AVSOLA™ (infliximab-axxq) CLINICAL FACT SHEET

INDICATIONS

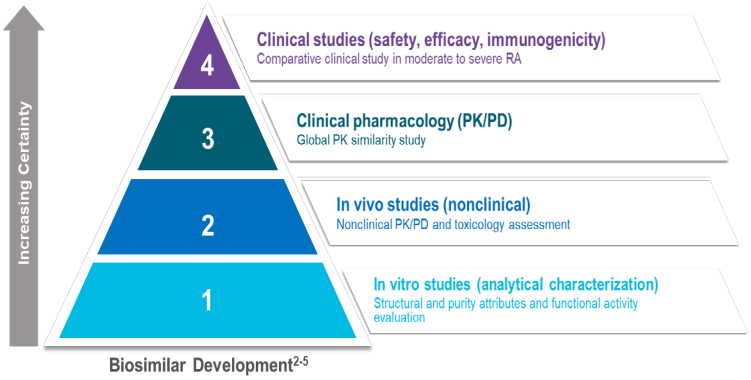
AVSOLA is a tumor necrosis factor (TNF) blocker indicated for:[1]

- **Crohn's Disease:**
  - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
  - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
- **Pediatric Crohn's Disease:** reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- **Ulcerative Colitis:** reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.
- **Pediatric Ulcerative Colitis:** reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.
- **Rheumatoid Arthritis:** in combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
- **Ankylosing Spondylitis:** reducing signs and symptoms in patients with active ankylosing spondylitis.
- **Psoriatic Arthritis:** reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
- **Plaque Psoriasis:** treatment of adult patients with chronic severe (ie, extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy, and when other systemic therapies are medically less appropriate. AVSOLA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

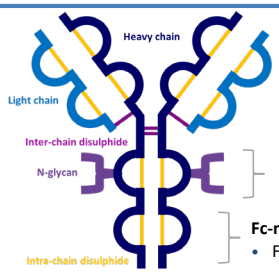
SUPPLY AND STORAGE

AVSOLA for injection 20 mL is supplied as a sterile, white-to-slightly yellow, lyophilized powder for IV infusion. Unopened AVSOLA vials should be stored in a refrigerator at 2° to 8°C (36° to 46°F) and protected from light.[1]

AVSOLA™ (infliximab-axxq) DEVELOPMENT PROGRAM



ANALYTICAL AND NONCLINICAL STUDIES



Fab-Mediated Activity[6,7]
- Similar soluble and membrane-bound antigen-binding activities
- Similar inhibition of TNFα-induced apoptosis in U937 cells

Fab- and Fc-Mediated Activity[6,7]
- Similar ADCC and CDC effector functions
- Similar reverse signaling functions

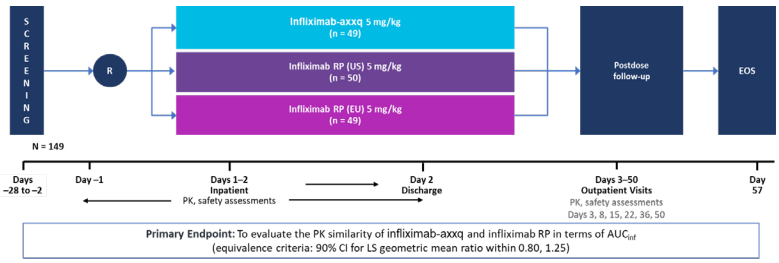
Fc-mediated Biological Activity[6,7]
- FcR binding • C1q binding • FcRn binding

Extensive analytical characterization was conducted to demonstrate that:[6,7]
(i) Infliximab-axxq and infliximab RP are highly similar and (ii) infliximab-axxq is manufactured in a well-controlled and consistent manner that meets the appropriate quality standards.

These analytical and in vitro studies include but are not limited to:[6,7]
- Evaluation of structural attributes and purity
- Binding to both soluble and membrane TNF-α
- TNF-α–induced apoptosis and reverse signaling
- Induction of effector functions (ADCC and CDC)
- FcRn binding of infliximab-axxq compared with infliximab RP
- Thermal stability and degradation rates

CLINICAL PHARMACOLOGY SIMILARITY ASSESSMENT IN HEALTHY ADULTS

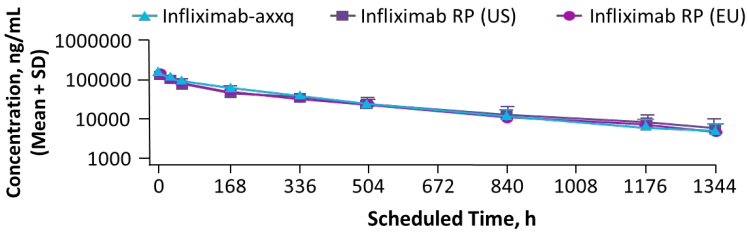
A randomized, single-blind, single-dose, three-arm, parallel-group study to determine the PK similarity of infliximab-axxq to infliximab RP[8]



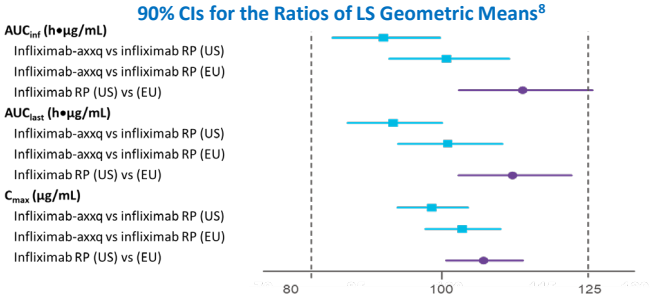
This clinical pharmacology study assessed the PK bioequivalence of 5 mg/kg infliximab-axxq vs 5 mg/kg infliximab RP (US) and 5 mg/kg infliximab RP (EU).[8]
- The mean serum concentration–time profiles were similar for all three treatment groups over the entire course of sampling.
- No new or unexpected safety signals were identified.
- Minor numerical differences were observed in binding antibodies, but more clinically relevant neutralizing antibody rates were similar.

The 90% CIs of the ratios of LS geometric means for C_{max}, AUC_{inf}, and AUC_{last} were fully contained within the predefined equivalence margins (0.80, 1.25), confirming bioequivalence between infliximab-axxq and infliximab RP (EU and US).

Mean Serum Concentration–Time Profiles[8]



90% CIs for the Ratios of LS Geometric Means[8]



SELECT IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with infliximab products are at an increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue AVSOLA™ if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before AVSOLA™ use and during therapy. Treatment for latent infection should be initiated prior to AVSOLA™ use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, pneumocystosis, and cryptococcosis. Patients may present with disseminated rather than localized disease. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections and who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella, Listeria, and Salmonella.**

Please see additional select Important Safety Information throughout and the accompanying full Prescribing Information, including BOXED WARNINGS.

AVSOLA™ (infliximab-axxq) For Injection 100mg/vial

CLINICAL PHARMACOLOGY SIMILARITY ASSESSMENT IN HEALTHY ADULTS (CONTINUED)

Immunogenicity After A Single Infused Dose[8]

	Infliximab-axxq (n = 49)		Infliximab RP (US) (n = 50)		Infliximab RP (EU) (n = 49)	
	Binding AAP n/N1* (%)	Neutralizing AAP† n/N1* (%)	Binding AAP n/N1* (%)	Neutralizing AAP† n/N1* (%)	Binding AAP n/N1* (%)	Neutralizing AAP† n/N1* (%)
Day 1, predose	0/49 (0)	0/49 (0)	0/50 (0)	0/50 (0)	0/49 (0)	0/49 (0)
Day 15	3/47 (6.4)	0/47 (0)	2/48 (4.2)	0/48 (0)	4/48 (8.3)	0/48 (0)
Day 36	16/47 (34.0)	3/47 (6.4)	11/49 (22.4)	0/49 (0)	13/48 (27.1)	1/48 (2.1)
Day 57 (EOS)	19/48 (39.6)	6/48 (12.5)	16/50 (32.0)	5/50 (10.0)	13/48 (27.1)	9/48 (18.8)

*N1, number of patients with ADA measured at the specified visit
†Neutralizing AAP is a subpopulation of the total binding AAP and inhibits functional activity of the therapeutic protein, generally directed against the biologically active site[9]

COMPARATIVE CLINICAL STUDY IN MODERATE TO SEVERE RHEUMATOID ARTHRITIS

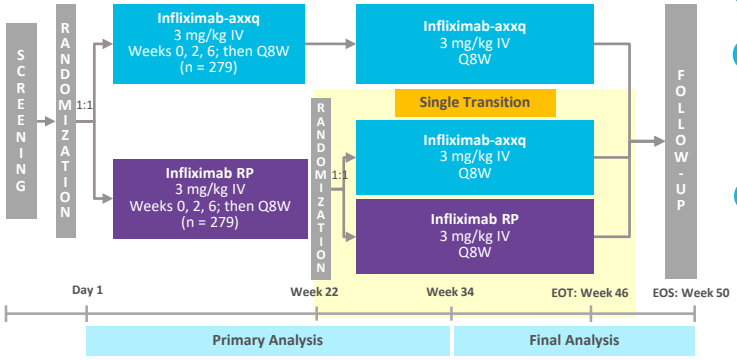
Objective: To assess the efficacy and safety of infliximab-axxq compared with infliximab RP in patients with moderate to severe RA[10-13]

- **RA as a Sensitive Patient Population:** Patients with moderate to severe RA are considered a sensitive population to detect any differences between a candidate biosimilar infliximab and the infliximab RP, should they exist.[14]

Study Design[10-13,15]

Inclusion Criteria
- Age 18–80 years
- RA diagnosis ≥ 3 months prior enrollment
- ≥ 6 swollen joints
- ≥ 6 tender joints
- Stable methotrexate dose of 7.5–25.0 mg/week for ≥ 8 weeks prior to receiving IP
- Infliximab RP or infliximab biosimilar naïve

Exclusion Criteria
- Previously received nonbiologic disease-modifying antirheumatic drugs (other than methotrexate)
- Previously received any biologic treatment for RA
- Received other specified treatments that could impact RA



Primary Endpoint
- RD of ACR20 at week 22

Secondary Endpoints
- RD of ACR20 at weeks 2, 6, 14, 30, 34, 38, 46, and 50
- RD of ACR50 and ACR70 at weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50
- DAS28-CRP change from baseline at weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50

Safety Endpoints
- TEAE, SAE, and adverse EOI
- Clinically significant changes in laboratory values and vital signs
- Incidence of ADAs

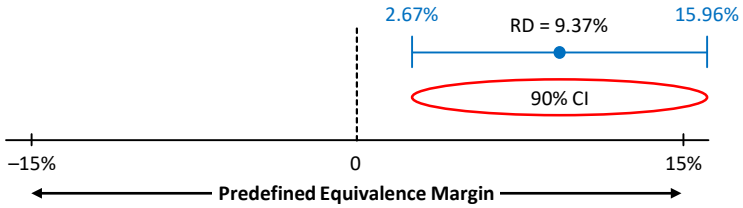
Post-hoc Analysis: Adjusted RD of ACR20 at week 22

Efficacy Analysis

Primary Endpoint Results: For the primary endpoint (RD of ACR20 at week 22), noninferiority was confirmed but superiority could not be ruled out.[10-13]

- The upper boundary slightly exceeded the prespecified margin of 15%.

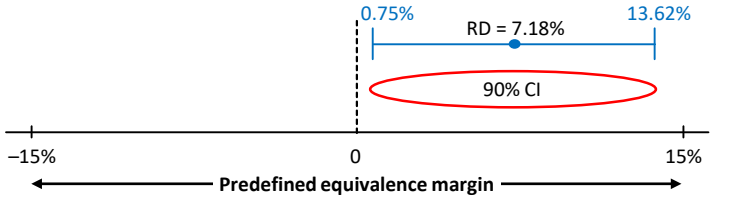
RD of ACR20 at Week 22[10-13]



Post-hoc Analysis: Post-hoc analysis of the primary endpoint adjusted for the impact of random imbalance in baseline demographics and disease characteristics between treatment arms.[10,13]

- Both upper (13.62%) and lower (0.75%) bounds of the 90% CI were within the prespecified margins (–15%, 15%).

Adjusted RD of ACR20 at Week 22[10,13]



CI of RD of ACR20 at week 22 in the ITT population with NRI based on the patient's randomized treatment. Clinical similarity was confirmed if the two-sided 90% CIs for RD were within the prespecified equivalence margin.[10,13]
- Prespecified equivalence margin for RD = (–15%, 15%)
- RD = ACR20 RR for infliximab-axxq (week 22) – ACR20 RR for infliximab RP (week 22)

Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

Key Secondary Endpoint Results: Mean DAS28-CRP change from baseline at weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50 was similar between the two groups.[15]

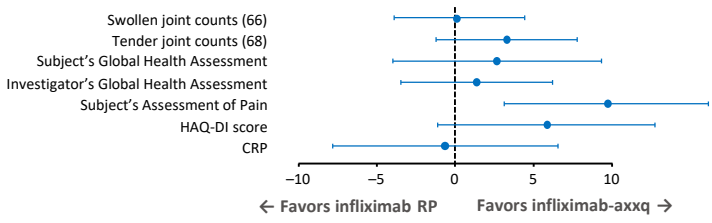
Difference Between Mean DAS28-CRP Change From Baseline[15]

	Week	Infliximab-axxq (n = 279)	Infliximab-RP (n = 279)	Infliximab RP/ Infliximab-axxq (n = 119)	Difference Between Means (90% CI)	
					Infliximab-axxq – Infliximab RP	Infliximab RP/ Infliximab-axxq – Infliximab RP
Initial Phase	Week 2	260	255	-	–0.07 (–0.20, 0.07)	–
	Week 6	259	253	-	0.00 (–0.17, 0.16)	–
	Week 14	253	250	-	–0.04 (–0.21, 0.14)	–
	Week 22	245	243	-	–0.01 (–0.20, 0.17)	–
Re-randomized Treatments	Week 30	225	112	112	0.16 (–0.08, 0.40)	0.00 (–0.27, 0.28)
	Week 34	222	113	111	0.11 (–0.12, 0.35)	–0.03 (–0.30, 0.24)
	Week 38	219	114	110	0.06 (–0.18, 0.30)	–0.08 (–0.36, 0.20)
	Week 46	205	108	108	0.11 (–0.14, 0.37)	–0.05 (–0.34, 0.25)
	Week 50	203	110	107	0.00 (–0.24, 0.24)	–0.20 (–0.47, 0.08)

For change in DAS28-CRP, the CI of the mean difference was estimated using an analysis of covariance model with relevant baseline values and stratification factors as covariates.[10] **Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.**

Other Analyses of ACR Components: ACR components with the largest RD between treatment groups at week 22 were Subject's Assessment of Disease-related Pain and HAQ-DI.[11]

RD (≥ 20% Improvement) at Week 22 in Seven Components in ACR[11]



The point estimates of RD were estimated by the Mantel-Haenszel estimate, and the 90% CI was estimated using stratified Newcombe confidence limits adjusting for the actual stratification factors (geographical region and prior antibody use for RA).[11] **Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.**

SELECT IMPORTANT SAFETY INFORMATION (CONTINUED)

The risks and benefits of treatment with AVSOLA™ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with AVSOLA™, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy, who are on treatment for latent TB, or who were previously treated for TB infection.

The risk of infection may be higher in patients greater than 65 years of age, pediatric patients, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressant therapy. In clinical trials, other serious infections observed in patients treated with infliximab products included pneumonia, cellulitis, abscess, and skin ulceration.

Please see additional select Important Safety Information throughout and the accompanying full Prescribing Information, including BOXED WARNINGS.

AVSOLA™ (infliximab-axxq) For Injection 100mg/vial

COMPARATIVE CLINICAL STUDY IN MODERATE TO SEVERE RHEUMATOID ARTHRITIS (CONTINUED)

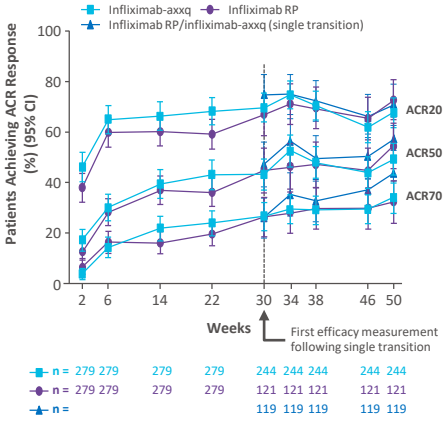
Secondary Endpoint Results: ACR20, ACR50, and ACR70 response rates for initial or initial/rerandomized groups were similar throughout the study.[16]
- Efficacy was not impacted by the single transition from infliximab RP to infliximab-axxq at week 22.[16]
- The 95% CIs of ACR20, ACR50, and ACR70 overlap at all time points.[12,16]

RD of ACR20, ACR50, and ACR70 Response Rates up to the End of Study (Week 50)[15,16*]

		ACR20 (%); RD (90% CI)		ACR50 (%); RD (90% CI)		ACR70 (%); RD (90% CI)	
		Infliximab-RP – Infliximab-axxq	Infliximab RP/ Infliximab-axxq – Infliximab RP	Infliximab-RP – Infliximab-axxq	Infliximab RP/ Infliximab-axxq – Infliximab RP	Infliximab-RP – Infliximab-axxq	Infliximab RP/ Infliximab-axxq – Infliximab RP
Initial Phase	Week 2	8.03 (1.15, 14.81)	N/A	4.41 (−0.56, 9.38)	N/A	−2.50 (−5.84, 0.83)	N/A
	Week 6	4.96 (−1.80, 11.64)	N/A	1.62 (−4.71, 7.94)	N/A	−2.43 (−7.47, 2.64)	N/A
	Week 14	6.22 (−0.51, 12.87)	N/A	2.30 (−4.45, 9.03)	N/A	5.46 (−0.01, 10.91)	N/A
	Week 22	9.37 (2.67, 15.96)	N/A	7.09 (0.27, 13.83)	N/A	4.58 (−1.21, 10.34)	N/A
Re-randomized treatments	Week 30	3.05 (−5.26, 11.73)	8.50 (−1.18, 17.97)	−1.33 (−10.40, 7.62)	3.24 (−7.28, 13.67)	0.20 (−8.12, 8.02)	−0.08 (−9.39, 9.28)
	Week 34	3.31 (−4.61, 11.70)	4.06 (−5.40, 13.40)	6.52 (−2.62, 15.48)	10.74 (0.12, 21.03)	1.50 (−7.00, 9.51)	7.49 (−2.39, 17.22)
	Week 38	0.82 (−7.34, 9.40)	2.79 (−6.86, 12.34)	0.56 (−8.54, 9.59)	2.93 (−7.62, 13.39)	−0.50 (−9.03, 7.59)	3.39 (−6.41, 13.14)
	Week 46	−3.74 (−12.27, 5.17)	1.12 (−8.89, 11.08)	−1.04 (−10.11, 7.93)	6.14 (−4.44, 16.54)	−0.43 (−8.98, 7.66)	7.87 (−2.13, 17.68)
	Week 50	−5.25 (−13.24, 3.29)	−1.49 (−11.01, 8.04)	−5.43 (−14.39, 3.71)	2.98 (−7.51, 13.37)	1.95 (−6.81, 10.29)	12.06 (1.74, 22.04)

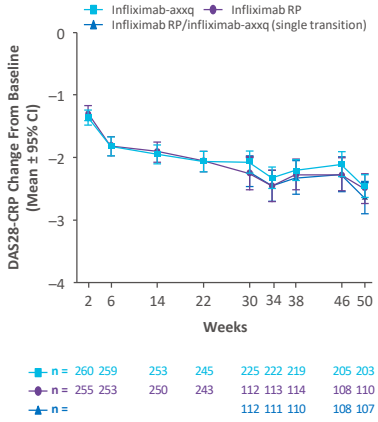
*ITT analysis set with NRI based on patient's randomized treatment[15]

Patients Achieving an ACR Response Through Week 50[12,13,15,*]



*ITT analysis set with NRI based on patient's randomized treatment[15]

Change From Baseline (Mean ± 95% CI) in DAS28-CRP by Study Week[13,15]



Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

Safety Analysis: The incidence of TEAEs, SAEs, and binding and neutralizing ADAs was similar between the infliximab-axxq and infliximab RP groups.[11–13,15]

Summary of Adverse Events

	Safety up to Week 22		Safety Post-transition From Weeks 22 to 50		
AE Category, n (%)*	Infliximab-axxq (n= 278)	Infliximab RP (n = 278)	Infliximab-axxq / Infliximab-axxq (n = 241)	Infliximab RP/ infliximab RP (n = 121)	Infliximab RP/ Infliximab-axxq (n = 119)
Any AE	144 (51.8)	138 (49.6)	130 (53.9)	69 (57.0)	69 (58.0)
Any grade ≥ 3 AE	12 (4.3)	14 (5.0)	18 (7.5)	7 (5.8)	5 (4.2)
Any TEAE	54 (19.4)	58 (20.9)	48 (19.9)	29 (24.0)	26 (21.8)
Any AE with outcome of death	1 (0.4)	1 (0.4)	0	0	0
Any SAE	9 (3.2)	14 (5.0)	15 (6.2)	4 (3.3)	1 (0.8)
Any AE leading to infusion delayed/not administered	30 (10.8)	30 (10.8)	19 (7.9)	11 (9.1)	8 (6.7)
Any TEAE leading to IP discontinuation	16 (5.8)	18 (6.5)	12 (5.0)	4 (3.3)	4 (3.4)
Any AE of interest	39 (14.0)	49 (17.6)	43 (17.8)	19 (15.7)	16 (13.4)
TEAE of interest†					
Upper respiratory tract infection	17 (6.1)	18 (6.5)	23 (9.5)	9 (7.4)	14 (11.8)
RA	14 (5.0)	11 (4.0)	23 (9.5)	9 (7.4)	7 (5.9)
Nasopharyngitis	12 (4.3)	4 (1.4)	13 (5.4)	11 (9.1)	8 (6.7)
Bronchitis	9 (3.2)	4 (1.4)	8 (3.3)	6 (5.0)	2 (1.7)
Pharyngitis	8 (2.9)	3 (1.1)	2 (0.8)	2 (1.7)	7 (5.9)

*For each category/preferred term, patients were included only once, even if they experienced multiple events in that category/preferred term[15]
†TEAEs Reported in ≥ 5% of patients in any treatment group[12,13]

Immunogenicity Before and After Transition[11–13,15]

	Antibody-positive by Week 22 With a Negative or No Result at Baseline		Antibody-positive by Week 50 With a Negative or No Result at Week 22		
	Infliximab-axxq	Infliximab RP	Infliximab-axxq/ Infliximab-axxq	Infliximab RP/ Infliximab RP	Infliximab RP/ Infliximab-axxq
Total, N	278	278	241	121	119
Patients, n	261	264	96	45	45
Binding antibody, n (%)	149 (57.1)	160 (60.6)	29 (30.2)	19 (42.2)	18 (40.0)
Neutralizing antibody, n (%)	47 (18.0)	55 (20.8)	3 (3.1)	1 (2.2)	2 (4.4)

REGULATORY GUIDANCE FOR THE REQUIREMENTS FOR EXTRAPOLATION

Extrapolation allows for the approval of a biosimilar for use in an indication held by the reference biologic, which is not directly studied in a comparative clinical trial with a biosimilar.[2]

4 Criteria for Scientific Justification for Extrapolation:

1. Is the MOA expected to differ across indications?
2. Do the PK, PD, and biodistribution vary across patient populations?
3. Is the immunogenicity expected to vary in different patient populations?
4. Are there differences in expected toxicities in different indications and patient populations?

Mechanism of Action	• The MOA of infliximab, regardless of inflammatory disease or location, is the binding and neutralization of TNF-α.[8,13] A comprehensive analytical similarity assessment demonstrated similarity between infliximab-axxq and infliximab RP, including that seen in functional assays reflecting the MOA.[7]
PK, Biodistribution, and Clearance	• A single-blind, single-dose, parallel-group study confirmed PK similarity between infliximab-axxq and infliximab RP.[8]
Clinical Considerations • **Expected Toxicities** • **Immunogenicity**	• Immunogenicity was comparable for infliximab-axxq and infliximab RP in healthy subjects[8] as well as in patients with moderate to severe RA.[13] • Safety data from the comparative clinical study in moderate to severe RA support that the type and incidence of AEs were similar for infliximab-axxq and infliximab RP, and no clinically meaningful differences between treatment arms were seen.[13,15]

AVSOLA™ (infliximab-axxq) For Injection 100mg/vial

SELECT IMPORTANT SAFETY INFORMATION (CONTINUED)

MALIGNANCIES

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphomas. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

Post-marketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including infliximab products. These cases have had a very aggressive disease course and have been fatal. A majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. Carefully assess the risks and benefits of treatment with AVSOLA™, especially in these patient types.

In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and with the expected rate in the general population. However, patients with Crohn's disease, rheumatoid arthritis, or plaque psoriasis may be at a higher risk for developing lymphoma.

In clinical trials of some TNF inhibitors, including infliximab products, more cases of other malignancies were observed compared with controls. The rate of these malignancies among patients treated with infliximab products was similar to that expected in the general population, whereas the rate in control patients was lower than expected. Cases of acute and chronic leukemia have been reported with post-marketing TNF blocker use. Because the potential role of TNF inhibitors in the development of malignancies is not known, caution should be exercised when considering treatment of patients with a current or a past history of malignancy or other risk factors such as chronic obstructive pulmonary disease (COPD).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab products. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

A population-based retrospective cohort study found a 2- to 3-fold increase in the incidence of invasive cervical cancer in women with rheumatoid arthritis treated with infliximab compared with biologics-naïve patients or the general population, particularly those over 60 years of age. A causal relationship between infliximab products and cervical cancer cannot be excluded. Periodic screening should continue in women treated with AVSOLA™.

CONTRAINDICATIONS

AVSOLA™ is contraindicated in patients with moderate to severe (NYHA Class III/IV) congestive heart failure (CHF) at doses greater than 5 mg/kg. Higher mortality rates at the 10 mg/kg dose and higher rates of cardiovascular events at the 5 mg/kg dose have been observed in these patients. AVSOLA™ should be used with caution and only after consideration of other treatment options. Patients should be monitored closely. Discontinue AVSOLA™ if new or worsening CHF symptoms appear. AVSOLA™ should not be (re)administered to patients who have experienced a severe hypersensitivity reaction or to patients with hypersensitivity to murine proteins or other components of the product.

HEPATITIS B REACTIVATION

TNF inhibitors, including infliximab products, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients should be tested for HBV infection before initiating AVSOLA™. For patients who test positive, consult a physician with expertise in the treatment of hepatitis B. Exercise caution when prescribing AVSOLA™ for patients identified as carriers of HBV and monitor closely for active HBV infection during and following termination of therapy with AVSOLA™. Discontinue AVSOLA™ in patients who develop HBV reactivation and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of TNF-blocker therapy and monitor patients closely**.**

HEPATOTOXICITY

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported in patients receiving infliximab products postmarketing. Some cases were fatal or required liver transplant. Aminotransferase elevations were not noted prior to discovery of liver injury in many cases. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (eg, ≥ 5 times the upper limit of normal) develop, AVSOLA™ should be discontinued, and a thorough investigation of the abnormality should be undertaken**.**

HEMATOLOGIC REACTIONS

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia (some fatal) have been reported in patients receiving infliximab products. The causal relationship to infliximab product therapy remains unclear. Exercise caution in patients who have ongoing or a history of significant hematologic abnormalities. Advise patients to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection. Consider discontinuation of AVSOLA™ in patients who develop significant hematologic abnormalities**.**

HYPERSENSITIVITY

Infliximab products have been associated with hypersensitivity reactions that differ in their time of onset. Anaphylaxis, urticaria, dyspnea, and hypotension have occurred in association with infusions of infliximab products. Medications for the treatment of hypersensitivity reactions should be available.

CARDIOVASCULAR AND CEREBROVASCULAR REACTIONS DURING AND AFTER INFUSION

Serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of infliximab product infusion. Cases of transient visual loss have been reported during or within 2 hours of infusion of infliximab. Monitor patients during infusion and if a serious reaction occurs, discontinue infusion. Manage reactions according to signs and symptoms**.**

NEUROLOGIC REACTIONS

Agents that inhibit TNF have been associated with CNS manifestation of systemic vasculitis, seizure, and new onset or exacerbation of CNS demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Exercise caution when considering AVSOLA™ in patients with these disorders and consider discontinuation if these disorders develop.

AUTOIMMUNITY

Treatment with infliximab products may result in the formation of autoantibodies and in the development of a lupus-like syndrome. Discontinue treatment with AVSOLA™ if symptoms of a lupus-like syndrome develop.

ADVERSE REACTIONS

In clinical trials with infliximab products, the most common adverse reactions occurring in >10% of patients included infections (eg, upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain.

USE WITH OTHER DRUGS

Concomitant use of AVSOLA™ with anakinra, abatacept, tocilizumab, or other biologics used to treat the same conditions as AVSOLA™ is not recommended because of the possibility of an increased risk of infection. Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

LIVE VACCINES/THERAPEUTIC INFECTIOUS AGENTS

Live vaccines or therapeutic infectious agents should not be given with AVSOLA™ due to the possibility of clinical infections, including disseminated infections.

Bring pediatric patients up to date with all vaccinations prior to initiating AVSOLA™. At least a 6-month waiting period following birth is recommended before the administration of any live vaccine to infants exposed *in utero* to infliximab products.

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see additional select Important Safety Information throughout, and the accompanying full Prescribing Information, including BOXED WARNINGS.

ABBREVIATIONS

AAP, antibody assay positive; ACR, American College of Rheumatology; ACR20, ≥ 20% improvement in ACR core set measurements; ACR50, ≥ 50% improvement in ACR core set measurements; ACR70, ≥ 70% improvement in ACR core set measurements; ADA, antidrug antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; AE, adverse event; AUC_{inf}, area under the serum concentration–time curve from time 0 extrapolated to infinite time; AUC_{last}, area under the serum concentration–time curve from time 0 to last quantifiable concentration; C1q, complement component 1q; CDC, complement-dependent cytotoxicity; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; C_{max}, maximum observed drug concentration during a dosing interval; CNS, central nervous system; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score-28 for rheumatoid arthritis with CRP; EOI, event of interest; EOS, end of study; EOT, end of treatment; EU, European Union; Fab, antigen binding fragment; Fc, fragment crystallizable; FcR, Fc receptor; FcRn, neonatal FcR; FDA, Food and Drug Administration; HAQ-DI, Health Assessment Questionnaire–Disability Index; HBV, hepatitis B virus; IP, investigational product; ITT, intent to treat; IV, intravenous; LS, least square; MOA, mechanism of action; N/A, not applicable; NRI, nonresponder imputation; NYHA, New York Heart Association; PD, pharmacodynamics; PK, pharmacokinetics; Q8W, every 8 weeks; R, randomization; RA, rheumatoid arthritis; RD, response difference; RP, reference product; RR, response rate; SAE, serious adverse event; SD, standard deviation; TB, tuberculosis; TEAE, treatment-emergent adverse event; TNF-α, tumor necrosis factor-α; US, United States.

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AVSOLA™ (infliximab-axxq) For Injection 100mg/vial