Table 7.4.11: Narratives of the 6 patients with possible Hy's Law (defined as ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN) through the last safety cut-off in the 13 submitted golimumab studies

	Patient # (Study)	Preferred Term (Type of AE)	Narrative	Possible Hy's law[1]
Golimumb100 & MTX				
1	2205-60689 (Study 6)	Hepatitis (SAE, DAE)	**49 year old female from Chile with RA for 30 years, HTN, taking acetaminophen, prednisone, MTX for over 3 years. Had epigastric pain and ultrasound showed fatty liver and Hy's Law (once) then jaundice. Hep A, B, and C viral serology were negative. golimumab/MTX discontinued when labs had Hy's law and liver enzymes resolved. Found to be hepatitis E IgG positive.**	Yes
Golimumab100				
2	5805-60569 (Study 6) [redacted] KR-JNJ [redacted] 20071004551	Fulminant Hepatic Failure (Death, SAE)	**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.	Yes b(6)
Golimumab50 q 2 than q 4weeks & MTX				
3	203-002 (Study 2)	Hepatotoxicity (hepatic event of interest)	**50 year old Canadian male with RA on concomitant naproxen, MTX. Had increased liver enzymes only AST and Tbilirubin increased once > 3x and > 2x respectively. MTX stopped but golimumab continued. No symptoms and liver enzyme elevations resolved**	Yes
Golimumab50				
4	5209-80378 (Study 8)	ALT, AST,ALP elevation (AE)	**44 year old Polish male with PsA taking diclofenac, concomitant alcohol. No reported symptoms.**	Yes
Placebo				
5	2016-80454 (Study 8)	ALT, AST, ALP, bilirubin elevation (AE)	**52 year old Canadian male with PsA and gout on celecoxib, MTX had asymptomatic liver enzyme elevations (met Hy's law criteria once).**	Yes
6	7444-10409 (Study 11)	Hepatotoxicity (SAE, DAE)	**54 year old U.S. female with HTN, RA on NSAIDs, NSAIDs, acetaminophen, isoniazid started 3 weeks prior to study. At baseline had high Tbil. Had nausea, fever, jaundice and transaminases about 20x ULN and Tbil 10x ULN.**	Yes

The case with a white background is a 24 year old with baseline liver disease with early RA and baseline liver disease who died of acute liver failure and complications of a liver biopsy.

1 Possible Hy's Law according to the 2007 Drug-Induced Liver Injury: Premarketing Clinical Evaluation Guidance, a possible Hy's Law case is an ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN

In addition to the 6 possible Hy's law cases, there were 9 cases of system organ class (SOC) hepatobiliary SAEs in the 13 submitted studies of golimumab through the last safety cut-off date (see Table 7.4.12). All of these cases were not possible Hy's law cases because they did not meet Hy's law criteria (ALT or AST $\geq$ 3 x ULN and total bilirubin $\geq$ 2 x ULN). Many of these cases involved gallbladder disease (biliary colic, cholecystitis) and they were not likely related to golimumab. There were two golimumab-treated patients who developed liver infections (Patient 5210-50284 with hepatitis B infection and Patient 6603-50758 with amoebic abscess) and these cases are likely related to the immunosuppressive effects of golimumab, rather than a hepatotoxic effect. Golimumab will receive WARNINGS regarding the risk of serious infections including hepatitis B reactivation and protozoal infections.

Of these 9 hepatobiliary SAEs there was a notable case. Patient 7436-90006 in Study 9 is a 25 year old male with AS who was taking two concomitant hepatotoxins (MTX and indomethacin) and had asymptomatic liver enzymes elevations (> 5 x ULN) without bilirubin elevation, coagulopathy, or symptoms after taking two doses of golimumab. His asymptomatic liver elevations may have been due to the concomitant use of golimumab with two hepatotoxins. The golimumab label will include the proportions of patients with significant liver enzyme elevations (e.g., $\geq$ 5 x ULN, $\geq$ 3 x ULN).

Table 7.4.12: Narratives of the 9 additional patients with a SOC hepatobiliary SAE who did not meet Hy's Law criteria in all the SC golimumab studies as of the last safety cut-off

	Treatment Group	Patient # (Study)	Preferred Term (Type of AE)	Narrative	Possible Hy's law[1]
1	Golimumb100 & MTX	5403-50304 (Study 5)	Hepatitis toxic (SAE)	59 year old Russian female with a history of liver disease, PVD, DM, HTN, hyperlipidemia, RA taking MTX. Developed sepsis and cholecystitis.	No
2	Golimumb100 & MTX	5210-50284 (Study 5)	Hepatitis B infection (SAE)	37 year old male with RA for 1 year taking diclofenac and methylprednisolone who was hospitalized with acute hepatitis B (did not have elevated bilirubin)	No
3	Golimumab100	6603-50758 (Study 5)	Hepatomegaly (SAE)	44 year old Asian female in Thailand with DM type II and RA and taking NSAID, acetaminophen, prednisolone, clotrimazole (anti-fungal). Had epigastric pain and nausea and hepatomegaly and hospitalized. Possible amoebic abscess which resolved with treatment with Flagyl; however, amoebic serology was negative. No liver enzyme elevations.	No
4	Golimumab100	7210--80524 (Study 8)	Elevated liver enzymes (SAE)	44 year old British male with PsA taking NSAIDs, acetaminophen, doxycycline had epigastric pain and elevated ALT 1-2 X ULN but no increased bilirubin and was hospitalized	No
5	Golimumab100	7436-90006 (Study 9)	Hepatitis (SAE)	24 year old U.S. male with AS taking MTX, indomethacin, with asymptomatic increased ALT and AST > 5 x normal and increase bilirubin slightly (1.2x ULN). Study drug discontinued after 2 doses of golimumab at Weeks 0 and 4. His viral hepatitis panel was negative.	No
6	Golimumab100	1607-90133 (Study 9)	Hepatic steatosis (SAE)	34 year old male with AS for about 26 years, history of IBD psoriasis, erosive esophagitis, pneumonia, receiving SSZ, omeprazole, acetominophen, indomethocin, domperidone, escitalopram. Started golimumab100 at Week 0 (June 20, 2006) and has received 26 injections (last injection was on Study Day 702, Week 88). Patient was last reported continuing golimumab100 treatment. On [redacted] after the Day 505 dose of golimumab, the patient had hepatic steatosis. Also on Day [redacted] after the Day 589 dose of golimumab. A liver biopsy indicated nonalcoholic steatohepatitis (NASH). The maximum ALT was slightly greater than 3 x ULN but the Total bilirubin did not rise.	No
7	Golimumb50 & MTX	1202-60043 (Study 6)	Cholelithiasis and biliary colic (SAE)	53 year old female with RA for 3 years, depression, had biliary colic and had a cholecystectomy.	No
8	Golimumab50	2022-90304 (Study 9)	Cholelithiasis and biliary colic (SAE)	48 year old Canadian female with AS for about 25 years with HTN had biliary colic and required a cholecystectomy.	No
9	placebo	5210-80327 (Study 8)	ALT increased (SAE, DAE)	31 year old Polish male with PsA, alcoholic, DM type II, taking MTX, NSAIDs, and prednisone had elevated ALT and AST > 3x ULN and increased Tbil 1.5X ULN. He was hospitalized.	No

1 Possible Hy's Law according to the 2007 Drug-Induced Liver Injury: Premarketing Clinical Evaluation Guidance, a possible Hy's Law case is an ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN

b(6)

The TNF inhibitors have been associated with elevated liver enzymes. Table 7.4.13 displays the portion of patients with abnormal post-baseline ALT measurement in the 5 Phase 3 trials through Week 24. Table 7.4.13 includes patients with normal ALT measurements at baseline and patients with abnormal ALT measurements at baseline. Patients may have enrolled in the 5 Phase 3 trials if their baseline ALT and AST did not exceed 1.5 x ULN; therefore, it was possible for patients to have abnormal liver enzymes and enroll in the trials. The majority of patients enrolled with these mild liver enzyme elevations continued to have mild elevations between 1 and 3 x ULN. Of the few patients

who experienced worsening liver enzyme elevations, a similar proportion was observed in each treatment group, including the control group.

For patients with normal baseline ALT and for patients with an abnormal baseline ALT, a similar proportion of patients in the golimumab and placebo groups had post-baseline ALT elevations with similar degree of elevations. For the patients with normal baseline ALT levels, a slightly greater proportion of patients in the golimumab100 group compared to the golimumab50 and placebo groups that had post-baseline ALT elevations ≥ 8 x ULN.

Table 7.4.13: Post-baseline ALT measurements in the 5 Phase 3 trials through Week 24 (double-blind controlled data)[1]

		Treatment Groups Assigned at Randomization			Escape Treatment Groups	
		placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients		639	683	977	205	109
Mean duration of therapy		21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations		5.0	5.5	5.8	2.0	2.0
Patients with baseline ALT ≤ ULN		576	636	885	190	101
Patients with Post-baseline ALT	≤ ULN (in normal range)	463 (80%)	447 (70%)	661 (75%)	159 (84%)	84 (83%)
	> 1 x ULN	113 (20%)	189 (30%)	224 (25%)	31 (16%)	17 (17%)
	≥ 3 x ULN	16 (3%)	19 (3%)	24 (3%)	3 (2%)	1 (1%)
	≥ 5 x ULN	3 (1%)	7 (1%)	10 (1%)	0 (0%)	1 (1%)
	≥ 8 x ULN	1 (0.2%)	1 (0.2%)	5 (0.6%)	0 (0%)	0 (0%)
Patients with baseline ALT > ULN[2]		57	46	90	15	8
Patients with Post-baseline ALT	≤ ULN (in normal range)	15 (26%)	10 (22%)	28 (31%)	9 (60%)	1 (13%)
	> 1 x ULN	42 (74%)	36 (78%)	62 (69%)	6 (40%)	7 (88%)
	≥ 3 x ULN	1 (2%)	1 (2%)	2 (2%)	2 (13%)	0 (0%)
	≥ 5 x ULN	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
	≥ 8 x ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

1 Patients may appear in more than one row
2 In the 5 Phase 3 trials, patients may have enrolled if the baseline ALT and AST did not exceed 1.5 x ULN. Therefore, the baseline ALT abnormality could have ranged from > 1 x ULN to ≤ 1.5 x ULN.
Reference: Adapted from the SCS, Appendix B.99, Pages 668-669ISS, Table 23, Pages 183-230.

7.4.4 Congestive Heart Failure

All four approved TNF inhibitors have WARNINGS and/or PRECAUTIONS regarding the risk of congestive heart failure (CHF). Infliximab and etanercept and have additional language because one controlled trial evaluating the efficacy of infliximab in CHF and one out of two controlled trials evaluating the efficacy of etanercept in CHF demonstrated higher mortality and/or worsening of CHF in the TNF inhibitor arms compared to controls.

In the golimumab trials, patients with a history of CHF, including medically controlled, asymptomatic CHF were appropriately excluded from participation. In the controlled and uncontrolled portions of the 13 submitted studies of golimumab through the last safety cut-off date, four patients developed

congestive heart failure (3 received golimumab and 1 received placebo). Given that the golimumab exposure was about 9 times as great as the placebo exposure, no firm conclusions can be drawn regarding the relationship of golimumab exposure to CHF. However, golimumab should receive similar CHF WARNINGS as adalimumab and certolizumab pegol (cases of worsening CHF and new onset CHF have been reported with TNF inhibitors and in trials of other TNF inhibitors in the treatment of CHF, the TNF inhibitors were associated with higher mortality and/or worsening of CHF).

7.4.5 Demyelinating Disorders

All 4 approved TNF inhibitors have WARNINGS regarding rare reports of new onset or exacerbation of CNS demyelinating disease including multiple sclerosis. In the golimumab trials, patients with a history of known demyelinating disease such as multiple sclerosis or optic neuritis were appropriately excluded from participation.

In the controlled and uncontrolled portions of the 13 submitted studies of golimumab through the last safety cut-off date, one patient who received golimumab100 monotherapy had a possible CNS demyelinating disorder in Study 11. The patient at the time was a 53 year old female with refractory RA who developed hypoaesthesia of the right leg. This patient had multiple confounders including a history of recurrent episodes of hypoaesthesia of her lower and upper extremities and a history of a possible CNS demyelinating disease prior to study enrollment. In addition, this patient received infliximab for 36 to 48 weeks in the past and received etanercept for 4 to 12 weeks in the past.

Although there is no definitive evidence of an association, golimumab appears to be similar to the other approved TNF inhibitors in most other aspects; therefore the golimumab label should be consistent with other class labeling regarding the risk of CNS demyelinating disorders.

7.4.6 Immunogenicity

Table 7.4.14 displays the number and proportion of patients who received golimumab in the controlled portions of 5 Phase 3 trials who developed HAHA through Week 24. In the controlled portions of the 5 Phase 3 trials, the liquid in a vial (LIV) presentation of golimumab was used exclusively. For discussion of the immunogenicity of the proposed to-be-marketed presentation of golimumab [pre-filled syringe (PFS)] see Section 7.7.1 (Safety and Immunogenicity of the To-Be-Marketed Presentation).

The proportion of golimumab-treated patients who developed HAHA was low. The proportion of patients in the low and high dose golimumab groups who developed HAHA was similar. The use of MTX in combination with golimumab was associated with a lower proportion of HAHA. This finding has been seen with other TNF inhibitors and other biologics. This difference in HAHA does not appear to be clinically significant, as discussed in Sections 6.1.8, 6.2.8, and 6.3.8 (Persistence of Efficacy, Tolerance, and Efficacy by Immunogenicity) and below.

Table 7.4.14: Patients who received SC golimumab with positive HAHA by dose and by MTX use in the 5 Phase 3 trials through Week 24 (DB, controlled portion)

	Treatment Groups Assigned at Randomization				Escape Treatment Groups	
	golimumab50		golimumab100		golimumab50 to golimumab100	
MTX use	+ MTX	- MTX	+ MTX	- MTX	+ MTX	- MTX
All patients treated	308	179	386	411	50	43
All patients with appropriate samples	300	169	370	392	49	42
n (%) with positive antibodies to golimumab at any time	5 (2%)	12 (7%)	7 (2%)	27 (7%)	2 (4%)	4 (10%)

Reference: Adapted from SCS, Table 12, Page 72

It is important to assess AEs that may be due to immunogenicity of golimumab. Table 7.4.15 displays allergic-type reactions in the 5 Phase 3 trials through Week 24.

No patient in a golimumab group in the controlled portions of the 5 Phase 3 trials developed an anaphylactic reaction or serum sickness. There was no significant difference in the proportion of patients in the golimumab and placebo groups who developed urticaria, hypersensitivity, and/or rash. Since there was no evidence of concerning allergic-type reactions associated with golimumab treatment, no subgroup safety analysis of allergic-type reactions by HAHA status was performed.

Table 7.4.15: Allergic-type reactions by selected MedDRA preferred term in the 5 Phase 3 trials through Week 24[1] (double-blinded, controlled data)

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients	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
Anaphylactic reactions	0%	0%	0%	0%	0%
Serum sickness	0.2%	0%	0%	0%	0%
Urticaria	0.3%	0.6%	0.5%	0.5%	0%
Hypersensitivity	0.3%	0%	0.4%	0%	0%
Rash	3%	2.8%	3.6%	1%	0%

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.
Adapted from the ISS, Table 23, Pages 201, 228, and 229

7.4.7 Injection Site Reactions

Table 7.4.16 presents the injection-site reactions in the controlled portions of the 5 Phase 3 trials. In the controlled portions of the 5 Phase 3 trials the liquid in a vial (LIV) presentation of golimumab was

used exclusively. For discussion of the injection site reactions of the proposed to-be-marketed presentation of golimumab [pre-filled syringe (PFS)] see Section 7.7.1 (Safety and Immunogenicity of the To-Be-Marketed Presentation). Of the 1864 patients who received a mean of 5.4 SC golimumab injections in the controlled portions of the 5 Phase 3 trials, 1 (0.1%) patient had a severe injection-site reaction.

The golimumab groups had a greater proportion of injection site reactions than the placebo group and the high dose group had a greater proportion of injection site reactions than the low dose group. It is likely that the injection site reactions were related to golimumab and the label should include the injection site reactions as a possible adverse reaction to golimumab administration.

Table 7.4.16: Injection site reactions (≥ 3 reactions in any treatment group) by MedDRA preferred term in the 5 Phase 3 trials 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
Total # of golimumab injections	0	3732	5645	407	214
Injection site reactions	**3.2%**	**6.8%**	**9.1%**	**2.0%**	**5.5%**
Injection site erythema	1.1%	3.1%	5.3%	0.5%	3.7%
Injection site pruritus	0.3%	0.7%	0.9%	0%	0%
Injection site pain	0.6%	0.7%	0.6%	0.5%	0%
Injection site bruising	0.2%	0.4%	0.5%	0%	0.9%
Injection site swelling	0%	0.3%	0.5%	0%	0%
Injection site irritation	0.3%	0.9%	0.4%	0%	0.9%
Injection site induration	0.2%	0.3%	0.4%	0.5%	0%
Injection site rash	0%	0.1%	0.3%	0%	0%
Injection site haemorrhage	0.5%	0.3%	0.2%	0.5%	0%

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; Table 49, Page 335

7.4.8 Autoimmunity and Autoimmune Disorders

All four approved TNF inhibitors have WARNINGS or PRECAUTIONS regarding the association of TNF inhibitor use and the formation of autoantibodies and rarely, autoimmune syndromes such as lupus. The golimumab trials appropriately excluded patients with lupus erythematosus.

In the controlled and uncontrolled portions of the 13 submitted studies of golimumab through the last safety cut-off date:

- 1 patient in the golimumab-treated group and 0 patients in the placebo-treated group had new onset cutaneous lupus erythematosus. The golimumab-treated patient with new onset cutaneous lupus had a new skin rash (biopsy consistent with lupus) and a newly positive antibody to dsDNA after receiving one dose of golimumab100.
- 2 patients in the golimumab-treated group and 0 patients in the placebo-treated group had vasculitis.
- 6 patients in the golimumab-treated group and 0 patients in the placebo-treated group had pustular psoriasis.

Given that the golimumab exposure was about 9 times as great as the placebo exposure, no firm conclusions can be drawn regarding the relationship of golimumab exposure to SLE, vasculitis, or pustular psoriasis. Golimumab should receive the standard PRECAUTIONS regarding the association of TNF inhibitors with autoimmune disorders. TNF inhibitor new-onset psoriasis particularly the pustular type is a newly recognized safety concern.

[redacted] b(4)

Autoimmune Lab Tests: In addition to the clinical assessment of autoimmune disorders, it is also important to determine if patients developed new auto-antibodies.

See Table 7.4.17 for patients that developed newly positive ANA and antibodies to dsDNA through the primary efficacy assessment (Week 14 for Studies 6, 8, 9, and 11 and Week 24 for Study 5). In the controlled portions of the 5 Phase 3 trials, ANA testing was performed at baseline and at Weeks 14 in Studies 6, 11, 8, and 9 and at baseline and at Week 24 in Study 5 (the time points for the primary efficacy assessment). If the ANA was newly positive ($\geq$ 1:160) then anti-dsDNA testing was performed.

In Studies 5, 6, 11, 8, and 9, 60%, 56%, 50%, 23%, and 22% of patients had positive ANAs at baseline, respectively. This finding is not unexpected because patients with inflammatory disorders, particularly RA, frequently have positive ANA tests. Patients who were ANA positive at baseline were not included in Table 7.4.17.

Only one golimumab-treated patient and one placebo-treated patient had both a newly positive ANA test and anti-dsDNA test. Both of these patients did not have clinical features of SLE. There was no evidence of an association of positive autoimmune tests and golimumab treatment.

Table 7.4.17: ANA and anti-dsDNA test results in Studies 6, 11, 8, and 9 at Week 14 and in Study 5 at Week 24[1]

Study 5 (MTX naive)	MTX (n=160)	Golimumab100 (n=157)	Golimumab50 & MTX (n=158)	Golimumab100 & MTX (n=159)
Patients ANA negative at baseline[2]	53	49	57	60
Patient newly positive for ANA	2	7	13	12
Patients (%) newly positive for ANA and dsDNA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Study 6 (inadequate MTX response)	**MTX (n=133)**	**Golimumab100 (n=133)**	**Golimumab50 & MTX (n=89)**	**Golimumab100 & MTX (n=89)**
Patients ANA negative at baseline[2]	47	58	35	39
Patient newly positive for ANA	7	17	2	7
Patients (%) newly positive for ANA and dsDNA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Study 11 (prior use TNF inhibitor)	**Placebo ± DMARDs (n=155)**	**—**	**Golimumab50 ± DMARDs (n=152)**	**Golimumab100 ± DMARDs (n=152)**
Patients ANA negative at baseline[2]	70	—	69	74
Patient newly positive for ANA	15	—	5	8
Patients (%) newly positive for ANA and dsDNA	1 (7%)	—	0 (0%)	0 (0%)
Study 8 (PsA)	**Placebo ± MTX (n=113)**	**—**	**Golimumab50 ± MTX (n=146)**	**Golimumab100 ± MTX (n=146)**
Patients ANA negative at baseline[2]	102	—	139	139
Patient newly positive for ANA	13	—	13	13
Patients (%) newly positive for ANA and dsDNA	0 (0%)	—	0 (0%)	0 (0%)
Study 9 (AS)	**Placebo ± DMARDs[1] (n=78)**	**—**	**Golimumab50 ± DMARDs[1] (n=138)**	**Golimumab100 ± DMARDs[1] (n=140)**
Patients ANA negative at baseline[2]	62	—	99	108
Patient newly positive for ANA	8	—	10	16
Patients (%) newly positive for ANA and dsDNA	0 (0%)	—	0 (0%)	1 (6%)

1. These time points were when the primary efficacy endpoints were measured. ANA positive was ≥ 1:160. dsDNA positive was ≥ 1:10 Crithidia and ≥ 5.4 IU/mL FARR RIA
2. Patients evaluated were patients who were newly positive for ANA

Adapted from Final Study Report for Study 5, Attachment 4.59, Page 761; Final Study Report for Study 6, Attachment 4.77, Page 807; Final Study Report for Study 11, Attachment 4.69, Page 777; Final Study Report for Study 8, Attachment 4.75, Page 275; and Final Study Report for Study 9, Attachment 4.73, Page 681.

7.4.9 Hematologic Cytopenias

All four approved TNF inhibitors have WARNINGS regarding hematological cytopenias including pancytopenia, aplastic anemia, leukopenia, and thrombocytopenia; therefore, it is important to assess for these cytopenias in the golimumab safety database. Patients in the golimumab trials were allowed to participate with mild cytopenias (Hemoglobin ≥ 8.5 g/dL, White blood cells ≥ 3.5 x 10^9 cells/L, Neutrophils ≥ 1.5 x 10^9 cells/L, and Platelets ≥ 100 x 10^9 cells/L).

In the controlled portions of the 5 Phase 3 trials through Week 24, there were no pancytopenia, leukopenia, or thrombocytopenia SAEs and there were 2 (0.3%), 0 (0%), and 2 (0.2%) anemia SAEs, in the placebo, golimumab50, and golimumab100 groups, respectively. Table 7.4.18 displays cytopenia AEs in the controlled portions of the 5 Phase 3 trials through Week 24. Patients in the

placebo and golimumab groups had a similar portion of anemia AEs and thrombocytopenia AEs. Slightly greater proportions of patients in the golimumab groups, compared to the placebo groups, had leukopenia and neutropenia AEs.

Table 7.4.18: Cytopenias AEs 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			Escape Treatment Groups	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients	639	683	977	205	109
Mean duration of therapy	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
Anemia AEs					
Anaemia	9 (1.4%)	7 (1.0%)	9 (0.9%)	1 (0.5%)	1 (0.9%)
Iron deficiency anaemia	2 (0.3%)	2 (0.3%)	3 (0.3%)	0 (0%)	0 (0%)
Anaemia of chronic disease	0 (0%)	1 (0.1%)	2 (0.2%)	0 (0%)	0 (0%)
Hypochromic anaemia	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Haematocrit decreased	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Haemoglobin decreased	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Pernicious anaemia	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Low WBC AEs					
Leukopenia	1 (0.2%)	2 (0.3%)	6 (0.6%)	0 (0%)	0 (0%)
Neutropenia	0 (0%)	0 (0%)	4 (0.4%)	0 (0%)	0 (0%)
Neutrophil count decreased	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
White blood cell count decreased	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Thrombocytopenia AEs					
Thrombocytopenia	1 (0.2%)	0 (0%)	2 (0.2%)	0 (0%)	0 (0%)
Idiopathic thrombocytopenic purpura	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Thrombocytopenic purpura	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)
Platelet count decreased	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)

Patients may appear in more than one row
Reference: Adapted from the ISS, Table 23, Pages 183-230.

Patients were allowed to participate in the 5 Phase 3 trials if they had mild cytopenias at baseline [mild anemia (hemoglobin $\geq$ 8.5 g/dL), mild leukopenia (white blood cells $\geq$ 3.5 x 10^9 cells/L), mild neutropenia (neutrophils $\geq$ 1.5 x 10^9 cells/L), or mild thrombocytopenia (platelets $\geq$ 100 x 10^9 cells/L)]. Since patients may have entered the trials with mild cytopenias, it is important to assess for moderate to severe cytopenias after treatment with the study treatments.

Table 7.4.19 presents the markedly abnormal low hematocrit, hemoglobin, WBC, neutrophil count, and platelet counts in the controlled portions of the 5 Phase 3 trials through Week 24. Marked cytopenias were defined as Hemoglobin decrease > 2.0 g/dL **and** value < 8.0 g/dL; Hematocrit value < 27%; WBC value < 2.0 x10^3/μL; Absolute Neutrophils percent decrease $\geq$ 33 **and** value < 1.5 x 10^3/μL; and Platelets percent decrease $\geq$ 50 **and** value < 75 x 10^3/μL.

The golimumab and placebo groups had similar proportions of moderate to severe anemia, leukopenia, and thrombocytopenia. The golimumab-treated groups had greater proportions of moderate to severe neutropenia.

Table 7.4.19: Patient with at least one markedly abnormal post-baseline cytopenias in the 5 Phase 3 trials through Week 24 (double-blind controlled data)[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients	639	683	977	205	109
Mean duration of therapy	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
Hemoglobin decreased	1 (0.2%)	1 (0.1%)	2 (0.2%)	1 (0.5%)	0 (0%)
Hematocrit decreased	4 (0.6%)	1 (0.1%)	8 (0.8%)	2 (1.0%)	0 (0%)
WBC decreased	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutrophils decreased	3 (0.5%)	12 (1.8%)	19 (1.9%)	2 (1.0%)	0 (0%)
Platelets decreased	0 (0%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)

1 Patients may appear in more than one row
Reference: Adapted from the ISS, Table 50, Pages 336-338; Table 51, Pages 339-341; Table 52, Pages 342-344

7.4.10 Vaccinations

In Study 8, the ability of patients after multiple doses of study agent to generate an antibody response to the 23-valent pneumococcal vaccine was assessed using a pneumococcal vaccine administered via intramuscular injection at Week 12. All patients were to receive the vaccination except patients with a history of hypersensitivity to the vaccine, vaccination with pneumococcal vaccine within the previous 5 years, received more than 1 administration of pneumococcal vaccine, had any infection within 7 days prior to vaccine administration, or had a bleeding disorder. Antipneumococcal antibody levels against 14 different serotypes of pneumococcus were assessed prior to vaccination and about 4 weeks later. Patients with at least a 2-fold increase from prevaccination to postvaccination in 7 or more serotypes were considered to have a positive vaccine response.

Table 7.4.20 displays the antibody response to pneumococcal vaccination by MTX use in Study 9. Similar proportions of golimumab-treated and placebo-treated patients had antibody responses to the pneumococcal vaccine. There is no evidence to suggest that golimumab suppresses the immune response to pneumococcal vaccine. The use of MTX was associated with a lower response.

Table 7.4.20: Patients with antibody response to pneumococcal vaccine by MTX use in Study 8

		Placebo ± MTX (n=113)	Golimumab50 ± MTX (n=146)	Golimumab100 ± MTX (n=146)
Patients not vaccinated at Week 12		14	22	17
Patients vaccinated at Week 12		92 (87%)	122 (85%)	127 (88%)
Received MTX at baseline	n	47	60	58
	with appropriate samples	46	56	55
	Proportion with antibody response	80%	77%	82%
Did not receive MTX at baseline	n	45	62	69
	with appropriate samples	44	62	67
	Proportion with antibody response	93%	95%	85%

Reference: Adapted from Final Study Report for Study 8, Attachment 4.76, Page 726; Attachment 4.77, Page 727; Attachment 4.78, Page 728; Attachment 4.81, Page 735, Attachment 4.82, Page 735.

7.5 Vital Signs, Labs, and ECGs

7.5.1 Vital Signs

In the 5 Phase 3 trials and the 1 Phase 2 trial in RA, vital signs were monitored by the investigators but not entered into the database. However, significant vital sign abnormalities were recorded as AEs. Table 7.5.1 displays AEs relating to vital sign abnormalities in the controlled portions of the 5 Phase 3 trials in RA, PsA, and AS through Week 24. There were a higher proportion of patients in the golimumab groups, compared to patients in the placebo groups, who had "HTN" and "Blood Pressure Increased" as adverse events. Patients in these trials were taking concomitant medications (e.g., NSAIDs, corticosteroids) that could increase the risk of developing HTN. The Adverse Reaction section of the golimumab label should include HTN as an adverse reaction.

In the Phase 2 asthma trial, in the Phase 1 [redacted] study, in the 2 Phase 1 RA studies, and in the 3 Phase 1 studies of golimumab in healthy subjects, vital signs were obtained and entered into the database. In the Phase 1 and Phase 2 studies of golimumab, there were no significant differences in vital sign abnormalities in the golimumab and placebo groups. b(4)

Appears This Way
On Original

Table 7.5.1: AEs relating to vital sign abnormalities 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			Escape Treatment Groups	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients	639	683	977	205	109
Mean duration of therapy	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
Hypertension	12 (1.9%)	28 (4.1%)	37 (3.8%)	4 (2.0%)	0 (0%)
Blood pressure increased	1 (0.2%)	3 (0.4%)	5 (0.5%)	1 (0.5%)	0 (0%)
Tachycardia	2 (0.3%)	2 (0.3%)	2 (0.2%)	0 (0%)	0 (0%)
Hypotension	0 (0%)	2 (0.3%)	2 (0.2%)	0 (0%)	1 (0.9%)
Orthostatic hypotension	1 (0.2%)	0 (0%)	2 (0.2%)	0 (0%)	0 (0%)
Body temperature increased	0 (0%)	2 (0.3%)	1 (0.1%)	0 (0%)	0 (0%)
Heart rate increased	1 (0.2%)	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Hyperthermia	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Reference: Adapted from the ISS, Table 23, Pages 183-230.

7.5.2 Laboratory Findings

See Section 7.4.5 (Hepatotoxicity) and Section 7.49 (Hematologic Cytopenias) for a discussion of post-baseline elevation of liver enzymes and drop in blood counts (cytopenias) in the 5 Phase 3 trials, respectively.

TNF inhibitors are not known to be associated with electrolyte abnormalities. However, it is important to assess if golimumab, a new molecular entity, is associated with electrolyte abnormalities. Markedly abnormally decreased chemistry tests were defined as Sodium decrease ≥ 5 mEq/L **and** value < 125 mEq/L; Potassium decrease ≥ 0.8 mEq/L **and** value < 3.0 mEq/L; Bicarbonate value < 15 mEq/L; Calcium decrease ≥ 1.5 mg/dL **and** Value < 7.5 mg/dL; Phosphate decrease ≥ 1.0 mg/dL **and** Value < 2.0 mg/dL. Markedly abnormally increased chemistry tests were defined as Sodium increase ≥ 10 mEq/L **and** value > 150 mEq/L; Potassium increase ≥ 0.8 mEq/L **and** value > 5.5 mEq/L; Bicarbonate value > 35 mEq/L; Calcium increase ≥ 2.0 mg/dL **and** value > 11.5 mg/dL; Phosphate increase ≥ 2.5 mg/dL **and** value > 6.0 mg/dL; Creatinine increase percent increase ≥ 66 **and** value > 2.5 mg/dL.

Table 7.5.2 presents markedly abnormal post-baseline chemistry measurements in the 5 Phase 3 trials through Week 24. In general, the golimumab and placebo groups had similar proportions of markedly abnormal chemistry values. A slightly greater proportion of patients in the golimumab groups had markedly increased sodium and increased potassium. However, since the number of patients who had these increased sodium and potassium values was small, no firm conclusions can be drawn. Overall, there is no clear evidence that golimumab is associated with electrolyte abnormalities.

Table 7.5.2: Markedly abnormal post-baseline chemistry measurements in the 5 Phase 3 trials through Week 24 (double-blind controlled data)[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
Treated patients	639	683	977	205	109
Mean duration of therapy	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
Decreased Chemistry Values					
Decreased sodium	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Decreased potassium	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)
Decreased bicarbonate	0 (0%)	1 (0.1%)	0 (0%)	1 (0.5%)	0 (0%)
Decreased calcium	4 (0.6%)	1 (0.1%)	6 (0.6%)	1 (0.5%)	1 (0.1%)
Decreased phosphorus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Chemistry Values					
Increased sodium	1 (0.2%)	3 (0.4%)	4 (0.4%)	0 (0%)	0 (0%)
Increased potassium	1 (0.2%)	2 (0.3%)	4 (0.4%)	1 (0.5%)	0 (0%)
Increased bicarbonate	1 (0.2%)	0 (0%)	2 (0.2%)	0 (0%)	0 (0%)
Increased calcium	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased phosphorus	2 (0.3%)	4 (0.6%)	3 (0.3%)	0 (0%)	0 (0%)
Increased creatinine	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

1 Patients may appear in more than one row
Reference: Adapted from the ISS, Table 53, Pages 345-352; Table 54, Pages 353-360; Table 55, Pages 361-368

Tocilizumab, an investigational monoclonal antibody to the IL-6 receptor for the treatment of RA is associated with increased LDL. Although TNF inhibitors have not been associated with increased LDL, it is important to assess the effect of golimumab on possible cardiovascular markers including LDL, HDL, and glucose. In Study 5, fasting glucose, fasting lipid panels, and other cardiovascular (CV) markers were obtained at baseline and Week 24 (see Table 7.5.3) and in Study 6 these CV markers were obtained at Weeks 14 and 24 (see Table 7.5.4).

In general, there did not appear to be any differences in the change from baseline at Weeks 14 and 24 for fasting LDL, fasting HDL, fasting triglycerides, fasting glucose, and homocysteine in the golimumab and MTX control groups. The combination groups appeared to have a greater reduction in the hsCRP compared to the MTX control group. This may be due to the reduction of inflammation.

In Study 6, the golimumab groups appeared to have a slightly greater increase in LDL compared to the MTX control group. However, there were no differences in the change in baseline of LDL measurements in Study 5.

Table 7.5.3: Mean (SD) change from baseline at Week 24 in selected cardiovascular markers in Study 5[1]

	Mean (SD) Baseline Value for all groups[2]	MTX (n=160)[3]	Golimumab100 (n=159)[3]	Golimumab50 & MTX (n=159)[3]	Golimumab100 & MTX (n=159)[3]
Number of patients with samples[4]	628	126	125	120	123
LDL, mg/dL	112	6 (27)	8 (24)	3 (25)	6 (23)
HDL, mg/dL	58	0 (8)	3 (11)	2 (13)	2 (10)
Triglycerides, mg/dL	130	3 (65)	-5 (56)	15 (89)	1 (51)
Glucose, mg/dL	91	3 (12)	2 (25)	2 (17)	1 (14)
hsCRP, mg/dL	25	-13 (30)	-10 (23)	-17 (27)	-15 (23)
Homocysteine, µmole/L	9.4	-0.3 (3)	-1.4 (4)	-0.6 (3)	-0.1 (3)

1 Lipid panels and glucose were performed after fasting.
2 The mean baseline value for all treatment groups. The baseline value is to provide an approximate baseline value to help put the change from baseline values into context. There were some slight differences in the baseline value between the groups. More patients had baseline values than had Week 24 values.
3 Number of randomized patients.
4 The number of patients with certain blood tests varied
Reference: Final Study Report for Study 5; Attachment 3.53, Pages 500-511

Table 7.5.4: Mean (SD) change from baseline at Weeks 14 and 24 in selected cardiovascular markers in Study 6[1]

		Mean (SD) Baseline Value for all groups[2]	MTX (n=133)[3]	Golimumab100 (n=133)[3]	Golimumab50 & MTX (n=89)[3]	Golimumab100 & MTX (n=89)[3]
Number of patients with samples[4]		440	126	128	86	81
LDL, mg/dL (Δ from baseline at W14)		111	1 (22)	9 (22)	11 (23)	11 (29)
HDL, mg/dL (Δ from baseline at W14)		60	0 (10)	2 (10)	3 (8)	4 (11)
Triglycerides, mg/dL (Δ baseline at W14)		128	-1 (56)	3 (46)	12 (58)	-2 (50)
Glucose, mg/dL (Δ from baseline at W14)		89	2 (13)	4 (21)	1 (8)	-1 (19)
hsCRP, mg/dL	Δ from baseline at W14	19	-2 (15)	-5 (20)	-14 (19)	-8 (18)
	Δ from baseline at W24	19	-2 (21)	-4 (24)	-12 (17)	-10 (16)
Homocysteine, µmole/L (Δ from baseline at W14)	Δ from baseline at W14	9.3	-0.1 (2)	-1.4 (3)	-0.1 (2)	-0.2 (3)
	Δ from baseline at W24	9.3	-1 (3)	-2 (3)	-1 (3)	-1 (4)

1 Lipid panels and glucose were performed after fasting.
2 The mean baseline value for all treatment groups. The baseline value is to provide an approximate baseline value to help put the change from baseline values into context. There were some slight differences in the baseline value between the groups. More patients had baseline values than had Week 24 values.
3 Number of randomized patients.
4 The number of patients with certain blood tests varied and also varied at the W14 and W24 timepoints
Reference: Final Study Report for Study 6; Attachment 3.48, Pages 503-514, Attachment 3.49, Pages 515-518.

7.5.3 Electrocardiograms (ECGs)

In the controlled portions of the 5 Phase 3 trials, there was no evidence of concerning arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, or torsades de pointes) associated with golimumab treatment. ECGs were performed at baseline and post-treatment in 4 Phase 1 studies of golimumab (2 studies of golimumab in patients with RA and 2 studies of golimumab in healthy subjects). There were no significant ECG abnormalities in the golimumab or placebo control treated patients/subjects.

Golimumab, like other biologics that are large in size, are not likely to affect the QTc interval like some small molecules that are able to interfere with important electrolyte channels in the myocardial tissue.

7.6 Safety Explorations

7.6.1 Dose Dependency for Adverse Events

Overall, the safety of the low dose (50 mg every 4 weeks) and the high dose (100 mg every 4 weeks) of golimumab were similar in the rheumatology trials. However, there was a suggestion of possible increased toxicity of the higher dose in the rheumatology trials. A greater proportion of patients who received the high dose compared to the low dose had infection AEs and infection AEs that required oral or parental anti-microbial therapy [see Section 7.4.1 (Infections)]. In addition, in a Phase 2 trial of golimumab in patients with persistent asthma there was a dose-related increase in all malignancies. In the 50 mg, 100 mg, and 200 mg golimumab groups, there were 1 (1%), 2 (3%), and 3 (4%) malignancies other than NMSC seen [see Section 7.7.2 (Safety in Asthma Trial)]. Note, in the asthma trial, there was an initial loading dose (50% higher dose) followed by a maintenance dose every 4 weeks.

7.6.2 Time Dependency for Adverse Events

Assessments of time dependency for AEs were performed in two types of analyses: analyses in Study 5 the trial with the longest controlled period and analyses of deaths, serious infections, and malignancies in the controlled and uncontrolled portions of the trials.

Table 7.6.1 presents the major safety results of Study 5 (the only Phase 3 trial with a 52 week double-blind, controlled period) through two different time periods (Weeks 24 and 52). The exposure to study agent was approximately 2-fold higher in the Week 52 analysis compared to the Week 24 analysis. The yellow highlights represent AEs that more than doubled in the Week 52 time period compared to the Week 24 time period. The proportion of patients who developed a malignancy other than NMSC remained constant through Week 24 and through Week 52. In this analysis, there was no clear increase in AEs in the golimumab-treated patients compared to the MTX control treated patients after increased exposure of study agents.

Table 7.6.1: Major safety results of Study 5 through Week 24 and through Week 52[1]

	Study 5 through Week 24				Study 5 through Week 52[1]			
	MTX (n=159)	golimumab100 (n=157)	golimumab50 & MTX (n=158)	golimumab100[2] & MTX (n=160)	MTX (n=159)	golimumab100 (n=157)	golimumab50 & MTX (n=158)	golimumab100[2] & MTX (n=160)
Mean duration of therapy	23.4 weeks	23.7 weeks	24.0 weeks	23.5 weeks	45.1 weeks	46.0 weeks	47.2 weeks	49.6 weeks
Mean # SC administrations	5.8	5.7	5.8	5.8	11.1	11.2	11.5	12.0
Deaths	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (1%)
SAEs	11 (7%)	5 (3%)	10 (6%)	10 (6%)	22 (14%)	13 (8%)	18 (11%)	21 (13%)
DAEs	2 (1%)	1 (1%)	6 (4%)	7 (4%)	6 (4%)	7 (5%)	9 (6%)	16 (10%)
Malignancies except NMSC	2 (1%)	0 (0%)	1 (1%)	1 (1%)	2 (1%)	1 (1%)	2 (1%)	1 (1%)
AEs	116 (73%)	107 (68%)	129 (82%)	121 (76%)	134 (84%)	127 (81%)	145 (92%)	147 (92%)
Serious Infections[3]	3 (2%)	2 (1%)	2 (1%)	7 (4%)	6 (4%)	3 (2%)	3 (2%)	12 (8%)
Infection AEs[4]	52 (33%)	52(33%)	52 (33%)	51 (32%)	81 (51%)	77 (49%)	81 (53%)	89 (56%)

1 Treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses. The safety analysis through Week 52 only includes the treatment groups assigned at randomization.
2 The golimumab100 & MTX combination group for the Week 52 results includes patients who did not escape and who escaped to the same treatment.
3 Serious Infections were SAEs that were infections according to the investigator.
4 Infections AEs were AEs that were identified as infections by the investigators.
Reference: Adapted from the Final Study Report for Study 5, Attachment 4.4, Page 584 and 586 and 603; Attachment 4.11, Page 632; Attachment 4.14, Page 644; Table 27, Page 139; also adapted from the 120-Day Safety Update, Appendix A.10, Pages 284-292, Appendix A.15, Pages 316-322; Table 10, Page 42, Appendix A.4, Page 156; also adapted from JMP dataset in 120-Day Safety Update of Study 5 through Week 52.

Additionally, assessment of time dependency for AEs for deaths, serious infections, and malignancies were performed [see Table 7.3.1 in Section 7.3.1 (Deaths), Tables 7.4.2 and 7.4.3 in Section 7.4.1 (Infections), and Table 7.4.6 in Section 7.4.2 (Malignancies)]. There was no evidence of an increase in exposure-adjusted deaths, serious infections, or malignancies over time in the rheumatology trials.

7.6.3 Drug-Demographic Interactions

In the controlled portions of the Phase 3 trials in patients with RA, PsA, and AS, the golimumab-treated patients had a greater proportion of infection AEs compared to the placebo-treated groups. A similar proportion of patients in the golimumab and placebo groups had SAEs, DAEs, and serious infections. Therefore, subgroup safety analyses by demographics were performed using infection AEs (see Table 7.6.2).

The demographic subgroups (age, gender, race, and weight) had similar proportions of infection AEs in the golimumab treatment groups.

Since Centocor proposes a fixed dosage regimen for golimumab; rather than, a weight based dosing, it is important to assess if patients with low body weights have a greater toxicity after golimumab administration (see Table 7.6.2). There was no clear evidence that patients at low body weights were at higher risk of infection AEs than patients at higher body weights. This supports the safety of fixed dosing of golimumab.

Table 7.6.2: Proportion of patients with an infection AE by age, gender, race, and weight in the 5 Phase 3 trials through Week 24[1]

		Placebo	Golimumab50	Golimumab100
Entire Population[1]		**195/639 (31%)**	**247/683 (36%)**	**373/977 (38%)**
Age	< 65 years	175/562 (31%)	224/617 (36%)	340/886 (38%)
	≥ 65 and < 75 years	15/55 (27%)	19/54 (35%)	27/77 (35%)
	≥ 75 years	7/22 (32%)	4/11 (36%)	4/13 (31%)
Gender	Female	151/442 (34%)	147/411 (36%)	260/658 (40%)
	Male	46/197 (23%)	100/271 (37%)	111/318 (35%)
Race	Caucasian	156/515 (30%)	205/561 (37%)	306/779 (39%)
	Asian	22/67 (33%)	31/83 (37%)	45/134 (34%)
	Black	5/18 (28%)	3/11 (27%)	5/17 (29%)
Weight[2]	< 63 kg	51/171 (30%)	60/153 (39%)	94/249 (38%)
	63 ≥ and < 73.5 kg	46/146 (32%)	61/177 (34%)	88/245 (36%)
	73.5 ≥ and < 87.8 kg	48/157 (31%)	66/179 (37%)	89/243 (37%)
	≥ 87.8 kg	51/163 (31%)	60/172 (35%)	101/238 (42%)

1 Includes treatments assigned at randomization. Patients who escaped are not included in this table except for patients who were assigned golimumab100 at randomization and received the same treatment after they escaped (golimumab100).
2 Weight is divided into four quartiles. The 25%, 50%, and 75% quartile weights of patients in the treatment by randomization group were 63.0, 73.5, and 87.8 kg, respectively.
Adapted from JMP AE and Demo datasets from ISS.

7.6.4 Drug-Disease Interactions

It is important to determine if there is a different safety profile of the use of SC golimumab in the three proposed populations (RA, PsA, and AS).

The safety of SC golimumab in patients with RA is evaluated in the individual study reports for Studies 5, 6, and 11 in Sections 9.4.1, 9.4.2, and 9.4.3, respectively. Although the 3 RA populations in these trials have different refractoriness to therapies and have different disease durations, it is important to pool these safety results to increase the precision of detecting safety signals in the RA population. In this section, the pooled safety results (deaths, SAEs, DAEs, AEs, serious infections, infections requiring antibiotics, and infection AEs) of the 3 Phase 3 RA trials will be presented through Week 24 (the common, double-blinded controlled period). The safety of SC golimumab in the PsA population is evaluated by assessing the safety of SC golimumab in Study 8, since this trial was the only trial of SC golimumab in patients with PsA. Similarly, the safety of SC golimumab in the AS population is evaluated by assessing the safety of SC golimumab in Study 9, since this trial was the only trial of SC golimumab in patients with AS.

Tables 7.6.3, 7.6.4, and 7.6.5 present a summary of the major safety results in the RA, PsA, and AS populations, respectively (deaths, SAEs, DAEs, AEs, serious infections, infections requiring antibiotics, and infection AEs in the controlled portions of the trials through Week 24).

In the RA, PsA, and AS populations, the golimumab groups, compared to the placebo groups, had a greater proportion of AEs, Infection AEs, and Infection AEs that required oral or parental anti-microbial therapy. In the 3 arthritis populations, the golimumab and placebo groups had similar

proportions of deaths and SAEs through Week 24. In general, the safety of golimumab in the 3 arthritis populations appeared similar.

Table 7.6.3: Patients with ≥ 1 death, non-fatal SAE, DAE, AE, and infections in the pooled 3 Phase 3 RA trials through Week 24

	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]	449	399	691	113	56
Mean duration of therapy	21.0 weeks	22.5 weeks	23.5 weeks	7.9 weeks	7.8 weeks
Mean # of SC administrations	5.1	5.5	5.8	2.0	2.0
Deaths	1 (0.2%)	1 (0.3%)	2 (0.3%)	0 (0%)	0 (0%)
SAEs	31 (7%)	27 (7%)	41 (6%)	6 (5%)	3 (5%)
DAEs	19 (4%)	13 (3%)	22 (3%)	1 (1%)	0 (0%)
AEs	318 (71%)	295 (74%)	514 (74%)	51 (45%)	24 (43%)
Infections[6]					
Serious Infections	9 (2%)	9 (2%)	19 (3%)	1 (1%)	0 (0%)
Infections requiring anti-microbial therapy	81 (18%)	91 (23%)	159 (23%)	11 (10%)	3 (5%)
Infections AEs	140 (31%)	135 (34%)	245 (36%)	17 (15%)	7 (13%)

1 Data through Week 24 represents the double-blinded and controlled portions of the 3 Phase 3 RA trials (Studies 5, 6, and 11). Patients may appear in more than one column. One of the 3 trials (Study 5) included a double-blinded and controlled portion up to Week 52 (see the individual study report for Study 5 for the SAEs in Study 5 through Week 52).

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

3 Patients may have entered early escape at Week 16 in Studies 6 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).

6 Infections AEs were AEs that were identified as infections by the investigators. Infections could be from any SOC.

Adapted from the ISS, Table 24, Pages 231-238; Table 29, Pages 258-262; Table 10, Pages 31-69; Table 40, Pages 316-318; Table 34, Page 279; Table 37, Page 300.

Appears This Way
On Original

Table 7.6.4: Patients with ≥ 1 death, non-fatal SAE, DAE, AE, and infections in the Phase 3 PsA trial (Study 8) through Week 24[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	Placebo ± MTX[2] (n=113)	Golimumab50 ± MTX[2] (n=146)	Golimumab100 ± MTX[2,3] (n=146)	Placebo to Golimumab50 ± MTX[2] (n=51)	Golimumab50 to Golimumab100± MTX[2] (n=28)
Mean duration of follow-up	4.6	5.4	5.9	2.0	2.0
Mean # of SC administrations	19.4 weeks	22.2 weeks	24.0 weeks	8.1 weeks	8.2 weeks
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAEs	7 (6%)	3 (2%)	4 (3%)	0 (0%)	0 (0%)
DAEs	5 (4%)	2 (1%)	6 (4%)	0 (0%)	0 (0%)
AEs	67 (59%)	99 (68%)	95 (65%)	26 (51%)	4 (14%)
Infections[3]					
Serious Infections	4 (4%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Infections requiring anti-microbial therapy	17 (15%)	26 (18%)	24 (16%)	8 (16%)	0 (0%)
Infections AEs	27 (24%)	48 (33%)	60 (41%)	10 (20%)	0 (0%)

1 The treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses.

2 Patients may have taken stable doses of concomitant MTX, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks.

3 Infection AEs were AEs that were identified as infections by the investigators. Infections could be from any SOC.

Reference: Adapted from Final Study Report for Study 8, Table 4.13, Page 589; Table 4.20, Page 600; Table 4.5, Page 514; Table 4.5, Page 529; Table 4.27, Pages 612-616; Table 33, Page 163; Table 4.32, Pages 628-631

Table 7.6.5: Patients with ≥ 1 death, non-fatal SAE, DAE, AE, and infections in the Phase 3 AS trial (Study 9) through Week 24[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	Placebo ± DMARDs[2] (n=77)	Golimumab50 ± DMARDs[2] (n=138)	Golimumab100 ± DMARDs[2,3] (n=140)	Placebo to Golimumab50 ± DMARDs[2] (n=41)	Golimumab50 to Golimumab100± ± DMARDs[2] (n=25)
Mean number of SC administrations	4.8	5.4	5.8	2.0	1.9
Mean duration of follow-up	19.5 weeks	22.4 weeks	24.1 weeks	8.0 weeks	7.9 weeks
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAEs	5 (7%)	5 (4%)	9 (6%)	0 (0%)	1 (4%)
DAEs	1 (1%)	4 (3%)	4 (3%)	0 (0%)	0 (0%)
AEs	59 (77%)	117 (85%)	120 (86%)	17 (42%)	14 (56%)
Infections[4]					
Serious Infections	1 (1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)
Infections requiring anti-microbial therapy	11 (14%)	26 (19%)	39 (28%)	4 (10%)	2 (8%)
Infections AEs	28 (36%)	64 (46%)	68 (49%)	9 (22%)	5 (20%)

1 The treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses.
2 Patients may have taken stable doses of concomitant DMARDS (i.e., MTX, sulfasalazine, and/or hydroxychloroquine), NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks.
3 Patients in the golimumab100 group who escaped continued to receive golimumab100 at Week 16
4 Infection AEs were AEs that were identified as infections by the investigators. Infections could be from any SOC.
Reference: Adapted from Final Study Report for Study 9, Table 4.11, Page 544; Table 4.18, Page 557; Table 4.5, Page 481; Table 4.4, Page 480; Table 38, Page 149; Table 4.25, Pages 570-574; Table 4.30, Pages 586-589.

7.6.5 Drug-Drug Interactions

No formal DDI interactions studies of golimumab were performed.

Golimumab and MTX in RA: Centocor proposes the use of golimumab only with concomitant MTX in the treatment of signs and symptoms of patients with active RA. Therefore, it is important to evaluate the safety of golimumab with and without concomitant MTX in the RA population. A comparative safety analysis (golimumab with and without MTX) was performed using Studies 5 and 6 since these trials included a golimumab monotherapy arm (see Table 7.6.6).

In Studies 5 and 6, the monotherapy groups had slightly lower proportions of SAEs and serious infections compared to the combination groups. Also in Study 5, the monotherapy group had a lower proportion of DAEs than the combination groups. However, infection AEs appeared comparable in the combination and monotherapy groups in Studies 5 and 6. Overall, the safety of the monotherapy and combination therapies are similar; however, there is a suggestion that the monotherapy group may have a slightly better safety profile than the combination groups.

Table 7.6.6: Major safety results of Studies 5 and 6 through Week 24[1]

	Study 5 Treatments Assigned at Randomization				Study 6 Treatments Assigned at Randomization			
	MTX (n=159)	golimumab100 (n=157)	golimumab50 & MTX (n=158)	golimumab100 & MTX (n=160)	MTX (n=133)	golimumab100 (n=133)	golimumab50 & MTX (n=89)	golimumab100 & MTX[2] (n=89)
Mean duration of therapy	23.4 weeks	23.7 weeks	24.0 weeks	23.5 weeks	21 weeks	22 weeks	23 weeks	24 weeks
Mean # SC administrations	5.8	5.7	5.8	5.8	5.1	5.3	5.5	5.8
Deaths	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	1 (%)	0 (0%)	0 (0%)
SAEs	11 (7%)	5 (3%)	10 (6%)	10 (6%)	5 (4%)	6 (5%)	6 (7%)	11 (12%)
DAEs	2 (1%)	1 (1%)	6 (4%)	7 (4%)	6 (5%)	6 (5%)	2 (2%)	5 (6%)
AEs	116 (73%)	107 (68%)	129 (82%)	121 (76%)	90 (68%)	93 (70%)	65 (73%)	68 (76%)
Neoplasm AEs[3]	5 (3%)	1 (1%)	1 (1%)	1 (1%)	2 (2%)	4 (3%)	3 (3%)	2 (2%)
Serious Infections[3]	3 (2%)	2 (1%)	2 (1%)	7 (4%)	1 (1%)	3 (2%)	2 (2%)	5 (6%)
Infection AEs[4]	52 (33%)	52(33%)	52 (33%)	51 (32%)	37 (28%)	48 (36%)	28 (32%)	34 (38%)

1 Treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses
2 The golimumab100 & MTX combination group in Study 6 includes patients who did not escape and who escaped to the same treatment.
3 Neoplasm AEs were AEs in the Neoplasms benign, malignant, and unspecified SOC. Serious Infections were SAEs that were infections according to the investigator.
4 Infections AEs were AEs that were identified as infections by the investigators.
Reference: Adapted from the Final Study Report for Study 5, Attachment 4.4, Page 584 and 586 and 603; Attachment 4.11, Page 632; Attachment 4.14, Page 644; Table 27, Page 139. Also adapted from Final Study Report for Study 6, Table 4.14, Pages 632-635; Table 4.19, Pages 647-649; Table 4.20, Pages 650-652; Table 4.6, Pages 560-580; Table 26, Pages 151-152; Attachment 4.24, Page 662-668; Attachment 4.25, Page 669-673; Attachment 4.19, Page 647; Table 4.7, Page 602.

Golimumab and MTX in PsA: Centocor proposes the use of golimumab with and without concomitant MTX for the treatment of the signs and symptoms of patients with PsA. As shown in Table 7.6.7 below, overall, the safety profile of golimumab treatment was similar regardless of concomitant MTX use. Note the use of MTX at baseline (prior to and after the first administration of SC agent) was similar to the use of MTX during the 24 week controlled period. The proportions of patients who received MTX at baseline in the placebo, golimumab50, golimumab100 groups were 48%, 49%, and 47%, respectively. The proportions of patients who received concomitant MTX in the 24 week controlled period in the placebo, golimumab50, golimumab100 groups were 50%, 51%, and 49%, respectively.

Appears This Way
On Original

Table 7.6.7: Patients with ≥ 1 death, non-fatal SAE, DAE, and AE through Week 24 by baseline MTX use in Study 8[1]

		Placebo	Golimumab50	Golimumab100	Placebo to Golimumab50[2]	Golimumab50 to Golimumab100[2]
Patients who did not receive baseline MTX	# of patients	59	75	77	26	14
	Mean duration of follow-up	19.1 weeks	22.1 weeks	24.1 weeks	8.1 weeks	8.2 weeks
	Mean # of SC administrations	4.4	5.4	5.8	2.0	1.9
	Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	SAEs	6 (10%)	1 (1%)	3 (4%)	0 (0%)	0 (0%)
	DAEs	5 (9%)	0 (0%)	4 (5%)	0 (0%)	0 (0%)
	AEs	37 (63%)	54 (72%)	51 (66%)	16 (62%)	3 (21%)
	Infection AEs[3]	14 (24%)	27 (36%)	33 (43%)	7 (27%)	0 (0%)
		Placebo + MTX	Golimumab50 + MTX	Golimumab100 + MTX	Placebo to Golimumab50[2] + MTX	Golimumab50 to Golimumab100[2] + MTX
Patients who received baseline MTX	# of patients	54	71	69	25	14
	Mean duration of follow-up	19.7 weeks	22.3 weeks	24.0 weeks	8.1 weeks	8.2 weeks
	Mean # of SC administrations	4.8	5.4	5.9	2.0	2.0
	Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	SAEs	1 (2%)	2 (3%)	1 (1%)	0 (0%)	0 (0%)
	DAEs	0 (0%)	2 (3%)	2 (3%)	0 (0%)	0 (0%)
	AEs	30 (56%)	45 (63%)	44 (64%)	10 (40%)	1 (7%)
	Infection AEs[3]	13 (24%)	21 (30%)	27 (39%)	3 (12%)	0 (0%)

1 The treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses. The table is divided into two groups (i.e., patients who received MTX at baseline and patients who did not receive MTX at baseline). Patients may have taken stable doses of concomitant NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks.

2 The escaped groups

3 Infection AEs were all AEs that were considered due to an infection by the investigator.

Reference: Adapted from Final Study Report for Study 8, Attachment 4.7, Page 547; Attachment 4.8, Page 560; Attachment 4.16, Page 593; Attachment 4.17, Page 594; Attachment 4.23, Page 604; Attachment 4.24, Page 606; Attachment 4.30, Page 621; Attachment 4.31, Page 624.

Golimumab and MTX and SSZ in AS: Centocor proposes the use of golimumab for the treatment of the signs and symptoms of patients with AS. The AS trial (Study 9) allowed for the concomitant use of stable doses of NSAIDs and/or oral low-dose steroids and/or 3 DMARDs (MTX, SSZ, and HCQ). The use of multiple DMARDs may be associated with an increased risk of infection due to the use of multiple concomitant immunosuppressive products. Table 7.6.8 displays infection AEs in the overall study population and in patients who received concomitant MTX and SSZ during the trial.

In all treatment groups, a lower proportion of patients who received concomitant MTX and SSZ in Study 9 had infection AEs compared to the overall population. Although this analysis is limited by the small number of patients who received both these DMARDs, it does not appear that the use of golimumab with MTX and SSZ in patients with AS increases the risk of golimumab toxicity.

Table 7.6.8: Infection AEs in patients who received concomitant MTZ and SSZ during Study 9

	Placebo	Golimumab50	Golimumab100
Infections AEs in the overall population	28/77 (36%)	64/138 (46%)	68/140 (49%)
Infection AEs in patients who received concomitant MTX and SSZ during the trial	1/10 (10%)	6/18 (33%)	5/19 (26%)

Reference: Adapted from AE and CONMEDS JMP datasets in Study 9

Golimumab and Hydroxychloroquine (HCQ) in RA and AS: Only 2 of the 5 Phase 3 trials allowed the use of HCQ during the trials and in these 2 trials HCQ use was minimal (about 1% of patients in Study 9 received concomitant HCQ and about 8% of patients in Study 11 received concomitant HCQ). Therefore, no firm conclusions can be drawn about the safety of golimumab with concomitant HCQ.

7.7 Additional Safety Explorations

7.7.1 Safety and Immunogenicity of the To-Be-Marketed Presentation

Centocor proposes to market two pre-filled syringe (PFS) presentations of SC golimumab (with an [redacted] and in an auto-injector). However, only the liquid in a vial (LIV) presentation (not the PFS presentations) were used in the 24-week controlled portions of the 5 Phase 3 trials. Since in chemical comparability studies, the PFS presentation had increased subvisible particles compared to the LIV presentation, the PFS presentation may have greater immunogenicity than the LIV presentation. b(4)

To support the PFS presentations, the FDA required the following data:

1. Chemical comparability data of the PFS and LIV presentations (see Dr. Kurt Brorson's review, the primary CMC reviewer, for details).
2. Bioequivalence, safety, and immunogenicity results of Study 24 (the single-dose bioequivalence Phase 1 study of LIV and PFS golimumab in 156 healthy subjects) — see Table 7.7.1.
3. Analyses of safety and immunogenicity data after multiple dosing of PFS (see Table 7.7.2) including analyses of the comparison of immunogenicity rates between patients remaining on LIV compared to those switching from LIV to PFS.

Table 7.7.1 displays the major safety and immunogenicity results of Study 24 (the single-dose bioequivalence Phase 1 study of LIV and PFS presentations of golimumab) — see Table 5.3 for details of the design of Study 24.

In Study 24, the safety and immunogenicity of the LIV and PFS presentations of 100 mg of golimumab were similar. The LIV and PFS presentations fulfilled the bioequivalence criteria by AUC. Although the data did not quite meet bioequivalence standards with respect to Cmax, the difference was small and is not considered clinically significant because Centocor proposes a lower dose (50 mg). More details on the bioequivalent results of Study 24 see Dr. Lei Zhang's review, the primary clinical biopharmaceutical reviewer.