agent, either had both a negative tuberculin skin test and a negative QuantiFERON-TB Gold test. Patients who had a newly identified positive diagnostic TB test result in which active TB has been ruled out could have participated if appropriate treatment for latent TB was initiated prior to or simultaneously with the first study agent administration. 5. Had CXR taken within 3 months prior to administration of study agent with no evidence of active TB or old inactive TB.**	**CXR, tuberculin skin test, and a QuantiFERON-TB Gold test**
1 Phase 2 RA trial and 1 Phase 2 asthma trial	**Similar to above (except a negative TB test was only a negative tuberculin skin test)**	**CXR and tuberculin skin test**

1 In Study 11, patients were allowed to have "a history of latent TB ... and documentation of having completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent." According to Centocor, since all patients in Study 11 were treated with a TNF inhibitor in the past, it was likely that many patients were screened for latent TB. Given that these patients would have received anti-TNFα therapy under the close medical supervision of a rheumatologist, Centocor believed that it was feasible in most cases to verify the adequacy and compliance of any recent anti-TB treatment regimen.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific drug-drug interaction studies were required for possibly the fifth approved TNF inhibitor in the United States.

According to Dr. Zhang, pro-inflammatory cytokines including TNFα have reduced the expression level of multiple CYP enzymes including CYP3A4. Since golimumab decreases TNFα serum levels, golimumab could theoretically contribute to a relative increase in the expression of CYP3A4 and the levels of CYP3A4 substrates could decrease. Therefore, Dr. Zhang recommends a post-marketing commitment to study these theoretical DDIs with golimumab.

7.3 Major Safety Results

7.3.1 Deaths

SC golimumab (proposed route of administration in BLA)

In the controlled and uncontrolled portions of the 12 SC golimumab studies, 14 patients died (13 and 1 patients died in the rheumatologic and asthma Phase 2/Phase 3 trials, respectively). See Table 7.3.1 for a comparison of the incidence of deaths per 100 patient-years in the controlled portions of the Phase 3 trials compared to the controlled and uncontrolled portions of the Phase 2 and Phase 3 rheumatology trials. Of the 13 patients who died in the controlled and uncontrolled portions of the rheumatology Phase 2 and Phase 3 trials of SC golimumab, 1 (0.1%), 4 (0.3%), and 8 (0.6%) died in the placebo, golimumab50, and golimumab100 groups, respectively (incidence of deaths were 0.29, 0.27, and 0.46 per 100-patient years, respectively). In the controlled portions of the 5 Phase 3 trials of RA, PsA, and AS through Week 24, 1 (0.2%), 1 (0.1%), and 2 (0.2%) of the patients in the placebo, golimumab50, and golimumab100 groups died, respectively.

There was no significant difference in the proportion of deaths in the SC placebo, SC golimumab50, and SC golimumab100 groups in the 24-week controlled portions of the 5 Phase 3 trials.

The incidence of deaths per 100 patient-years was low during the 24-week controlled period and did not appear to increase with longer-term exposure in the uncontrolled portion of the rheumatology trials. The high dose golimumab group had a slightly greater exposure-adjusted death rate in both the controlled portions of the trials and the controlled and uncontrolled portions of the trials. However, the incidence of death in the combined golimumab groups was similar to the placebo group. The exposure-adjusted incidence rate of deaths in the golimumab clinical development program was lower than published background rates in the RA population (2.4 to 2.5 deaths per 100-patient years in the Olmstead County RA Cohort, Gonzalez 2007).

Table 7.3.1: Incidence of deaths per 100 patient-years in the controlled portions of the Phase 3 trials compared to the controlled and uncontrolled portions of Phase 2 and Phase 3 trials through the last safety cut-off[1]

	Controlled Portions of Phase 3 Trials (through Week 24)			Controlled & Uncontrolled Portions of Phase 2 & 3 Trials (through last Safety Cut-Off)[1]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	golimumab50 ± MTX	golimumab100 ± MTX
Patients treated	639	683	977	1301	1356
Patient-years of follow-up	256	294	440	1467	1757
n (%) of patients who died	1 (0.2%)	1 (0.1%)	2 (0.2%)	4 (0.3%)	8 (0.6%)
Incidence of deaths per 100 patient-years	0.39	0.34	0.45	0.27	0.46

1 As of the last safety cut-off date for deaths in the 120-Safety Update (i.e., July 31, 2008). The deaths in the IV golimumab study are not included in this table (see Tables 7.3.4 and 7.3.5). There were no deaths in the Phase 1 studies of golimumab in patients with RA and [redacted] and the Phase 1 studies in healthy subjects. Patients may appear in more than one column. b(4)

Reference: Adapted from the 120-Safety Update Report, Table 14, Page 59

Table 7.3.2 displays a summary of the 14 deaths in the controlled and uncontrolled portions of all the SC golimumab studies by study agent up until the last safety cut-off date and Table 7.3.3 displays the narratives of these 14 deaths by study agent. The types of deaths (e.g., serious infections, malignancies, cardiac disease) were typical of RA, PsA, and AS populations.

One notable death was a 24 year old female from Korea (Patient 5805-60569 in Study 6, [redacted] KR-JNJ [redacted] 20071004551) with early RA and baseline liver disease (possibly due to autoimmune hepatitis) who developed acute liver failure after receiving about 11 months of golimumab100 monotherapy. Of note, during screening her normal liver enzymes were within the normal range and her viral hepatitis tests were negative and she was allowed to enroll. It is likely that her underlying liver disease, her prior use of MTX, her concomitant use of three known hepatotoxins (methimazole, nabumetone, and ketoprofen), and her concomitant use of a possible fourth hepatotoxin (an herbal medication that was associated with increased liver enzymes) contributed to her acute liver failure and her death. The golimumab label should state that acute liver failure has been reported with TNF inhibitor use including golimumab. b(6)

Table 7.3.2: Summary table of 14 deaths in the controlled and uncontrolled portions of all the SC golimumab studies through the last safety cut-off date[1]

Treatment Group[2]	Study	Population	Patient#[3]	Death during controlled period	Study Day of Last Dose	Study Day of Death	Cause of Death
Golimumab200	Study 3	Asthma	1. 1441-005	Yes	116		Septic shock
Golimumab100 q2W and MTX then q4W and MTX	Study 2	RA	2. 114-004	No	343		Acute cardiac failure
Golimumab100 & MTX	Study 5	RA	3. 7454-50342	Yes	311		Tramadol overdose
			4. 1004-50710	Yes	1		Cardio-respiratory arrest following surgery for a gluteal abscess
Golimumab100	Study 6	RA	5. 5001-50186	No	397		Cerebral hemorrhage
			6. 5201-60307	No	449		Cardiac arrest
			7. 4602-60073	Yes	28		Sepsis
			8. 5805-60569	No	286		Acute liver failure
Golimumab100	Study 5	RA	9. 1604-50395	No	589		Unknown
Golimumab50 and MTX	Study 5	RA	10. 1008-50820	Yes	84		Hypoglycemic coma
Golimumab50	Study 8	PsA	11. 2018-80239	No	253		Metastatic small cell lung CA
			12. 5202-80466	No	309		Accident due to Alpine[3] climbing
MTX to Golimumab50 and MTX	Study 5	RA	13. 1204-50069	No	217[4]		Metastatic non-small cell lung cancer
Placebo	Study 11	RA	14. 7483-10562	Yes	141		Pancreatic CA

b(6)

1 As of the last safety cut-off date for deaths in the SC golimumab studies in the 120-Safety Update (i.e., July 31, 2008). For the narratives of these deaths see Table 7.3.3 and for the deaths in the golimumab IV studies see Tables 7.3.4 and 7.3.5.

2 Golimumab200 was only used in the one asthma trial (i.e., Study 3). The dose was 300 mg of SC golimumab initially followed by 200 mg of SC golimumab every 4 weeks. Golimumab100 q 2W then q 4W was 100 mg of SC golimumab every 2 weeks (W0-18) then 100 mg of SC golimumab every 4 weeks (W20-W48). Golimumab100 was 100 mg of SC golimumab every 4 weeks. Golimumab50 was 50 mg of SC golimumab every 4 weeks.

3 Alpine style of climbing is the refusal of fixed ropes, high altitude porters, and the use of supplemental oxygen.

b(6)

4 Patient 1204-50069 initially received MTX monotherapy at randomization and then received combination golimumab50 and MTX at Week 52 (Day 352). The patient's first dose of SC golimumab 50 mg every 4 weeks was on Day 352. The patient received 217 days of golimumab50 (last dose was on Day 589) and the patient died — after golimumab50 was started (on Day 711).

Reference: Adapted from the SCS, Appendix B19, Page 344, 120-Day Safety Report, Case Report forms in Studies 2, 3, 5, 6, 8, 11, and 12

Table 7.3.3: Narratives of the 14 deaths in the controlled and uncontrolled portions of all the SC golimumab studies through the last safety cut-off date[1]

	Patient # (Study)	Narrative
Golimumab200 Monotherapy (initial 300 mg dose followed by 200 mg every 4 weeks)		
1	1441-005 (Study 3)	**60-year-old female** with a 26-year **history of asthma** and a history of obesity, sinusitis, depression, anxiety, allergic rhinitis. Received inhaled salbutamol, inhaled fluticasone, amitripyline, chlorphenamine, cyclobenzaprine, diclofenac, diphenhydramine, montelukast, fluconazole, naproxen, and calcium. She received her first dose of SC golimumab (i.e., 300 mg) on March 13, 2006 then received four doses of SC golimumab 200 mg every 4 weeks. Her last SC golimumab dose was on Day 116 (Week 26, July 6, 2006). The week after her last dose, she had extreme thirst, anorexia, polyuria. On [redacted] days after her last SC golimumab dose) she was diagnosed and hospitalized for new-onset diabetes, diabetic ketoacidosis, renal failure, pancreatitis, free air in the abdomen, and **septic shock**. She was treated with fluids, potassium, and insulin. She died on [redacted] b(6)
Golimumab100 q2W then q4W and MTX		
2	114-004 (Study 2)	**44-year-old male** with a history of RA for 4 years, CAD, hyperlipidemia, and a current smoker. Received MTX, folate, celecoxib. Received background MTX and golimumab 100 mg SC every 2 weeks (first dose was on June 1, 2004) from W0 to W20, subsequently received golimumab 100 SC every 4 weeks from W24 to W48 (his last dose was on Week 48 on May 9, 2005, Day 343 – he completed treatment). He finished the study on June 21, 2005. On [redacted] months after the last golimumab administration, he was chasing someone as a police officer developed **acute cardiac failure** and then died. Autopsy revealed **CAD** (with two vessels over 70% narrowed). b(6)
Golimumab100 & MTX		
3	7454-50342 (Study 5)	**57 year old female** from the United States with history of RA for 0.3 years and HTN. She received lansoprazole, celecoxib, folate, aspirin 325 mg/day, and ramipril. She received her first dose of golimumab 100 mg SC and MTX on October 2, 2006 (MTX was initially 10 mg then titrated up to 20 mg once weekly). She received 12 injections of golimumab 100 mg and her last injection was on August 8, 2007 (Day 311, Week 44). She started tramadol on March 19, 2007 (Day 169, Week 24). She died on [redacted] due to an **overdose of tramadol**. b(6)
4	1004-50710 (Study 5)	**50 year old female** with history of RA for 2 years on concomitant diclofenac and 10 mg of prednisone. She received the first SC administration of 100 mg of golimumab on February 27, 2007 and 3 weekly doses of PO MTX up to 12.5 mg (with folic acid). On [redacted] days after first dose of golimumab) had abdominal pain, diarrhea, vomiting, and fever, was diagnosed with gastroenteritis and a **right gluteal abscess**, and was admitted to the hospital that day. She was treated with cefalotin, ciprofloxacin, and metronidazole and had a surgical procedure on [redacted] to evacuate the gluteal abscess. After surgery she had **cardiorespiratory arrest** and required ventilatory support until her death from a cardiorespiratory arrest on [redacted] b(6)
Golimumab100 Monotherapy		
5	5001-50186 (Study 6)	**54 year old female** from the Philippines with history of RA for 1 year and chronic gastritis. She received prednisone 10 mg/day, folic acid, ranitidine, INH, calcium, and amoxicillin-clavulonic acid. She received the first SC administration of 100 mg of golimumab on July 17, 2006 (and sham MTX). She received 13 doses of SC golimumab 100 mg and sham MTX and she did not enter early escape. She received her last dose of SC golimumab 100 mg on August 17, 2007 (Day 397, Week 56). She was hospitalized for abdominal pain on [redacted] and was diagnosed with gastritis by EGD. On [redacted], she became hypertensive, comatose and required intubation. She was diagnosed with an intercerebral hemorrhage and had a cardiac arrest. She died on [redacted] due to an **intercerebral hemorrhage**. b(6)
6	5201-60307 (Study 6)	**65 year old female** with history of RA for 2 years, HTN, hyperlipidemia. Received diltiazem, bisoprolol, methylprednisolone 8 mg/day, ketoprofen, folate, and MTX. Received the first dose of 100 mg of SC golimumab on September 21, 2006 and sham MTX once weekly. Entered early escape and received PO MTX weekly in addition to SC golimumab every 4 weeks. Received 14 injections of SC golimumab 100 mg mostly every 4 weeks. Her last dose was on December 13, 2007 (Day 450). On [redacted] she was hospitalized for one month of fever, right ear pain, sore throat and was found to have RA exacerbation and Streptococcal pharyngitis and otitis. She was discharged on [redacted] Her last injection of SC golimumab 100 mg was on. She died on [redacted] due to **circulatory arrest** (no autopsy was performed). b(6)
7	4602-60073 (Study 6)	**61 year old female** smoker, with a history of RA for 14.5 years taking diclofenac, MTX (17.5 mg/week), triazolam, omeprazole, amitriptyline, acetominophen, metoclopramide, and folic acid. One month prior to receiving study agent, she had a positive PPD and was started on INH for latent tuberculosis she was also started on didronel. She received the first SC administration of 100 mg of golimumab on July 11, 2006. She subsequently received one additional dose of golimumab on August 7, 2006 (Day 28). She was treated with amoxicillin/clavulanate potassium for a URI on August 21, 2006 (Day 42). On 23 Aug 2006 (Day 44), 16 days after the second dose of golimumab, she had nausea, diarrhea, and dehydration and isoniazid and amoxicillin/clavulanate potassium were discontinued and she was hospitalized on [redacted]. She was empirically treated for Clostridium difficile colitis with metronidazole (subsequently her C. difficile toxin and stool cultures were negative). On September 12, 2006 (Days 64) she had abdominal pain, vomiting, and diarrhea. On [redacted], she had an episode of coffee-ground emesis. Colonoscopy showed colitis with ulceration (most severe in the transverse colon). She was treated with intravenous hydrocortisone. On [redacted] she was transferred to the ICU and diagnosed with an ileus with clear evidence of obstruction. An ngt was placed and she was treated with cefuroxime for possible aspiration pneumonia. She was diagnosed with b(6)

		sepsis on [redacted] and had a cardiorespiratory arrest and died.
8	5805-60569 (Study 6) [redacted] KR-JNJ [redacted] 20071004551	**24 year old female** from Korea with a history of RA for 0.7 years and a history of hypothyroidism, hyperthyroidism, baseline liver enzyme elevations (prior hospitalization 8 months prior to receiving study agent for a liver disorder with elevated liver enzymes). Received methimazole, nabumetone, calcium, folate, prednisolone 5 mg/day, ketoprofen, MTX, and an herbal medication. Her screening and Week 0 liver enzyme tests were normal and she enrolled in Study 6. Received her first dose of SC golimumab 100 mg every 4 weeks on December 8, 2006 (Day 1) and sham MTX and received a total of 11 SC injections of golimumab. Her last SC golimumab dose was on September 19, 2007 (Week 40, Day 286). She did not enter early escape. Although, she received MTX prior to study entry, she did not receive MTX during the study. During the study on January 31, 2007 (Day 55), she had elevated liver enzymes (5x ULN), her herbal medication was stopped, and this resolved on February 13, 2007 (Day 68). The study drug was continued. On [redacted], she was hospitalized with 7 days of fever, chills, cough, nausea, vomiting, left upper quadrant abdominal pain, weight loss, enlarged liver and spleen, elevated liver enzymes (ALT, AST, Tbil, alkaline phosphatase). She had positive hepatitis B antigen by EIA method (negative at admission) but had negative Hepatitis B virus PCR titers, negative hepatitis B antigen by RIA, negative anti-hepatitis Be antibody, and negative hepatitis Be antigen. She was negative for anti-hepatitis C virus, EBV anti-VCA IgM, and Hepatitis E IgM antibody. Had an enterococcus UTI. Liver biopsy showed mild to moderate hepatocellular injury, mild sinusoidal dilation and congestion, minimal portal inflammation, and portal fibrosis on [redacted] She was diagnosed with acute hepatic failure. Hours after the liver biopsy, she had hemoperitoneum and required FFP and pRBC. She had embolization of a branch of the hepatic artery. She became hypotensive (requiring pressors) and lethargic on [redacted] She died on [redacted] of **acute liver failure and bleeding complications from a liver biopsy** and an autopsy was not performed. b(6)
9	1604-50395 (Study 5)	**38 year old male** with a history of RA for 0.3 years, current smoker (one pack/day for 23 years). Received piroxicam, acetominophen, and propoxyphene. Received 100 mg of SC golimumab and sham MTX (first dose on October 11, 2006) and then received 100 mg of SC golimumab (a total of 22 doses) every 4 weeks. He did not require early escape and continued to receive SC golimumab 100 mg every four weeks in the long-term extension. His last dose was on Day 589 (May 21, 2008, Week 76). On [redacted] he had anogenital warts which required hospitalization. The warts required surgical removal and then he was discharged from the hospital. He continued SC golimumab. He was found **dead at home** on [redacted] and no autopsy was performed. b(6)
Golimumab50 & MTX		
10	1008-50820 (Study 5)	**64 year old female** with a history of HTN, breast cancer, RA for 0.7 years taking concomitant 5 mg of prednisone, ibuprofen, carvedilol, clonazepam, midazolam, calcium, and vitamin D. She received the first SC administration of 50 mg of golimumab and first 10 mg PO MTX dose on March 21, 2007. She subsequently received 3 additional SC injections of 50 mg of golimumab each month (last on June 12, 2007) and she received weekly PO MTX starting increasing to 20 mg (last dose on June 6, 2007). On June 18, 2007 (Day 90) she self-administered an injection of rapid insulin (she took insulin from her husband, a known diabetic) and was hospitalized for a **hypoglycemic coma** and required mechanical respiratory assistance. A **suicide** note was found. She died on July [redacted] from respiratory failure. b(6)
11	2018-80239 (Study 8)	**61 year old female** from Canada with a history of psoriatic arthritis for over 25 years, psoriasis, MI, s/p coronary stents, fatty liver, GERD, hypothyroidism, hyperlipidemia, anemia, celiac disease, anxiety, insomnia, 0.75 pack/day smoker for 30 years. She was taking cyclobenzaprine, loperamide, fenofibrate, isosorbide dinitrate, amlodipine, levothyroxine, hydroxyzine, trimipramine, nitrazepam, alimemazine, pantoprazole, acetominophen, alendronate, calcium, bromazepam, domperidone, conjugated estrogens conjugated, quinapril, salbutamol, combivent, celecoxib, azithromycin, and clonidine. She received her first dose of SC golimumab 50 mg on June 22, 2006 and received a total of 10 SC injections every 4 weeks (last injection was on Day 253, March 1, 2007). She did not enter early escape and continued to receive golimumab 50 mg. On Day [redacted] she was hospitalized for a **MI** and on this day was found to have a lung mass with enlarged lymph nodes. Biopsy on [redacted] revealed **metastatic small cell lung carcinoma**. She died of metastatic small cell lung cancer on [redacted] b(6)
12	5202-80466 (Study 8)	**41 year old female** from Poland with a history of psoriatic arthritis for about 5 years and psoriasis. She was receiving diclofenac. She received her first dose of 50 mg of SC golimumab on September 6, 2006 and received a total of 12 doses of 50 mg of golimumab SC once weekly (she did not enter early escape). Her last dose of 50 mg of SC golimumab was on July 11, 2007 (Week 44, Day 309). On [redacted] days after the last dose of golimumab, the patient died as a result of an accident during **alpine climbing**. No autopsy was performed. b(6)
MTX only to Golimumab50 & MTX		
13	1204-50069 (Study 5)	**53 year old male** with a history of RA for 0.7 years, current smoker (quarter pack for 32 years), . Received acetominophen, 7.5 mg of prednisone/day, INH, pyridoxine, sertraline, venlafaxine, ibuprofen, codeine/acetominophen. He was assigned to the MTX monotherapy group and received his first dose of 10 mg of MTX on June 16, 2006 (Day 2) and he received placebo SC injections every 4 weeks. His weekly MTX was titrated to 20 mg/week by Week 6. On Day 372 (June 21, 2007, Week 52) he received his first dose of 50 mg of SC golimumab at the start of long-term extension and continued his weekly MTX. He continued to receive 50 mg of SC golimumab every 4 weeks for a total of 9 doses and his last golimumab 50 mg dose was given on January 24, 2008 (Week 76, Day 589, 217 days after the first golimumab dose). On [redacted] he presented with an 8 cm mass on his left breast and a fine needle aspiration on [redacted] diagnosed a malignancy. He was diagnosed with **metastatic non-small lung cancer**. He was also diagnosed with a subacute ischemic infarct on [redacted] by CT scan of the head. He died on Day [redacted] days after golimumab50 was started). b(6)
Placebo		
14	7483-10562	**80 year old female** with a history of RA for over 23 years, MI, CABG, osteoporosis, anxiety, HTN, DVT, asthma, total knee

	(Study 11)	arthroplasty. Who was taking 4 mg of prednisone daily, alendronate, warfarin, hydrocodone, acetominophen, atenolol, folic acid, MTX 15 mg/day. She received the first SC administration of placebo on March 7, 2007 and she received 5 additional SC injections of placebo every four weeks (last at Week 20, Study Day 141 on July 25, 2007). On [redacted], she was hospitalized for generalized weakness and anorexia and was diagnosed with **metastatic pancreatic cancer**. She died on [redacted] due to pancreatic cancer. b(6)

1 As of the last safety cut-off date for deaths in the SC golimumab studies in the 120-Safety Update (i.e., July 31, 2008). The golimumab studies include the 5 Phase 3 trials (i.e., Studies 5, 6, 11, 8, and 9), the Phase 2 asthma study (Study 3), the Phase 2 RA study (Study 2), and the phase 1 studies. There were no deaths in the phase 1 studies.

Reference: Adapted from Final Study Report for Study 5, Pages 763-764; Pages 768-769; also adapted from the Final Study Report for Study 6, Page 808-811; also adapted from the Final Study Report for Study 11; Pages 867-869; also adapted from the ISS, Pages 517-520; Pages 521-522; Pages 508-510; Pages 511-513. Also adapted from Final Study Report for Study 2, Pages 466-467. Also adapted from the 120-Day Safety Update, Appendix B.1, Pages 471-475, Appendix B.2, Pages 476-480. Also adapted from the Final Study Report for Study 3, Pages 852-855.

IV golimumab

The current BLA submission is to support the SC route of administration of golimumab. [redacted] There are 3 studies of IV golimumab [1 completed single ascending dose Phase 1 study in patients with RA (Study 466-1), 1 ongoing multiple-dose bioavailability study (Study 14)], and 1 ongoing safety/efficacy trial in patients with RA (Study 12)]. There were no deaths in Studies 466-1 and Study 14. As of the last safety cut-off (which includes safety data through the Week 24 database lock), there were 4 deaths in 550 (0.7%) IV golimumab-treated patients and no deaths in 129 (0%) MTX-treated patients in Study 12 (an ongoing, randomized, double-blind, global, MTX-controlled, 5-arm, Phase 3 trial of golimumab in patients with active RA with insufficient response to MTX). See Tables 7.3.4 and 7.3.5 for a summary and the narratives of these 4 deaths. All of the deaths occurred after receiving about 10 months of golimumab treatment. b(4)

A notable case in Study 12, was a 32 year old Asian female with early RA who died of probable sepsis and a possible MI after receiving about 10 months of golimumab 2 mg/kg treatment. It is likely that golimumab's immunosuppressive effects contributed to her probable sepsis and her death. Serious infections including sepsis are a known toxicity of the TNF inhibitors including golimumab. The golimumab label should include the standard Boxed Warnings of the risk serious infections and a REMS should be instituted to educate physicians about golimumab-associated serious infections including tuberculosis, invasive fungal infections, and other serious infections..

Table 7.3.4: Four deaths in the 3 IV golimumab studies up until the last safety cut-off date[1]

Study	Population	Treatment Group	Patient #	Study Day of Death	Study Day of Last Dose	Cause of Death
Study 12	RA	golimumab 4 mg/kg and MTX	1. 3422-20366	264	[redacted]	MI
		golimumab 4 mg/kg	2. 1001-20397	295		Acute pulmonary edema
		golimumab 2 mg/kg	3. 4020-20253	320		MI
			4. 1023-20485	352		Unknown

b(6)

1 As of the last safety cut-off date for deaths in the 120-Safety Update (i.e., July 31, 2008).
Reference: Adapted from the 120-day safety update.

Table 7.3.5: Narratives of the 4 deaths in the 3 IV golimumab studies through the last safety cut-off date[1]

Patient # (Study)	Narrative
golimumab 4 mg/kg & MTX	
3422-20366 (Study 12)	**59 year old male** with history of RA for 9 years, DM, HTN, hyperlipidemia, obesity. Received moxonidine, amlodipine, clopamide, vaseretic, potassium, simvastatin, nimesulide (an NSAID), metformin, tramadol, folate. Received first dose of IV golimumab 4 mg/kg and MTX 15 mg on June 15, 2007. Received the second dose of IV golimumab on Day 88 (Week 12), the third dose on November 20, 2007 (Day 169, Week 24), the fourth and last dose on February 22, 2008 (Day 253, Week 36). [redacted] days later, the patient died of an MI on [redacted] An autopsy was not performed. b(6)
golimumab 4 mg/kg monotherapy	
1001-20397 (Study 12)	**58 year old female** with history of RA for 5 years, HTN, smoker, CAD, prior UGI ulcer. Received etoricoxib, folate, carvedilol, meprobamate, estradiol, alprazolam, lansoprazole, and MTX. Received first dose of IV golimumab 4 mg/kg and sham MTX on June 21, 2007, received the second golimumab IV dose on September 11, 2007 (Week 12) received the third golimumab IV dose on December 6, 2007 (Week 24) and the fourth golimumab IV dose on February 28, 2008 (Week 36, Day 253). On [redacted] she had acute abdominal pain and was hospitalized on [redacted] with abdominal pain, cough, dyspnea, and hemoptysis and then discharged on [redacted] She was readmitted on [redacted] with acute dyspnea and chest pain. She had CHF and a possible MI and experienced a cardiac arrest and died on [redacted] . She died of an MI, CHF, and cardiogenic shock. b(6)
golimumab 2 mg/kg monotherapy	
4020-20253 (Study 12)	**32 year old Asian female** with history of RA for 3 years, received folate, diclofenac, and MTX. Received first dose of IV golimumab 2 mg/kg and sham MTX on May 17, 2007. Received her second dose of IV golimumab at Week 12 (Day 83), her third dose at Week 24, and her fourth and final dose at Week 36 (January 22, 2008, Day 250). At Week 20, MTX weekly was added. On [redacted] days after the last dose of golimumab IV) she was hospitalized for **possible sepsis** (fever, leukocytosis, tachycardia, tachypnea) and GERD. She was treated with an IV cephalosporin and a blood transfusion. She also had an EGD which showed chronic gastritis and was treated with twice a day PPI. On [redacted] she had chest pain and shortness of breath, ECG was suggestive of an **IMI**. She required resuscitation, but she died on [redacted] b(6)
1023-20485 (Study 12)	**65 year old female** with a history of RA for 15 years and a history of HTN. Received enalapril, diclofenac, prednisone, chlorhexidine. Received golimumab IV 2 mg/kg on July 6, 2007 and sham weekly MTX, second dose of IV golimumab on September 28, 2007 (Week 12), a third dose on December 21, 2007 (Week 24), and a fourth and final dose on March 12, 2008 (Week 36). Developed anemia. Was hospitalized for hypotension. Died on [redacted] of an unknown cause and an autopsy was not performed. b(6)

1 As of the last safety cut-off date for deaths in the 120-Safety Update (i.e., July 31, 2008). There is 1 completed single ascending dose Phase 1 study of IV golimumab in patients with RA (i.e., Study 466-1) and there are 2 additional ongoing IV golimumab studies: one safety/efficacy trial of IV golimumab (i.e., Study 12) and 1 bioavailability study of IV golimumab (i.e., Study 14). Study 12 is a R, DB, MC, global, MTX-control, 5-arm, Phase 3 trial of golimumab in patients with active RA with insufficient response to MTX (with possible prior exposure to anti-TNF). Possible EE at W16 and W24; then LE from W48 to W120 patients will switch to SC golimumab. The original BLA submission is for the SC administration of golimumab. [redacted] (see Tables 5.3 and 5.4 in Section 5.1 for the design of the IV golimumab studies). b(4)

Reference: Adapted from the ISS, Pages 523-525, 526-527, 528-530.

7.3.2 Serious Adverse Events

In the golimumab studies, SAEs were defined as any AE that resulted in death; were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability and/or incapacity (i.e., a substantial disruption in a person's ability to conduct normal activities of daily living), were a congenital anomaly and/or birth defect, or an important medical event that could have been considered an SAE if it required medical or surgical intervention to prevent one of the outcomes listed above.

Table 7.3.6 displays the SAEs in the 5 Phase 3 trials of SC golimumab through Week 24. A lower proportion of patients in the golimumab groups, compared to the placebo groups, experienced SAEs. Notably, the golimumab100 group, compared to the placebo group, had a higher proportion of patients who had sepsis and URI SAEs. These SAEs may be golimumab-related given the association of TNF inhibitors and increased incidence of serious infections.

The exposure-adjusted rate of SAEs in the placebo to golimumab50 escape treatment group was slightly higher than the placebo group and the exposure-adjusted rate of SAEs in the golimumab50 to golimumab100 escape treatment group was slightly higher than the golimumab50 group (see Table 7.3.6). However, since there were few SAEs and there was a limited duration exposure in each of the escape treatment groups (7.9 weeks), no firm conclusions can be drawn about the differential rates of SAEs in the escape treatment groups and the treatment groups assigned at randomization groups.

Table 7.3.6: SAEs (≥ 2 in any treatment group) by MedDRA preferred term in the 5 Phase 3 trials of RA, PsA, and AS through Week 24 (double-blinded, controlled data)[1]

	Treatment Groups Assigned at Randomization[2]			Escape Treatment Groups[2,3]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100[4] ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients[5]	639	683	977	205	109
Patient years of follow up	252	296	443	31	17
Mean duration of therapy	20.5 weeks	22.4 weeks	23.6 weeks	7.9 weeks	7.9 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
n (%) patients with ≥ 1 SAE	43 (6.7%)	35 (5.1%)	54 (5.5%)	6 (2.9%)	4 (3.7%)
Sepsis, %	0%	0%	0.6%	0%	0%
Arthralgia, %	0%	0.1%	0.4%	0%	0%
Pneumonia, %	0.6%	0.3%	0.3%	0%	0%
URI, %	0%	0%	0.3%	0%	0%
Skin laceration, %	0%	0%	0.3%	0%	0.2%
UTI, %	0.3%	0.1%	0.2%	0.5%	0%
Anaemia, %	0.3%	0%	0.2%	0%	0.9%
Pneumonitis, %	0.2%	0%	0.2%	0%	0%
Chest pain, %	0%	0%	0.2%	0.5%	0%
Arthritis bacterial	0%	0%	0.2%	0%	0%
Hepatitis, %	0%	0%	0.2%	0%	0%
Abdominal pain upper, %	0%	0%	0.2%	0%	0%
Depression, %	0%	0%	0.2%	0%	0%
Rheumatoid arthritis, %	0.6%	0.1%	0.1%	0.5%	0%
Myocardial infarction, %	0.3%	0.1%	0.1%	0%	0%
Cellulitis, %	0.3%	0.1%	0.1%	0%	0%
Vomiting, %	0%	0.3%	0%	0%	0%
Basal cell carcinoma, %	0.3%	0%	0%	0%	0%
Patients with an SAE per 100-patient-years	17.1	11.8	12.2	19.4	23.5

1 Data through Week 24 represents the double-blinded and controlled portions of the 5 Phase 3 Trials. Patients may appear in more than one column. One of the 5 trials (Study 5) included a double-blinded and controlled portion up to Week 52 (see the individual study report for Study 5 for the DAEs in Study 5 through Week 52). All MedDRA preferred terms are included in which ≥ 2 SAEs occurred in any treatment group. 3 The Phase 3 trials include Studies 5, 6, 8, 9, and 11.

2 In all of the Phase 3 trials, patients received study agent and may have received concomitant MTX, NSAIDs, and/or ≤ 10 mg/day of prednisone. Patients in Studies 9 and 11 may also have received concomitant SSZ, and/or HCQ.

3 Patients may have entered early escape at Week 16 in Studies 6, 8, 9, and 11 and at Week 28 in Study 5.

4 The golimumab100 and MTX combination group includes all patients assigned to this regimen at baseline. Patients in this group that escaped continued to receive the same treatment and are included in this column.

5 Treated patients includes patients who received at least one SC study agent administration (placebo or golimumab)
Adapted from the ISS, Table 28, Pages 249-257

7.3.3 Dropouts and/or Discontinuations

Table 7.3.7 displays the adverse events leading to discontinuation (DAEs) in the 5 Phase 3 trials of SC golimumab through Week 24.

Overall, a very small proportion (3 to 4% in each treatment group) of patients discontinued from the study. A slightly lower proportion of patients in the golimumab groups, compared to the placebo

groups, experienced DAEs. Notably, the golimumab100 group, compared to the placebo group, had a higher proportion of patients who had sepsis DAEs. These SAEs may be golimumab-related given the association of TNF inhibitors and an increased incidence of serious infections.

The exposure-adjusted rate of DAEs in the placebo to golimumab50 escape treatment group was lower than the placebo group and the exposure-adjusted rate of SAEs in the golimumab50 to golimumab100 escape treatment group was lower than the golimumab50 group (see Table 7.3.7). However, since there was only 1 DAE in the escape groups and there was a limited duration exposure in each of the escape treatment groups (8 weeks), no firm conclusions can be drawn about the differential rates of DAEs in the escape treatment groups and treatment groups assigned at randomization groups.

Table 7.3.7: DAEs (≥ 2 in any treatment group) by MedDRA preferred term in the 5 Phase 3 trials of RA, PsA, and AS through Week 24 (double-blinded, controlled data)[1]

	Treatment Groups Assigned at Randomization[2]			Escape Treatment Groups[2,3]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100[4] ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients[5]	639	683	977	205	109
Patient years of follow up	252	296	443	31	17
Mean duration of therapy	20.5 weeks	22.4 weeks	23.6 weeks	7.9 weeks	7.9 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
n (%) patients with ≥ 1 DAE	25 (3.9%)	19 (2.8%)	32 (3.3%)	1 (0.5%)	0 (0%)
Sepsis, %	0%	0%	0.4%	0%	0%
Abscess, %	0%	0.1%	0.2%	0%	0%
ALT increased, %	0%	0.1%	0.2%	0%	0%
AST increased, %	0%	0.1%	0.2%	0%	0%
Basal cell carcinoma, %	0.2%	0%	0.2%	0%	0%
Hepatitis, %	0.2%	0%	0.2%	0%	0%
Pneumonitis, %	0%	0%	0.2%	0%	0%
Arthralgia, %	0%	0%	0.2%	0%	0%
RA, %	0.6%	0%	0.1%	0%	0%
Nausea, %	0.2%	0.3%	0%	0%	0%
Vomiting, %	0%	0.3%	0%	0%	0%
Headache, %	0.5%	0%	0%	0%	0%
Pregnancy, %	0.3%	0%	0%	0%	0%
Patients with a DAE per 100-patient-years	9.9	6.4	7.2	3.2	0

1 DAEs are AEs leading to discontinuation. Data through Week 24 represents the double-blinded and controlled portions of the 5 Phase 3 trials (Studies 5, 6, 8, 9, and 11). One of the 5 trials (Study 5) included a double-blinded and controlled portion up to Week 52 (see the individual study report for the DAEs in Study 5 through Week 52). Patients may appear in more than one column. All MedDRA preferred terms are included in which ≥ 2 DAEs occurred in any treatment group.

2 In all of the Phase 3 trials, patients received study agent ± NSAIDs and/or ≤ 10 mg/day of prednisone. Patients in the 5 trials may also have received concomitant MTX. Patients in Studies 9 and 11 may also have received concomitant SSZ, and/or HCQ.

3 Early escape could have occurred at Week 16 in Studies 6, 8, 9, and 11 and at Week 28 in Study 5.

4 Patients in the golimumab100 group who escaped, continued with golimumab100.

5 Treated patients includes patients who received at least one SC study agent administration (placebo or golimumab)

Adapted from the ISS, Table 33, Pages 272-278

7.3.4 Common Adverse Events

Table 7.3.8 displays the AEs in the 5 Phase 3 trials of SC golimumab through Week 24. A slightly higher proportion of patients in the golimumab groups, compared to the placebo group, had AEs. The differential proportion was due to a higher proportion of infection-related AEs such as URIs, nasopharyngitis, and sinusitis. There appeared to be a possible dose-related increase in injection site erythema AEs.

Table 7.3.8: AEs (with frequency ≥ 2% in any treatment group) by MedDRA preferred term in the 5 Phase 3 trials of RA, PsA, and AS through Week 24[1] (double-blinded, controlled data)

	Treatment Groups Assigned at Randomization[2]			Escape Treatment Groups[2,3]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100[4] ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients[5]	639	683	977	205	109
Patient years of follow up	252	296	443	31	17
Mean duration of therapy	20.5 weeks	22.4 weeks	23.6 weeks	7.9 weeks	7.9 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
n (%) patients with ≥ 1 AE	444 (70%)	511 (75%)	729 (75%)	93 (45%)	42 (39%)
URI, %	7%	10%	10%	2%	2%
Nasopharyngitis, %	6%	8%	8%	5%	3%
Nausea, %	6%	6%	7%	2%	0%
Headache, %	5%	5%	6%	2%	2%
Fatigue, %	4%	4%	6%	2%	0%
ALT increased, %	4%	5%	5%	1%	0%
Injection site erythema, %	1%	3%	5%	1%	4%
Cough, %	5%	6%	4%	3%	2%
Diarrhoea, %	5%	5%	4%	2%	2%
AST increased, %	3%	4%	4%	1%	0%
Back pain, %	3%	4%	4%	1%	1%
Hypertension, %	2%	4%	4%	2%	0%
Arthralgia, %	4%	3%	4%	1%	2%
Rash, %	3%	3%	4%	1%	0%
Sinusitis, %	1%	3%	3%	2%	2%
Bronchitis, %	3%	2%	3%	1%	0%
Influenza, %	2%	2%	3%	0%	0%
Insomnia, %	1%	2%	3%	1%	1%
Dyspepsia, %	2%	4%	2%	1%	0%
Pharyngolaryngeal pain, %	2%	4%	2%	1%	3%
Abdominal pain upper, %	1%	3%	2%	1%	0%
Dizziness, %	1%	3%	2%	1%	0%
RA, %	3%	2%	2%	2%	1%
Abdominal pain, %	2%	2%	2%	0%	0%
Vomiting, %	2%	2%	2%	2%	0%
Pruritus, %	1%	2%	2%	2%	1%
Pharyngitis, %	2%	1%	2%	2%	0%
Alopecia, %	1%	1%	2%	1%	0%
UTI, %	2%	2%	1%	1%	0%
Oral herpes, %	0.3%	1%	1%	1%	3%

1 Data through Week 24 represents the double-blinded and controlled portions of the 5 Phase 3 Trials. Patients may appear in more than one column. The Phase 3 trials include Studies 5, 6, 8, 9, and 11.
2 In all of the Phase 3 trials, patients received study agent ± NSAIDs and/or ≤ 10 mg/day of prednisone. Patients in Studies 6, 8, 9, and 11 may also have received concomitant MTX. Patients in Studies 9 and 11 may also have received concomitant SSZ, and/or HCQ.
3 Early escape at Week 16 in Studies 6, 8, 9, and 11. Early escape at Week 28 in Study 5.
4 Patients in the golimumab100 group who escaped, continued with golimumab100.
5 Treated patients includes patients who received at least one SC study agent administration (placebo or golimumab)
Adapted from the ISS, Table 23, Pages 183-230.

7.4 Evaluation of Specific Safety Concerns of TNF Inhibitors

7.4.1 Infections

In the controlled portions of the 5 Phase 3 trials through Week 24, there were 14, 10, and 31 **serious infections** (SIEs) in the placebo, golimumab50, and golimumab100 groups, respectively. Table 7.4.1 displays the **number and proportion of patients** with (SIEs), infection AEs requiring oral or parental anti-microbial therapy, and infection AEs in the 5 Phase 3 trials through Week 24.

A similar proportion of patients in the golimumab groups, compared to the placebo group, had a SIE. Notably, patients in the golimumab100 group had a higher proportion of sepsis, URI, and bacterial arthritis serious infections than the placebo group. A slightly greater proportion of patients in the golimumab groups had an infection AE and had an infection AE that required oral or parental anti-microbial therapy compared to the placebo group.

Table 7.4.1: Patients with SIEs, infections requiring anti-microbial therapy, and infection AEs in the 5 Phase 3 trials of RA, PsA, and AS through Week 24 (double-blinded, controlled data)[1]

	Treatment Groups Assigned at Randomization[2]			Escape Treatment Groups[2,3]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100[4] ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients[5]	639	683	977	205	109
Mean duration of follow-up	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
n (%) patients with ≥ 1 SIE	14 (2.2%)	10 (1.5%)	22 (2.3%)	1 (0.5%)	0 (0%)
Sepsis, %	0%	0%	0.6%	0%	0%
Pneumonia, %	0.6%	0.3%	0.3%	0%	0%
URI, %	0%	0%	0.3%	0%	0%
Urinary tract infection, %	0.3%	0.1%	0.2%	0.5%	0%
Arthritis bacterial, %	0%	0%	0.2%	0%	0%
Cellulitis, %	0.3%	0.1%	0.1%	0%	0%
n (%) patients with ≥ 1 infection AE requiring antimicrobial therapy	109 (17%)	143 (21%)	222 (23%)	23 (11%)	5 (5%)
n (%) patients with ≥ 1 infection AE	195 (31%)	247 (36%)	373 (38%)	36 (18%)	12 (11%)

1 Data through Week 24 represents the double-blinded and controlled portions of the 5 Phase 3 trials (Studies 5, 6, 8, 9, and 11). Serious infections were SAEs which were infections according to the investigators. All MedDRA preferred terms are included in which ≥ 2 serious infections occurred in any treatment group. Patients may appear in more than one column.
2 In all of the Phase 3 trials, patients received study agent ± NSAIDs and/or ≤ 10 mg/day of prednisone. Patients in the 5 trials may also have received concomitant MTX. Patients in Studies 9 and 11 may also have received concomitant SSZ, and/or HCQ.
3 Early escape could have occurred at Week 16 in Studies 6, 8, 9, and 11 and at Week 28 in Study 5.
4 Patients in the golimumab100 and MTX combination group who escaped and who did not escape.
5 Treated patients includes patients who received at least one SC study agent administration (placebo or golimumab).
Adapted from the ISS, Table 44, Pages 322-324; Table 34, Page 279; Table 35, Page 389; Table 36, page 294; Table 37, Page 300; Table 38, Page 308; Table 39, Page 312

Table 7.4.2 compares patients with SIEs per 100 patient-years in the controlled portions of the Phase 3 trials to the patients with SIEs per 100 patient-years in the controlled and uncontrolled portions of the Phase 3 trials through the last safety cut-off. Table 7.4.3 displays the exposure-adjusted incidence of SIEs in the controlled and uncontrolled portions of the Phase 3 trials. Note, Table 7.4.2 displays the **number of patients** with serious infection; whereas, Table 7.4.3 presents the **number of serious infections**.

The number of patients with SIEs per 100-patient years in the low and high dose golimumab groups did not increase in the open-label portions of the Phase 3 trials.

In the controlled and uncontrolled portions of the Phase 3 trials, the incidence of SIEs per 100 patient-years was lower in combined golimumab group compared to the placebo group; however the exposure-adjusted incidence rate of SIEs in the placebo group of these trials was 1.5 to 3 times higher

than published background rates of SIEs in RA patients taking non-biologic DMARDS (2 to 4 SIEs per 100 pt-years, Listing 2005, Dixon 2007). Nonetheless, the exposure adjusted incidence rate of SIEs in the golimumab groups is consistent with published rates for TNF inhibitors (5 to 6 SIEs per 100 pt-years, Listing 2005, Dixon 2007). These results support the conclusion that golimumab is similar to other TNF inhibitors with respect to the risk of infection.

Table 7.4.2: Patients with SIEs in the controlled and uncontrolled portions of the Phase 3 trials of SC golimumab through the last safety cut-off[1]

	Controlled Portions of Phase 3 Trials (through Week 24)			Controlled & Uncontrolled Portions of Phase 3 Trials (through last Safety Cut-Off)[1]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	golimumab50 ± MTX	golimumab100 ± MTX
Patients treated	639	683	977	1233	1286
Patient-years of follow-up	256	294	440	1397	1679
n (%) of patients with ≥ 1 SIE	14 (2.2%)	10 (1.5%)	22 (2.3%)	34 (2.8%)	64 (5.0%)
# of patients with SIEs per 100 patient-years	5.5	3.4	5.0	2.4	3.8

Adapted from the ISS, Table 44, Pages 322-324; also adapted from the 120-Safety Update Report, Appendix A.24, Page 364

Table 7.4.3: Incidence of SIEs in the controlled and uncontrolled portions of the Phase 3 trials of SC golimumab through the last safety cut-off[1]

	Phase 3 trials	
Treatment Groups	placebo ± MTX	golimumab ± MTX
Patients treated	639	2210
Patient-years of follow-up	332	2953
n (%) of patients with ≥ 1 SIE[3]	17 (2.7%)	98 (4.4%)
# of SIEs	19	131
Incidence of SIEs per 100 patient-years (95% CI)	5.7 (3.5, 9.0)	4.4 (3.7, 5.3)

1 As of the last safety cut-off date in the 120-Safety Update (i.e., June 2, 2008). Serious infections were SAEs which were infections according to the investigators.
2 All Phase 2 & 3 trials include the 3 RA Phase 3, 1 Phase 3 PsA, 1 Phase 3 AS, and 1 Phase 2 RA.
Adapted from the 120-Safety Update Report, Appendix A.26, Page 368

Table 7.4.4 displays SIEs of interest in the controlled and uncontrolled portions of the 13 submitted studies of golimumab through the last safety cut-off.

There were 7 cases of tuberculosis and 4 cases of invasive fungal infection (2 cases of histoplasmosis, 1 case of coccidioidomycosis, and 1 case of pneumocystosis) in the 13 submitted golimumab studies through the last safety cut-off date. Since tuberculosis and invasive fungal infections are known and labeled toxicities of all the TNF inhibitors, these SIEs were probably related to golimumab. The majority of the patients who developed tuberculosis were appropriately screened prior to initiation of golimumab. However, as with the other TNF inhibitors, appropriate screening for tuberculosis does not eliminate the risk of tuberculosis; in part because this does not prevent infections related to new TB exposures, and in part because no screening is 100% accurate. The golimumab labeling should include similar boxed warnings and warnings as the other TNF inhibitors regarding the risk of SIEs, particularly tuberculosis and invasive fungal infections. Also similar to the other TNF inhibitors, golimumab should include a REMS to educate health care providers about the increased risks of SIEs including tuberculosis and invasive fungal infections.

Table 7.4.4: SIEs of interest in the 13 submitted studies of golimumab through the last safety cut-off date[1]

Treatment Group	Study (population)	Patient#	Comment[2]
Tuberculosis			
MTX to golimumab50 & MTX	Study 6 (RA)	6401-60408	Screening PPD was positive but was not appropriately treated for latent TB. 38 year old female from Taiwan had tuberculosis pleurisy at Week 36. Received concomitant prednisone.
golimumab50 & MTX	Study 5 (RA)	7004-50139	Appropriate screening tests for TB were negative. A 64 year old female from the Ukraine with RA for 7 years received 3 doses of golimumab50 and on Day 90 developed bone tuberculosis of the spine. She developed paralysis of the lower extremities and bowel and bladder dysfunction and required a surgical procedure.
golimumab50 & MTX	Study 5 (RA)	5005-50326	Appropriate screening tests for TB were negative according to local guidelines. 67 year old women from the Philippines with RA on concomitant prednisone diagnosed with pulmonary TB at Week 24.
golimumab100	Study 9 (AS)	5806-90255	Appropriate screening tests for TB were negative. 24 year old man from South Korea with AS, received concomitant prednisone. Diagnosed with pulmonary TB at Week 40.
golimumab100	Study 3 (asthma)	0402-029	Appropriate screening tests for TB were negative. 73 year old male from France receiving 20 mg of prednisolone for asthma had pleural tuberculosis diagnosed about 6 months after the last golimumab dose (last dose given at Week 48). Grew up in an endemic region to TB in North Africa.
golimumab100& MTX	Study 5 (RA)	5601-50352	N/A
golimumab100 & MTX	Study 5 (RA)	5004-50848	Appropriate screening tests for TB were negative. 66 year old female from the Philippines had tuberculosis pleurisy at Week 42. Was receiving concomitant prednisone.
Invasive Fungal Infections			
golimumab (concomitant MTX and prednisone)	Study 11 (RA)	7446-10614	67 year old male from Illinois with lung histoplasmosis

golimumab100 (concomitant MTX)	**Study 8 (PsA)**	**7429-80468**	**49 year old male from Ohio with liver histoplasmosis. Hospitalized and discharge home on oral anti-fungal medications.**
golimumab	**Study 9 (AS)**	**7437-90124**	**85 year old male from Arizona with weight loss. Diagnosed with coccidioidomycosis and treated with oral antifungals.**
golimumab and MTX	**Study 5 (RA)**	**2204-50480**	**25 year old female from Chile with meningoencephalitis, had seizures, required intubation. Diagnosed with pneumocystosis**
Opportunistic Bacterial Infections			
Placebo/MTX to infliximab/MTX	**Study 2 (RA)**	**403-006**	**Listeria sepsis considered an opportunistic infection**
golimumab100 & MTX	**Study 2 (RA)**	**106-006**	**Legionella pneumonia considered an opportunistic infection**
Opportunistic Viral Infections			
golimumab100 & MTX	**Study 5 (RA)**	**5210-50284**	**Acute Hepatitis B infection was taking concomitant methylprednisolone**
placebo	**Study 1** [redacted]	**103-007**	**Herpes Zoster was receiving concomitant prednisolone and mycophenolate mofetil and had diabetes**

b(4)

1 As of the last safety cut-off date in the 120-Safety Update (i.e., June 2, 2008). No serious infections of interest occurred in Phase 1 studies in RA (Studies 466-1 and 466-2) or the Phase 1 studies in healthy subjects (Studies 13, 23, and 24)

2 All patients in the 5 Phase 3 trials were supposed to have the following three TB screening tests: tuberculin test, QuantiFERON-TB Gold test, and a CXR. All patients in the Phase 2 trials were supposed to have the following two TB screening tests: tuberculin test and a CXR.

7.4.2 Malignancies

Epidemiologic data regarding whether TNF inhibitors increase the risk of malignancies are mixed. Generally, in large registries of RA patients, TNF inhibitor treatment does not appear to increase the risk of malignancy, with the possible exception of lymphoma and skin cancers, for which RA patients have an underlying increased risk (Wolfe 2007, Smitten 2007). Nonetheless, there are data that suggest that blocking TNF, which is important for immune surveillance, may have a permissive effect on malignancies that may be initiated from other causes. For example, patients with Wegener's granulomatosis who were treated with etanercept and cyclophosphamide (a DNA alkylating agent) did exhibit an increase in malignancies, as did patients with COPD (a population with higher exposure to cigarette smoking) who were treated with infliximab. Interestingly, a similar signal may be present with high dose (200 mg) golimumab in a Phase 2 asthma trial [see Tables 7.7.4 and 7.7.5 in Section 7.7.2 (Safety in Asthma Trial)].

This section evaluates malignancies in the controlled portions of the 5 Phase 3 trials and in the controlled and uncontrolled portions of the rheumatology trials (1 Phase 2 RA and 5 Phase 3 trials).

Controlled Portions of the Phase 3 Trials: Table 7.4.5 displays the malignancies in the controlled portions of the 5 Phase 3 trials.

Overall, the combined golimumab groups did not have a greater proportion of malignancies compared to the placebo control group. The placebo and golimumab50 group had a similar proportion of malignancies. However, the golimumab100 group had a greater proportion of malignancies than the

golimumab50 group and the placebo group. The types of malignancies observed were consistent with the types of malignancies seen in the RA population.

Table 7.4.5: Malignancies by preferred term in the 5 Phase 3 trials of RA, PsA, and AS through Week 24 (double-blinded, controlled data) [1]

	Treatment Groups Assigned at Randomization[2]			Escape Treatment Groups[2,3]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100[4] ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients[5]	639	683	977	205	109
Mean duration of follow-up	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
All Malignant Neoplasms except NMSC[6]	2 (0.3%)	1 (0.1%)	5 (0.5%)	0 (0%)	0 (0%)
Breast cancer	1 (0.2%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Hodgkin's disease	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Lung neoplasm	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Lymphoma	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Prostate cancer	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Breast cancer in situ	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)
Pancreatic carcinoma metastatic	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
NMSC[6]	3 (0.5%)	1 (0.1%)	6 (0.6%)	0 (0%)	0 (0%)
Basal cell carcinoma	2 (0.3%)	0 (0%)	4 (0.4%)	0 (0%)	0 (0%)
Squamous cell carcinoma	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Lip neoplasm malignant stage unspecified	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bowen's disease	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)

1 Data through Week 24 represents the double-blinded and controlled portions of the 5 Phase 3 trials (Studies 5, 6, 8, 9, and 11). Patients may appear in more than one column.
2 In all of the Phase 3 trials, patients received study agent ± NSAIDs and/or ≤ 10 mg/day of prednisone. Patients in Studies 6, 8, 9, and 11 may also have received concomitant MTX. Patients in Studies 9 and 11 may also have received concomitant SSZ, and/or HCQ.
3 Early escape at Week 16 in Studies 6, 8, 9, and 11. Early escape at Week 28 in Study 5.
4 Patients in the golimumab100 group who escaped, continued with golimumab100.
5 Treated patients includes patients who received at least one SC study agent administration (placebo or golimumab)
6 The yellow highlighted rows include all malignancies by treatment group. One patient may have had one or more malignancy. NMSC is non-melanoma skin cancer.
Adapted from the ISS, Table 23, Pages 226-227

Controlled and Uncontrolled Portions of the Phase 2 and Phase 3 Rheumatology Trials: Table 7.4.6 displays the exposure-adjusted malignancies in the controlled and uncontrolled portions of the rheumatology trials of SC golimumab (5 Phase 3 trials and the 1 Phase 2 RA trial) through the last safety cut-off date.

The exposure-adjusted incidence of all malignancies (including NMSC) in the golimumab groups was similar or lower than the placebo control group in the rheumatology trials. The exposure-adjusted incidence of all malignancies did not increase over time in the combined golimumab groups. The exposure-adjusted incidence of all malignancies in the low and high dose golimumab groups was similar in the rheumatology trials and is consistent with published background rates of malignancy in RA patients (e.g., 0.8 to 1.4 malignancies per 100 patient-years in the British Society for Rheumatology Biologics Registry).

Table 7.4.6: All malignancies in the controlled and uncontrolled portions of the Phase 2 and Phase 3 rheumatology trials of SC golimumab through the last safety cut-off[1]

		Controlled Portions of Phase 3 Trials (through Week 24)			Controlled & Uncontrolled Portions of Phase 2 and Phase 3 Trials (through last Safety Cut-Off)[1]	
		placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	golimumab50 ± MTX	golimumab100 ± MTX
Patients treated		639	683	977	1301	1356
Patient-years of follow-up[3]		252	294	443	1467	1757
Median patient-years of follow-up		—	—	—	1.2	1.5
All Malignancies except NMSC	n of patients	2	1	5	11	8
	Incidence per 100 patient-years	0.8	0.3	1.1	0.7	0.5
NMSC	n of patients	3	1	6	9	11
	Incidence per 100 patient-years	1.2	0.3	1.4	0.6	0.6

1 As of the last safety cut-off date in the 120-Safety Update (i.e., June 2, 2008). Patients may appear in more than one column.

2 The rheumatologic Phase 2 and Phase 3 Trials included 1 Phase 2 RA (Study 2), 3 Phase 3 RA (Studies 5, 6, and 11), 1 Phase 3 PsA (Study 8), 1 Phase 3 AS (Study 9).

Adapted from the 120-Safety Update Report, Appendix A.32, Pages 381-3

Table 7.4.7 displays the exposure-adjusted malignancies in the controlled and uncontrolled portions of the rheumatology trials of SC golimumab (5 Phase 3 trials and the 1 Phase 2 RA trial) through the last safety cut-off date compared to the expected rate, using the Surveillance, Epidemiology, and End Results (SEER) database, a general U.S. population database maintained by the National Cancer Institute (http://seer.cancer.gov/). Since NMSCs are not included in the SEER database, there is no comparison to the SEER database for the NMSCs. The exposure-adjusted malignancies other than NMSC rates in the golimumab and placebo groups were similar to the expected rate according to the SEER database.

Table 7.4.7: Malignancies in the controlled and uncontrolled portions of the SC golimumab rheumatology Phase 2 and Phase 3 trials through the last safety cut-off compared to the SEER database[1]

			placebo ± MTX	golimumab ± MTX
All Malignancies	All malignancies except NMSC[3]	Median patient-years of follow-up	0.5	1.4
		Total patient-years of follow-up	344	3099
		Observed # of patients with ≥ 1	2	19
		Observed incidence per 100 patient-years	0.6	0.6
		Expected # of patients with ≥ 1 (SEER)[2]	2.1	17.6
		SIR (95% CI)[2]	1.0 (0.1, 3.5)	1.1 (0.7, 1.7)
	NMSC[4]	Total patient-years of follow-up	342	3087
		Observed # of patients with ≥ 1	5	19
		Observed incidence per 100 patient-years	1.5 (0.5, 3.4)	0.6 (0.4, 1.0)

1 Based on the SEER database from 2004, adjusted for age, gender, and race. Patients may appear in more than one column. This table includes the results from all the rheumatologic trials of SC golimumab (5 Phase 3 trials and the 1 Phase 2 RA trial). The Phase 1 studies in patients with RA, the studies in healthy volunteers, and patients with [redacted] are not included in this table. The Phase 2 asthma study is not included. The malignancies in the [redacted] golimumab program in RA in Study 12 are not included in this table. b(4)

2 SIR is the standardized incidence ratio (**observed** number of patients with malignancy **divided by** the **expected** number of patients with malignancy).

3 All malignancies except NMSC includes lymphomas. There were 3 lymphomas in the golimumab groups and no lymphomas in the placebo groups (see Table 7.4.8).

4 Since the SEER database does not include NMSCs, no comparison was made to the SEER database.

Adapted from the 120-Safety Update Report, Appendix A.33, Pages 384-385; Appendix A.34, Page 386-388Appendix A.36, Pages 392-394

In the TNF inhibitor trials, a greater proportion of patients in TNF inhibitor arms, compared to control groups, have had lymphomas. In the controlled and uncontrolled portions of the golimumab rheumatology studies, there were no lymphomas in the placebo group and out of 19 malignancies other than NMSC, there were 3 lymphomas in the golimumab arms (see Table 7.4.8).

The exposure-adjusted lymphomas in the golimumab groups were greater than the expected rate in the general U.S. population according to the SEER database. This finding is similar to the other TNF inhibitors and is also consistent with the underlying increased risk of lymphoma in RA patients. As with the other TNF inhibitors, the label should include WARNINGS about the association of lymphomas with golimumab treatment.

Table 7.4.8: Lymphomas in the controlled and uncontrolled portions of the SC golimumab Phase 2 and Phase 3 rheumatology trials through the last safety cut-off compared to the SEER database[1]

		placebo ± MTX	golimumab ± MTX
Lymphoma	Median patient-years of follow-up	0.5	1.4
	Total patient-years of follow-up	344	3100
	Observed # of patients with ≥ 1	0	3
	Expected # of patients with ≥ 1 (SEER)[1]	0.1	0.8
	SIR (95% CI)[2]	0 (0, 33.4)	3.8 (0.8, 11.1)

1 Based on the SEER database from 2004, adjusted for age, gender, and race. This table includes the results from all the rheumatologic trials of SC golimumab (5 Phase 3 trials and the 1 Phase 2 RA trial). The Phase 1 studies in patients with RA, the studies in healthy volunteers, and patients with [redacted] are not included in this table. The Phase 2 asthma study is not included. The malignancies in the [redacted] golimumab program in RA in Study 12 are not included in this table.

b(4)

2 SIR is the standardized incidence ratio (**observed** number of patients with malignancy **divided by** the **expected** number of patients with malignancy).

Adapted from the 120-Safety Update Report, Appendix A.33, Pages 384-385; Appendix A.34, Page 386-388Appendix A.36, Pages 392-394

Comparison of Malignancies in the Golimumab Trials to Other TNF Inhibitor Trials: Table 7.4.9 presents the malignancies in the controlled portions of golimumab and the 4 approved TNF inhibitors. The relative risks malignancies in the five TNF inhibitors cannot be directly compared because these trials included different populations with different susceptibilities to malignancy (e.g., different countries, ages, smoking history, family history of malignancy, alcohol history, concomitant immunosuppressive medication); these trials were conducted during different years with possible different rates of malignancy; and these analyses included different malignancies (the infliximab and adalimumab analyses excluded all lymphomas and NMSC, but the certolizumab and golimumab analyses only excluded NMSCs).

Although there are multiple problems with cross study comparisons, the relative risk of malignancies in the golimumab trials do not appear greater than the relative risk of malignancies in the other TNF inhibitor trials.

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Table 7.4.9: Malignancies in the controlled portions of TNF inhibitor trials[1]

Product	Malignancies	Populations	TNF inhibitor		Control		RR
			n/N	Events/ 100 pt-year	n/N	Events/ 100 pt-year	
Infliximab	All malignancies excluding lymphoma and NMSC	RA, PsA, AS, Ps, CD, UC,	14/4019	0.5	1/1597	0.1	4.7
Etanercept	N/A	RA, PsA, AS, Ps	N/A	N/A	N/A	N/A	N/A
Adalimumab	All malignancies excluding lymphoma and NMSC	RA, PsA, AS, Ps, CD	14/3853	0.6	5/2183	0.4	1.4
Certolizumab	All malignancies excluding NMSC	[redacted], CD	10/2725	0.7	3/1343	0.6	1.2
Golimumab[4]	All malignancies excluding NMSC	RA[2], PsA[2], AS[2]	6/1794	0.6	2/674	0.6	1.0

b(4)

n/N (patients with malignancies/number of patients);
1 Malignancies included in these analyses were different. Infliximab and adalimumab included all malignancies except lymphoma and NMSC and certolizumab and golimumab included all malignancies except NMSC.

[redacted]

b(4)

4 Golimumab studies include the 6 Phase 2 and 3 rheumatology trials (5 Phase 3 trials and the 1 RA Phase 2 trial)

7.4.3 Hepatotoxicity

TNF inhibitors have been associated with elevated liver enzymes and hepatitis. Infliximab includes a WARNING stating that "severe hepatic reactions, including acute liver failure ... have been reported rarely in postmarketing data in patients receiving" infliximab (see Table 7.4.10). Therefore, it is important to assess for golimumab-associated hepatotoxicity. Mechanistically, TNFα exerts pleiotropic effects in the liver, as both a mediator of hepatotoxicity and in maintaining functional liver mass by driving hepatocyte proliferation and regeneration (Schwabe 2006). Because of these dual roles, there is no clearly anticipated effect of TNF inhibition on the liver.

Table 7.4.10: Hepatotoxicity mentions in the 4 approved TNF inhibitors

Product	Location of hepatotoxicity	Mention
Infliximab	WARNINGS	"severe hepatic reactions, including acute liver failure ... have been reported rarely in postmarketing data in patients receiving" infliximab
Etanercept	N/A	N/A
Adalimumab	ADVERSE REACTIONS (postmarketing) line listing	"Hepatic necrosis"
Certolizumab pegol	ADVERSE REACTIONS (postmarketing) line listing	"Elevated liver enzymes and hepatitis"
Golimumab[1]	ADVERSE REACTIONS (clinical studies experience)[1]	Liver enzyme elevations (> 5 x ULN and

b(4)

1 Proposed labeling for golimumab

In the 13 submitted golimumab studies, there were 6 cases of possible Hy's law (ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN) as of the last safety cut-off date (see Table 7.4.11 for the narratives of these 6 cases). Possible Hy's Law cases according to the 2007 *Drug-Induced Liver Injury: Premarketing Clinical Evaluation Guidance* is an ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN. However, according to the guidance, in order for these cases to be true Hy's Law cases other causes of liver chemistry abnormalities need to be ruled out (e.g., viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune hepatitis, biliary disorders, concomitant hepatotoxic drugs).

Of the 6 possible Hy's law cases (4 cases on golimumab and 2 cases on placebo) in the 13 submitted golimumab studies, none of these cases is likely a true Hy's Law case because of other confounders for the etiology of liver disease including the use of concomitant hepatotoxic drugs (MTX, diclofenac and other NSAIDs), baseline liver disease, and alcohol use.

b(6)

There was one patient (Patient 5805-60569 in Study 6, [redacted] KR-JNJ [redacted]-20071004551) death due to acute liver failure (ALF) and complications of a liver biopsy [see Section 7.3.1 (Deaths) and see Table 7.4.11 below]. She was a 24 year old female from Korea with early RA and baseline liver disease who developed ALF after receiving about 8 months of golimumab100 monotherapy. Note, during screening her liver enzymes were normal and her viral hepatitis tests were negative and she was allowed to enroll. It is likely that her underlying liver disease, her prior use of MTX, her concomitant use of three known hepatotoxins (methimazole, nabumetone, and ketoprofen), and her concomitant use of a possible fourth hepatotoxin (an herbal medication that was associated with increased liver enzymes) contributed to her ALF and her death. Experience with other approved TNF inhibitors suggests that liver enzyme abnormalities are not unexpected with TNF inhibitor treatment; however, there does not appear to be a significant risk for treatment-related hepatotoxicity, in the absence of confounding hepatotoxic insults. The clinical trial experience with golimumab suggests a similar situation. The golimumab label should state that ALF has been reported with TNF inhibitor use including golimumab.