Clinical and economic benefit of advanced therapies for the treatment of Active Ankylosing Spondylitis

Running title: Clinical and Economic Benefit of Advanced Therapies for Ankylosing Spondylitis

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Supplementary materials

Supplementary Table 1: RCTs Included in NMA

Study	Intervention arm(s)	Comparator arm(s)	Study design	NSAID/csDMARD experience	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
ATLAS (NCT00085644)	Adalimumab, 40 mg, SC injection, at Week 0 and Q2W for 24 Weeks	Placebo, SC injection, at Week 0 and Q2W for 24 Weeks	Phase 3 # treatment arms, 2 # centers, 43 Randomisation, 2:1 Blinding: Double	Prior: IR or intolerant to ≥1 NSAID or cDMARD Concurrent: Allowed stable (≥4w) doses of SSZ (≤3 g/d), MTX (≤25 mg/w), HCL (≤400 mg/d), CS (≤10 mg/d), NSAIDs	Naïve	315	12	ASAS20; Week 12	van der Heijde 2006[1]
Bao 2014 (NCT01248793)	Golimumab, 50 mg, SC injection at Week 0 and Q4W to Week 48	Placebo, SC injection, Q4W, Weeks 0-20	Phase 3 # treatment arms: 2 # centers: 12 Randomisation: 1:1 Blinding: Double	NR	Naïve	213	16	ASAS20; Week 14	Bao 2014[2]
Calin 2004 (NCT00421915; 0881A3-311-EU)	Etanercept, 25 mg, SC injection, at Week 0, BIW to Week 12	Placebo, SC injection, at Week 0, BIW to Week 12	Phase 3 # treatment arms, 2 # centers, 14 Randomisation, 1:1 Blinding: Double	NR	Naïve	84	12	ASAS 20; Week 12	Calin 2004[3] (Dijkmans 2009[4])
COAST-V (NCT02696785)	Ixekizumab, 80 mg Q2W or 80 mg Q4W, SC injections; starting dose of 80 mg or 160 mg (1:1) at Week 0 for both Q2W and Q4W groups	Placebo or Adalimumab 40 mg, Q2W, SC injections	Phase 3 # treatment arms, 4 # centers, 84 Randomisation, 1:1:1:1 Blinding: Double	Prior: IR or intolerant to ≥2 NSAIDs	Naïve	341	16	ASAS40; Week 16	van der Heijde 2018[5] (Dougados 2020[6], CADTH IXE Clinical Review Report[7])

Study	Intervention arm(s)	Comparator arm(s)	Study design	NSAID/csDMARD experience	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
COAST-W (NCT02696798)	Ixekizumab, 80 mg Q2W or 80 mg Q4W, SC injections; starting dose of 80 mg or 160 mg (1:1) at Week 0 for both Q2W and Q4W groups	Placebo, SC injections, Q2W	Phase 3 # treatment arms, 3 # centers, 106 Randomisation, 1:1:1 Blinding: Double	Concurrent: Allowed NSAIDs at stable dose	Prior: discontinued at least 1 TNFi, but no more than 2 TNFi, either due to intolerance or due to an IR to treatment with a single TNFi for at least 12 weeks at an adequate dose	316	16	ASAS40; Week 16	Deodhar 2019[8] (Dougados 2019[6])
Davis 2003	Etanercept, 25 mg, SC, BIW at Week 0 to Week 24	Placebo, SC, BIW at Week 0 to Week 24	Phase NR # treatment arms: 2 # centers: 28 Randomisation: 1:1 Blinding: Double	NR	Naïve	277	24	ASAS20; Week 12	Davis 2003[9]
GO-RAISE (NCT00265083)	Golimumab, 50 mg or 100 mg, SC injection, 2 injections Q4W at Week 0 to Week 24	Placebo, SC injection, 2 injections Q4W at Week 0 to Week 24	Phase 3 # treatment arms: 3 # centers: 57 Randomisation: 1:1.8:1.8 Blinding: Double	Prior: IR or intolerant to NSAID or DMARDs Concurrent: Allowed stable doses of SSZ, MTX, HCL, CS, NSAIDs	Naïve	356	16	ASAS20; Week 14	Inman 2008[10]
Gorman 2002	Etanercept, 25 mg, SC injection twice weekly	Placebo, SC injection twice weekly	Phase NR # treatment arms: 2 # centers: NR Randomisation: 1:1 Blinding: Double	Concurrent: Allowed stable (≥4w) doses of SSZ (≤3 g/d), MTX (≤20 mg/w), gold injections (50 mg/m), CS (≤10 mg/d), NSAIDs	Naïve (assumed as bDMARDs were likely not yet available[a])	40	16	ASAS20; Week 16	Gorman 2002[11]
Huang 2014 (NCT01114880)	Adalimumab, 40 mg, SC injection, at Week 0 and	Placebo, SC injection at Week 0 and Q2W for 12 Weeks	Phase 3 # treatment arms: 2 # centers: 9 Randomisation:	Prior: IR or intolerant to ≥1 NSAID Concurrent: Allowed stable doses of SSZ	Naïve	344	12	ASAS20; Week 12	Huang 2014[12]

Study	Intervention arm(s)	Comparator arm(s)	Study design	NSAID/csDMARD experience	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
	Q2W for 12 Weeks		2:1 Blinding: Double	(≤3 g/d), MTX (≤25 mg/w), CS (≤10 mg/d), NSAIDs, analgesics					
M03-606 Canadian AS Study (NCT00195819)	Adalimumab, 40 mg, SC injections at Week 0 and Q2W for 24 Weeks	Placebo, SC injection at Week 0 and Q2W for 24 Weeks	Phase 3 # treatment arms: 2 # centers: 11 Randomisation: 1:1 Blinding: Double	Prior: IR or intolerant to ≥1 NSAID or DMARD Concurrent: Allowed stable (≥4w) doses of SSZ (≤3 g/d), MTX (≤25 mg/w), HCL (≤400 mg/d), CS (≤10 mg/d), NSAIDs	Naïve	82	24	ASAS20; Week 12	Lambert 2007[13] (Maksymowych 2008[14])
MEASURE 1 (NCT01358175 (ext NCT01863732))	Secukinumab, 10 mg/kg (IV loading dose) at Weeks 0, 2, and 4, followed by SC injections of secukinumab 150 mg or 75 mg Q4W starting at Week 8, for 2 years	Placebo, IV at Week 0, 2, and 4, then SC injections Q4W until Week 16.	Phase 3 # treatment arms, 3 # centers, 65 Randomisation, 1:1:1 Blinding: Double	Prior: Maximum tolerated doses of NSAIDs	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	371	16	ASAS20; Week 16	Baeten 2015[15] (Deodhar 2016[16])
MEASURE 2 (NCT01649375)	Secukinumab, 150 mg or 75 mg, SC injections at Weeks 0, 1, 2, and 3 and Q4W starting at Week 4 for 5 years	Placebo, SC injection, at Weeks 0, 1, 2, and 3, and Q4W until Week 16	Phase 3 # treatment arms: 3 # centers: 53 Randomisation: 1:1:1 Blinding: Double	Prior: Previous used of DMARDs allowed Concurrent: Allowed stable doses of SSZ, MTX, CS, NSAIDs	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	219	16	ASAS20; Week 16	Baeten 2015[15] (Sieper 2017[17]; Deodhar 2019[18]; Marzo-Ortega 2019[19])

Study	Intervention arm(s)	Comparator arm(s)	Study design	NSAID/csDMARD experience	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
MEASURE 3 (NCT02008916)	Secukinumab, 10 mg/kg IV at Weeks 0, 2 and 4 (loading dose), followed by secukinumab 300 mg or 150 mg, SC injections, Q4W starting at Week 8 to end of study	Placebo, IV infusion at Weeks 0, 2, and 4, followed by SC injections, Q4W starting at Week 8 to Week 16	Phase 3 # treatment arms, 3 # centers, 54 Randomisation, 1:1:1 Blinding: Double	Prior: Maximum tolerated doses of NSAIDs	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	226	16	ASAS20; Week 16	Pavelka 2017[20]
MEASURE 4 (NCT02159053)	Secukinumab, 150 mg, with or without loading dose, SC injections at Weeks 0, 1, 2, and 3 (loading dose) and Q4W starting at Week 4 for 104 Weeks (both groups)	Placebo, SC injection, at Weeks 0, 1, 2, and 3, and Q4W until Week 16	Phase 3 # treatment arms: 3 # centers: 85 Randomisation: 1:1:1 Blinding: Double	Prior: Maximum tolerated doses of NSAIDs (≥2w)	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	350	16	ASAS20; Week 16	Kivitz 2018[21]
MEASURE 5 (NCT02896127)	Secukinumab, 150 mg, SC injection at Weeks 1, 2, 3, and 4, and Q4W to Week 52	Placebo, SC injection at Weeks 1, 2, 3, and 4, and Q4W to Week 16	Phase 3 # treatment arms, 2 # centers, NR Randomisation, 2:1 Blinding: Double	Prior: IR to ≥2 NSAIDs; stable (≥2w) dose of NSAIDs	Mixed (previous use of anti-TNFs allowed, but washout period required) - Data for naïve and IR subgroups available	458	16	ASAS20; Week 16	Huang 2020[22]
Pedersen 2016 (NCT00477893)	Adalimumab, 40 mg, SC, at	Placebo, SC, at Week 0	Phase 4 # treatment	Prior: Maximum tolerated doses of	Naïve	52	12	BASDAI50 ; Week 24	Pedersen 2016[23]

Study	Intervention arm(s)	Comparator arm(s)	Study design	NSAID/csDMARD experience	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
	Week 0 and Q2W for 24 Weeks	and Q2W for 12 Weeks	arms, 2 # centers, 7 Randomisation, 1:1 Blinding: Double	≥2 NSAIDs Concurrent: Allowed stable doses NSAIDs (-4 to 12w)					
SELECT-AXIS 1 (NCT03178487)	Upadacitinib, 15 mg, oral, at Week 0 and QD to Week 14	Placebo, oral, at Week 0 and QD to Week 14	Phase 2/3 # treatment arms, 2 # centers, 62 Randomisation, 1:1 Blinding: Double	Prior: IR or intolerant to ≥2 NSAIDs	Naïve	187	14	ASAS40; Week 14	van der Heijde 2019[24] (Data on file[25])
SELECT-AXIS 2, (NCT04169373) (AS bDMARD-IR sub-population)	Upadacitinib, 15 mg, oral, at Week 0 and QD to Week 14	Placebo, oral, at Week 0 and QD to Week 14	Phase 3 # treatment arms, 2 # centers, 212[b] Randomisation, 1:1 Blinding: Double	Prior: IR or intolerant to ≥2 NSAIDs	Previously exposed to 1 or 2 bDMARDs, discontinued due to either IR or intolerance	420	14	ASAS40; Week 14	Data on file[26]
SPINE (NCT00420238)	Etanercept, 50 mg, SC injection, QW for 12 Weeks	Placebo, SC injection, QW for 12 Weeks	Phase 4 # treatment arms, 2 # centers, 21 Randomisation, 1:1 Blinding: Double	Prior: IR or intolerant to ≥2 NSAIDs at max tolerated dose for ≥3m Concurrent: Allowed stable doses of NSAIDs (≥2w), SSZ/MTX (≥4w)	Naïve	82	12	BASDAI CFB; Week 12	Dougados 2011[27]
Tofacitinib Phase 3 Study (NCT03502616)	Tofacitnib 5 mg, twice daily, oral tablets, for 16 weeks	Placebo, twice daily, oral tablets, for 16 weeks	Phase 3 # treatment arms, 2 # centers, 75 Randomisation, 1:1 Blinding: Double	Prior: IR or intolerant to ≥2 NSAIDs	Mixed (approximately 20% of patients IR to ≤2 TNFi or have prior bDMARD use without IR) Data for naïve and IR	270	16	ASAS20; Week 16	Deodhar 2021 [28]

Study	Intervention arm(s)	Comparator arm(s)	Study design	NSAID/csDMARD experience	bDMARD experience	Total N	Duration of randomized phase (weeks)	Primary endpoint	Primary (secondary) reference(s) used
					subgroups available				
van Der Heijde 2006 (NCT00418548)	Etanercept, 50 mg QW or 25 mg BIW, SC injections at Week 0 to Week 12	Placebo, BIW, SC injections at Week 0 to Week 12	Phase 3 # treatment arms, 3 # centers, 38 Randomisation, 3:3:1 Blinding: Double	Concurrent: stable (≥4w) dose of NSAIDs	Mixed (patients previously treated with bDMARDs less than 4 weeks before baseline were not eligible)	356	12	ASAS20; Week 12	van der Heijde 2006[29] (Braun 2007[30])

[a]Assumption confirmed after consultation with clinical experts.

[b]Number of sites for both trial populations.

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARD, biologic DMARD; BIW, twice weekly; CFB, change from baseline; CRP, C-reactive protein; CS, corticosteroids; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; HCL, hydroxychloroquine; INF, infliximab; IR, inadequate response and/or intolerance; IV, intravenous; MTX, methotrexate; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; SSZ, sulfasalazine; TNF, tumor necrosis factor.

Supplementary Table 2: NMA inputs, ASAS40, Bio-naïve populations

Study	Intervention Arm	n	N
ATLAS	PBO	14	107
ATLAS	ADA40	83	208
Bao et al. 2014	PBO	10	105
Bao et al. 2014	GOL50	38	108
COAST-V	PBO	16	87
COAST-V	ADA40	32	90
COAST-V	IXE80Q2W	43	83
COAST-V	IXE80Q4W	39	81
Deodhar et al. 2021	PBO	15	105
Deodhar et al. 2021	TOF5	46	102
GO-RAISE	PBO	12	78
GO-RAISE	GOL100	69	140
GO-RAISE	GOL50	62	138
Huang et al. 2014	PBO	11	115
Huang et al. 2014	ADA40	102	229
MEASURE 1	PBO	14	89
MEASURE 1	SEC150	45	92
MEASURE 2	PBO	8	45
MEASURE 2	SEC150	19	44
MEASURE 3	PBO	14	59
MEASURE 3	SEC150	25	57
MEASURE 3	SEC300	25	57
MEASURE 4	PBO	25	83
MEASURE 4	SEC150	34	85
MEASURE 4	SEC150 (no LD)	33	85
MEASURE 5	PBO	22	122
MEASURE 5	SEC150	102	240
SPINE	PBO	10	43
SPINE	ETN25/50	17	39
SELECT-AXIS-1	PBO	24	94
SELECT-AXIS-1	UPA15	48	93

Abbreviations: ADA, adalimumab; ETN, etanercept; GOL, golimumab; IXE, ixekizumab; n, number achieving ASAS40; N, sample size; PBO, placebo; SEC, secukinumab; TOF, tofacitinib; UPA, upadacitinib

Supplementary Table 3: NMA inputs, ASAS40, Bio-IR populations

Study	Intervention Arm	n	N
COAST-W	PBO	13	104
COAST-W	IXE80Q2W	30	98
COAST-W	IXE80Q4W	29	114
Deodhar et al. 2021	PBO	2	31
Deodhar et al. 2021	TOF5	8	31
MEASURE 1	PBO	2	33
MEASURE 1	SEC150	7	33
MEASURE 2	PBO	0	29
MEASURE 2	SEC150	7	28
MEASURE 3	PBO	2	17
MEASURE 3	SEC150	5	17
MEASURE 3	SEC300	7	19
MEASURE 4	PBO	8	34
MEASURE 4	SEC150	11	31
MEASURE 4	SEC150 (no LD)	9	32
MEASURE 5	PBO	4	31
MEASURE 5	SEC150	32	65
SELECT-AXIS-2 Study 1	PBO	38	209
SELECT-AXIS-2 Study 1	UPA15	94	211

Abbreviations: IXE, ixekizumab; n, number achieving ASAS40; N, sample size; PBO, placebo; SEC, secukinumab; TOF, tofacitinib; UPA, upadacitinib

Supplementary Table 4: NMA inputs, AEs leading to discontinuation, Overall populations

Study	Intervention Arm	n	N
ATLAS	PBO	2	107
ATLAS	ADA40	5	208
Bao et al. 2014	PBO	1	105
Bao et al. 2014	GOL50	1	108
Calin et al. 2004	PBO	0	39
Calin et al. 2004	ETN25/50	0	45
COAST-V	PBO	0	86
COAST-V	ADA40	1	90
COAST-V	IXE80Q2W	3	83
COAST-V	IXE80Q4W	0	81
COAST-W	PBO	2	104
COAST-W	IXE80Q2W	3	98
COAST-W	IXE80Q4W	10	114
Davis et al. 2003	PBO	1	139
Davis et al. 2003	ETN25/50	7	138
Deodhar et al. 2021	PBO	1	136
Deodhar et al. 2021	TOF5	3	133
GO-RAISE	PBO	1	77
GO-RAISE	GOL100	4	140
GO-RAISE	GOL50	4	138
Gorman et al. 2002	PBO	0	20
Gorman et al. 2002	ETN25/50	0	20
Huang et al. 2014	PBO	0	115
Huang et al. 2014	ADA40	4	229
M03-606	PBO	0	44
M03-606	ADA40	0	38
MEASURE 1	PBO	5	122
MEASURE 1	SEC150	1	125
MEASURE 2	PBO	4	74
MEASURE 2	SEC150	5	72
MEASURE 3	PBO	0	75
MEASURE 3	SEC150	0	74
MEASURE 3	SEC300	0	76
MEASURE 4	PBO	1	117
MEASURE 4	SEC150	1	116
MEASURE 4	SEC150 (no LD)	2	117
MEASURE 5	PBO	1	153
MEASURE 5	SEC150	2	304
Pedersen et al. 2016	PBO	1	27
Pedersen et al. 2016	ADA40	1	25
SELECT-AXIS-1	PBO	3	94
SELECT-AXIS-1	UPA15	2	93
SELECT-AXIS-2 Study 1	PBO	3	209
SELECT-AXIS-2 Study 1	UPA15	0	211
van der Heijde et al. 2006	PBO	0	51
van der Heijde et al. 2006	ETN25/50	14	305

Abbreviations: ADA, adalimumab; ETN, etanercept; GOL, golimumab; IXE, ixekizumab; n, number achieving ASAS40; N, sample size; PBO, placebo; SEC, secukinumab; TOF, tofacitinib; UPA, upadacitinib

Appendix 1: Systematic Literature Review Citations

1. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis and rheumatism. 2006;54(7):2136-46.
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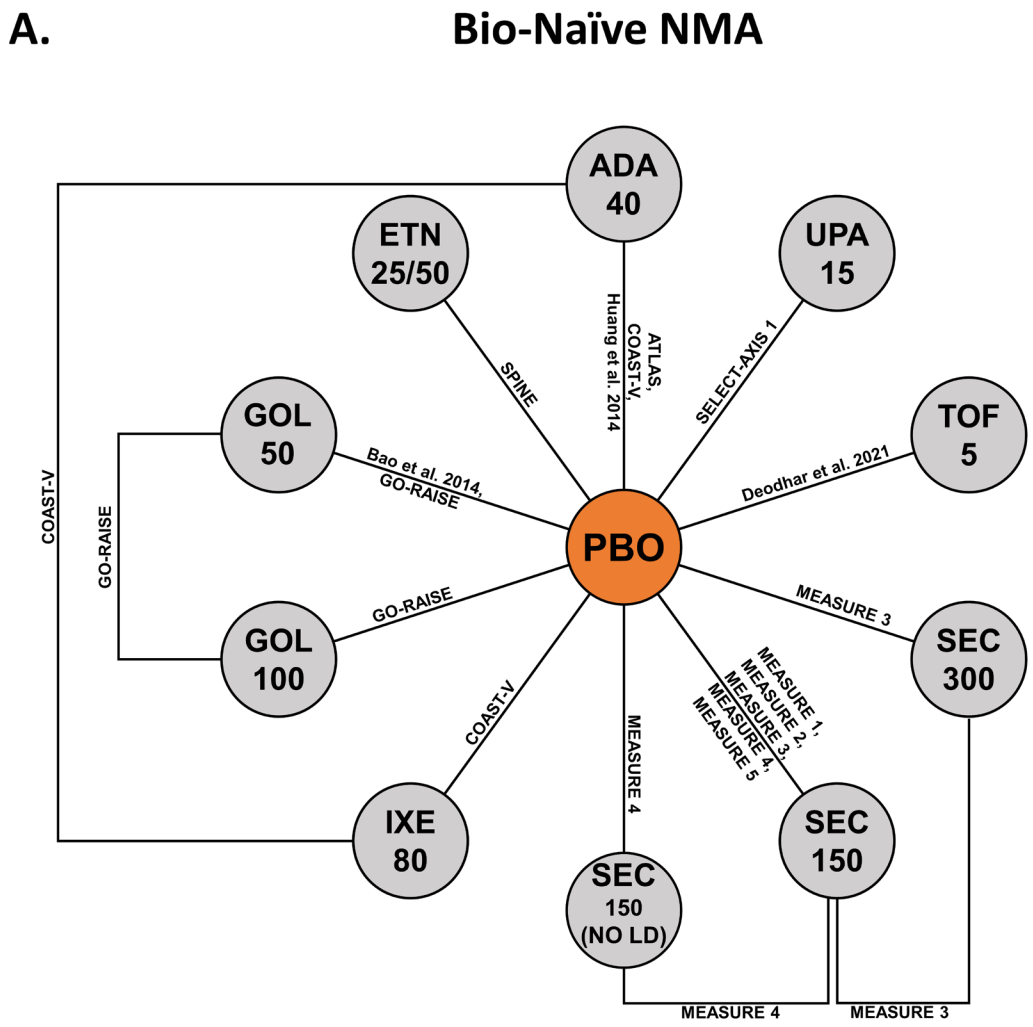
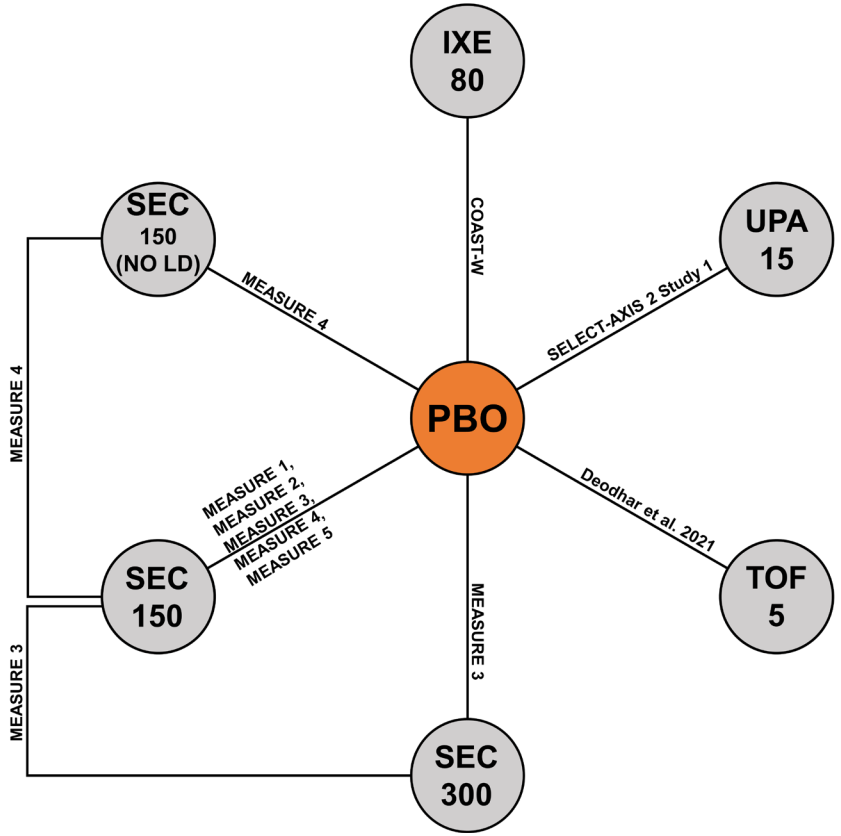
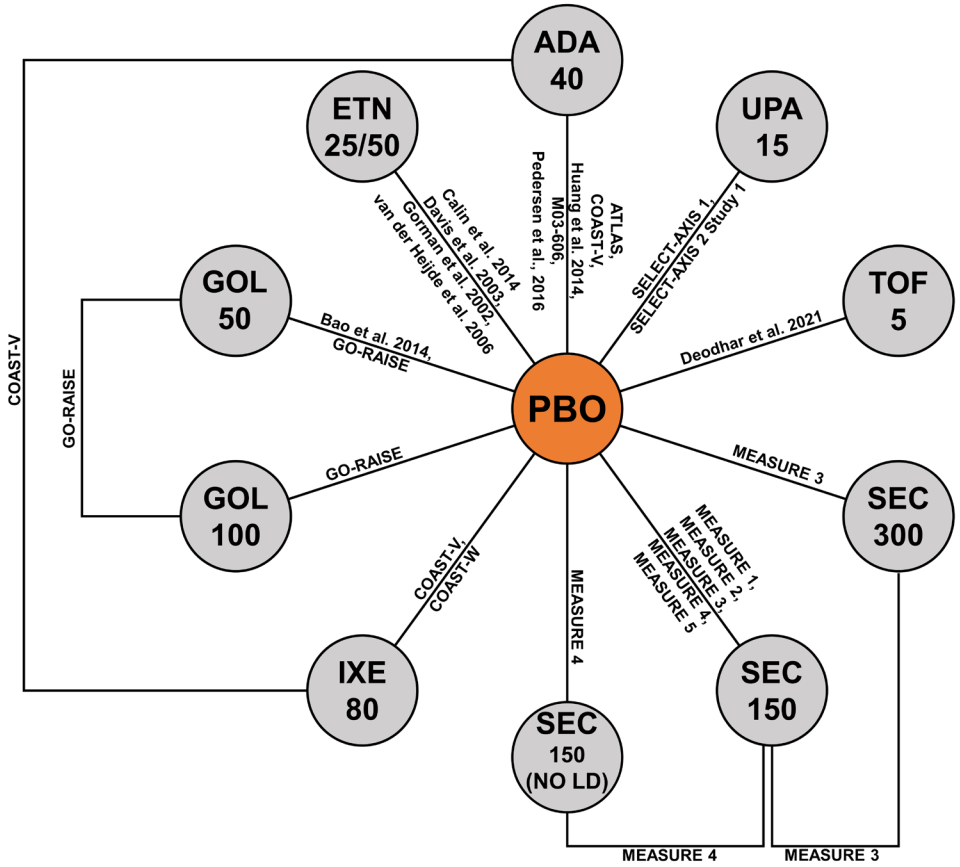
Supplementary Figure 1: Network Diagrams by Study Population



B. **Bio-IR and TNFi-Experienced NMA**

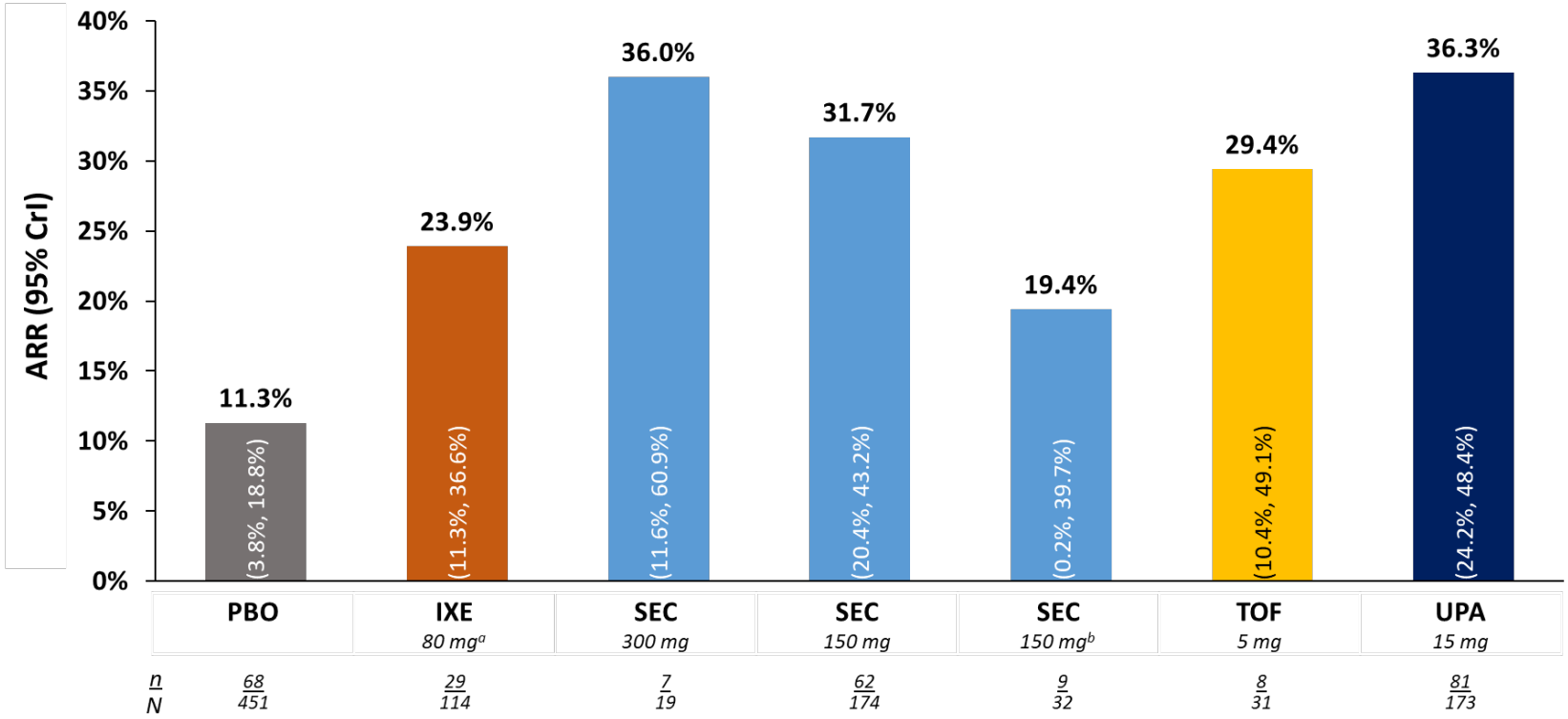


C. Safety Outcome NMA



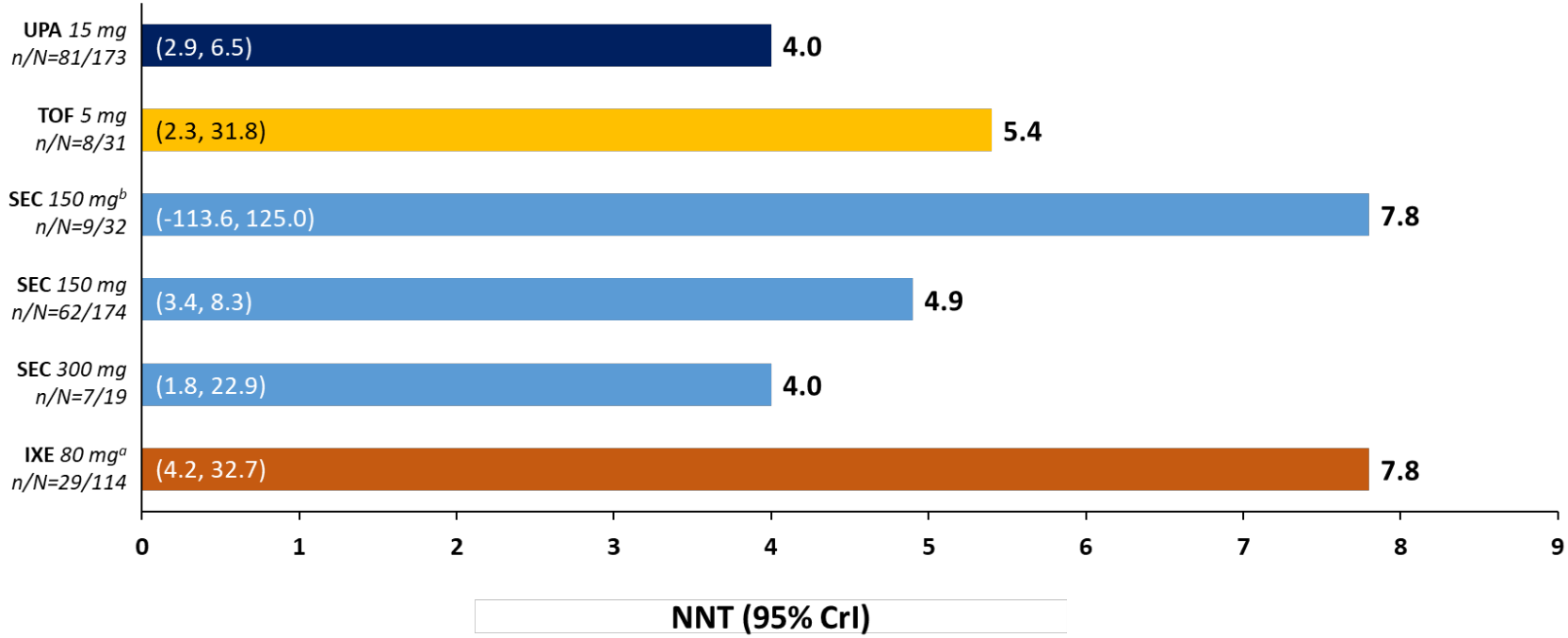
ADA 40, adalimumab 40 mg; Bio, biologic disease-modifying antirheumatic drug; ETN 25/50, etanercept 25/50 mg; GOL 50 or 100, golimumab 50 mg or 100 mg; IR, inadequate response or intolerance; IXE 80, ixekizumab 80 mg; LD, loading dose; NMA, network meta-analysis; PBO, placebo; SEC 300 or 150, secukinumab 300 mg or 150 mg; TNFi, tumor necrosis factor inhibitor; TOF 5, tofacitinib 5 mg; UPA 15, upadacitinib 15 mg.

Supplementary Figure 2: Absolute ASAS40 response rates at weeks 12—16 among TNF-IR patients



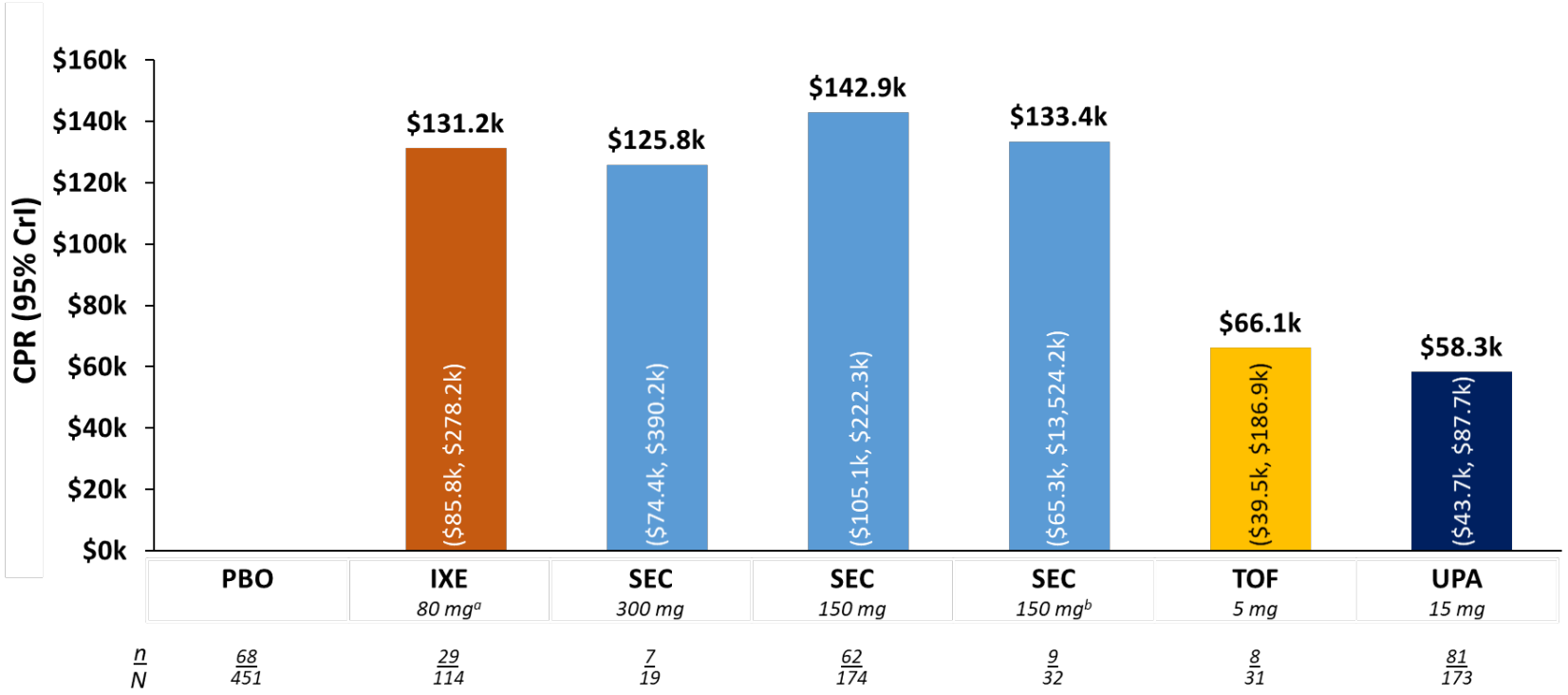
[a]IXE 80 mg was administered every 4 weeks. [b]Patients received SEC 150 mg without a loading dose. ARR, absolute rate ratio; ASAS40, Assessment of Spondyloarthritis International Society improvement ≥40%; CrI, credible interval; IR, inadequate response or intolerance; IXE, ixekizumab; PBO, placebo; SEC, secukinumab; TNF, tumor necrosis factor; TOF, tofacitinib; UPA, upadacitinib.

Supplementary Figure 3: Number needed to treat to achieve ASAS40 at weeks 12—16 among TNF-IR patients



[a]IXE 80 mg was administered every 4 weeks. [b]Patients received SEC 150 mg without a loading dose. ASAS40, Assessment of Spondyloarthritis International Society improvement ≥40%; CrI, credible interval; IR, inadequate response or intolerance; IXE, ixekizumab; NNT, number needed to treat; PBO, placebo; SEC, secukinumab; TNF, tumor necrosis factor; TOF, tofacitinib; UPA, upadacitinib.

Supplementary Figure 4: Cost per responder for ASAS40 over 16 weeks among TNF-IR patients



[a]IXE 80 mg was administered every 4 weeks. [b]Patients received SEC 150 mg without a loading dose. ARR, absolute rate ratio; ASAS40, Assessment of Spondyloarthritis International Society improvement ≥40%; CPR, cost per responder; CrI, credible interval; IR, inadequate response or intolerance; IXE, ixekizumab; PBO, placebo; SEC, secukinumab; TNF, tumor necrosis factor; TOF, tofacitinib; UPA, upadacitinib.