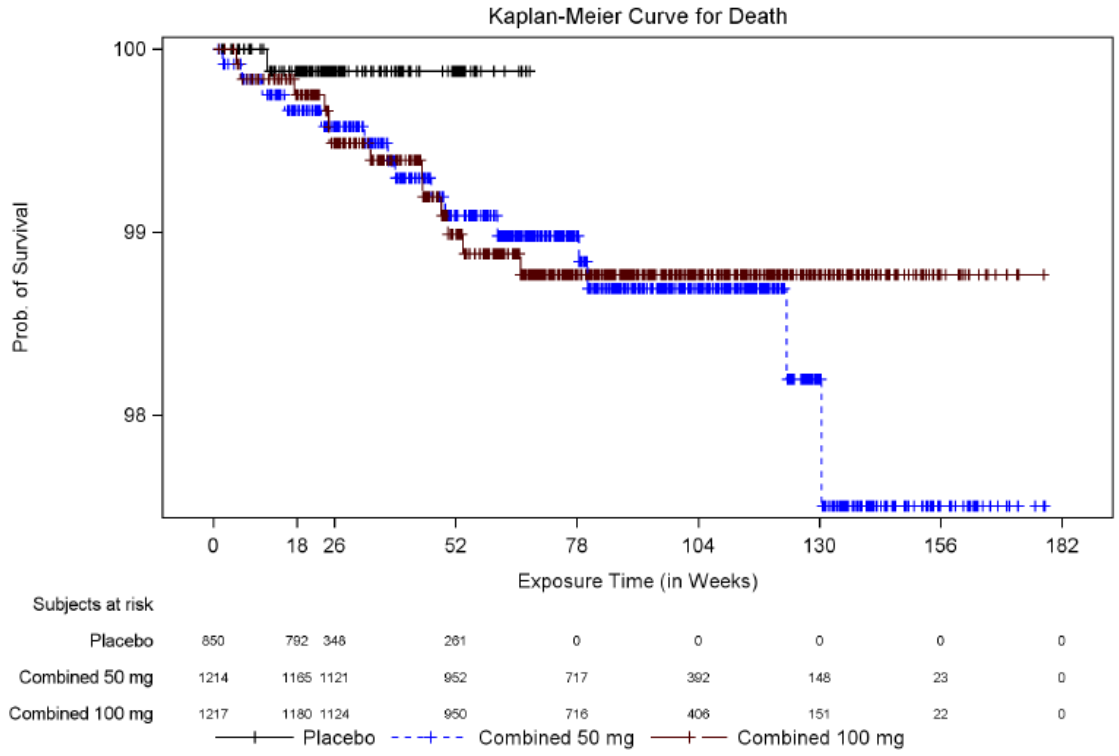
Addendum to the FDA Briefing Document
Arthritis Advisory Committee Meeting
August 2, 2017

This document contains additional safety data relevant to the August 2, 2017, Arthritis Advisory Committee Meeting. At this meeting, the committee will discuss biologics license application (BLA) 761057 for sirukumab injection for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). The information is provided according to the topic area in the FDA briefing document.

Death

In the FDA briefing document, Kaplan-Meier analyses of time to death through 52 weeks of exposure in studies ARA3002 and ARA3003 were provided (Figure 6 in the FDA briefing document). The figure included patients who were randomized to placebo, sirukumab 50 mg every 4 weeks (q4w), and sirukumab 100 mg every 2 weeks (q2w). The following figure includes data from patients who crossed over from placebo to sirukumab, referred to as the combined 50 mg and combined 100 mg sirukumab arms. Data are displayed to the end of the safety cutoff (Figure 1). The hazard ratios of death are shown in Table 1.

Figure 1: Kaplan-Meier Analysis of Time to Death for All Patients in Studies ARA3002 and ARA3003



Source: IR response, Figure 2, page 8, submitted 7/24/17

Table 1: Analysis of Time to Death Using Time-Dependent Covariate Cox Proportional Hazards Model during the Study; All Patients in ARA3002 and ARA3003

	PBO	SIR 50 mg q4w	SIR 100 mg q2w
N	850	1214	1217
Number of deaths	1	10	12
Total patient years of exposure	520	1109	1111
Hazard ratio (95% CI) with respect to the placebo group	--	3.5 (0.4, 28.0)	3.0 (0.4, 24.2)

Time-dependent covariate proportional hazards model with treatment as time-dependent covariate, stratified by study
Abbreviations: PBO=placebo; SIR=sirukumab; q4w=every 4 weeks; q2w=every 2 weeks; CI=confidence interval
Source: IR response, Table 2, page 9, submitted 7/24/17

Laboratory abnormalities

Data displayed in the FDA briefing document for AST, ALT, and bilirubin laboratory changes (Table 42) utilized the last scheduled visit on/prior to the end of the analysis period. The following three tables display the number and proportion of patients with post-baseline values for AST (Table 2), ALT (Table 3), and total bilirubin (Table 4) by maximum toxicity grade through 18 weeks of exposure in studies ARA3002 and ARA3003. For AST, ALT, and total bilirubin, the proportion of patients with grade 1 and grade 2 abnormalities was higher for each sirukumab group compared to placebo. In general, the proportion of patients with AST, ALT, and total bilirubin abnormalities was similar for the two doses of sirukumab.

Table 2: Number of Patients with Post-baseline values for AST by Maximum Toxicity Grade through 18 Weeks of Exposure (ARA3002 and ARA3003)

	ARA3002 and ARA3003		
	Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients with post-baseline maximum:			
Toxicity grade 0 (≤ULN)	704 (83.6%)	461 (54.7%)	464 (54.8%)
Toxicity grade 1 (>ULN-3x ULN)	132 (15.7%)	362 (42.9%)	354 (41.8%)
Toxicity grade 2 (>3-5x ULN)	3 (0.4%)	18 (2.1%)	22 (2.6%)
Toxicity grade 3 (>5-20x ULN)	3 (0.4%)	2 (0.2%)	6 (0.7%)
Toxicity grade 4 (>20x ULN)	0	0	0

Abbreviations: AST=aspartate aminotransferase; ULN=upper limit of normal; PBO=placebo; SIR=sirukumab
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Clinical Summary of Safety, Table 38, page 118, submitted 9/22/16

Table 3: Number of Patients with Post-baseline values for ALT by Maximum Toxicity Grade through 18 Weeks of Exposure (ARA3002 and ARA3003)

	ARA3002 and ARA3003		
	Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients with post-baseline maximum:			
Toxicity grade 0 (≤ULN)	662 (78.6%)	348 (41.3%)	358 (42.3%)
Toxicity grade 1 (>ULN-3x ULN)	170 (20.2%)	444 (52.7%)	419 (49.5%)
Toxicity grade 2 (>3-5x ULN)	6 (0.7%)	38 (4.5%)	51 (6.0%)
Toxicity grade 3 (>5-20x ULN)	2 (0.2%)	13 (1.5%)	18 (2.1%)
Toxicity grade 4 (>20x ULN)	2 (0.2%)	0	0

Abbreviations: ALT=alanine aminotransferase; ULN=upper limit of normal; PBO=placebo; SIR=sirukumab
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Clinical Summary of Safety, Table 37, page 117, submitted 9/22/16

Table 4: Number of Patients with Post-baseline values for Total Bilirubin by Maximum Toxicity Grade through 18 Weeks of Exposure (ARA3002 and ARA3003)

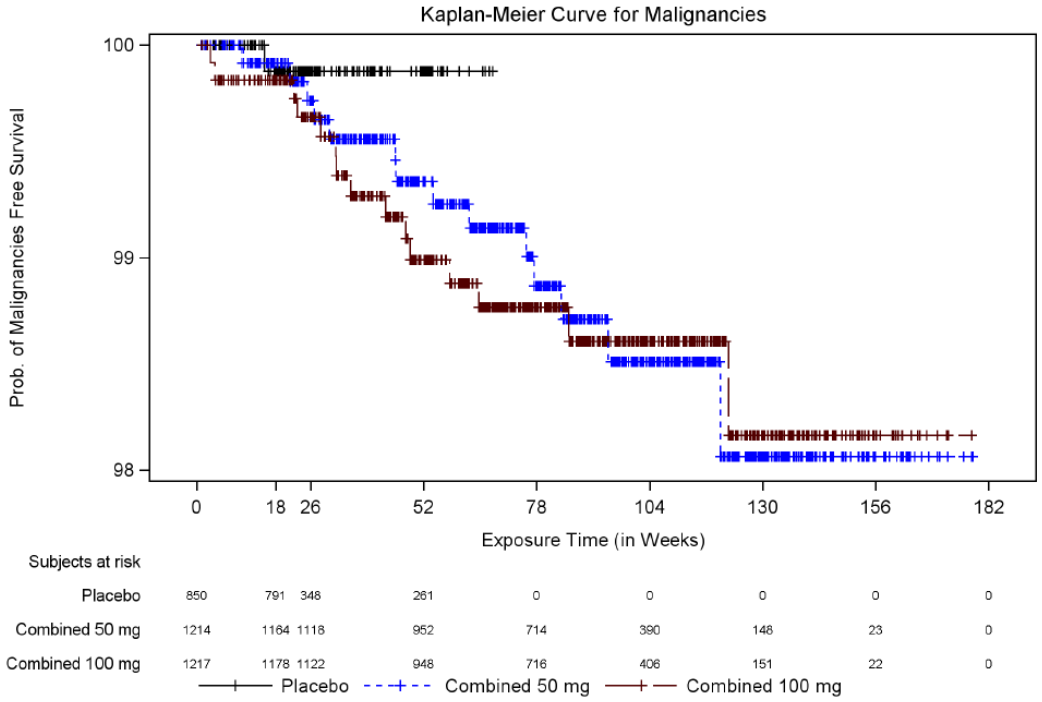
	ARA3002 and ARA3003		
	Through 18 weeks of exposure		
	PBO N=850	SIR 50 mg N=848	SIR 100 mg N=850
Patients with post-baseline maximum:			
Toxicity grade 0 (≤ULN)	832 (98.8%)	762 (90.4%)	744 (87.9%)
Toxicity grade 1 (>ULN-1.5x ULN)	10 (1.2%)	55 (6.5%)	54 (6.4%)
Toxicity grade 2 (>1.5-3x ULN)	0	25 (3.0%)	47 (5.6%)
Toxicity grade 3 (>3-10x ULN)	0	1 (0.1%)	1 (0.1%)
Toxicity grade 4 (>10x ULN)	0	0	0

Abbreviations: ULN=upper limit of normal; PBO=placebo; SIR=sirukumab
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Clinical Summary of Safety, Table 39, page 120, submitted 9/22/16

Malignancy

In the FDA briefing document, Kaplan-Meier analyses of time to onset of all malignancies and malignancies excluding non-melanoma skin cancer (NMSC) through 52 weeks of exposure in studies ARA3002 and ARA3003 were provided (Figures 12 and 13 in the FDA briefing document). The figures included patients who were randomized to placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w. The following figure includes data from patients who crossed over from placebo to sirukumab, referred to as the combined 50 mg and combined 100 mg sirukumab arms (Figure 2). Data are displayed to the end of the safety cutoff. The hazard ratios of malignancy excluding NMSC are shown in Table 5.

Figure 2: Kaplan-Meier Analysis of the Time to Onset of Malignancies excluding NMSC during the Study: ARA3002 and ARA3003



Abbreviations: NMSC=non-melanoma skin cancer
Source: IR Response, Figure 2, page 18, submitted 7/11/17

Table 5: Analysis of Time to Onset of Malignancy excluding NMSC Using Time-Dependent Covariate Cox Proportional Hazards Model during the Study: ARA3002 and ARA3003

Treatment comparisons	Hazard Ratio (95% CI)
100 mg q2w vs Placebo	2.6 (0.3, 21.6)
50 mg q4w vs Placebo	2.5 (0.3, 20.4)

Time-dependent covariate proportional hazards model with treatment as time-dependent covariate, stratified by study
Abbreviations: CI=confidence interval
Source: IR Response, Table 3, page 16, submitted 7/11/17

Comparison to Adalimumab

In study ARA3005, sirukumab 50 mg q4w and sirukumab 100 mg q2w were compared to adalimumab. In the FDA briefing document, safety data were displayed through Week 24. Table 6 provides an overall summary and incidence of adverse events by treatment arm in study ARA3005 through the 120 day safety update cutoff date (July 29, 2016). The incidence rates (per 100 patient years) of death, serious adverse events (SAEs), treatment-emergent adverse events, adverse events leading to discontinuation, malignancy, MACE (narrow), treatment-emergent infections, and SAEs of infection were higher in each sirukumab group compared to adalimumab. There was one gastrointestinal (GI) perforation that occurred in the sirukumab 50 mg group.

In the FDA briefing document, data related to AST and ALT elevations through Week 24 were included. Table 7 includes additional data related to total bilirubin elevations. The proportion of

patients with total bilirubin increases was higher in the sirukumab arms compared to the adalimumab arm.

Table 6: Overall Summary and Incidence Rate (Subject Based per 100 Patient Years of Exposure) of Treatment-emergent Adverse Events through the 120 Day Safety Update in Study ARA3005

	Combined adalimumab[a]	Combined sirukumab 50 mg[b]	Sirukumab 100 mg[c]
N	186	186	187
Patient years of exposure	217.5	207.8	214.5
Patients with ≥1 event, n (%), IR			
Death	0	2 (1.1%), 0.96	1 (0.5%), 0.47
Serious adverse event (SAE)	15 (8.1%), 7.13	28 (15.1%), 14.34	21 (11.2%), 10.26
Treatment emergent AEs	130 (69.9%), 126.37	138 (74.2%), 151.24	134 (71.7%), 152.27
AEs leading to discontinuation	14 (7.5%), 6.57	25 (13.4%), 12.45	20 (10.7%), 9.59
Malignancy	1 (0.5%), 0.46	3 (1.6%), 1.45	2 (1.1%), 0.94
MACE (narrow)[d]	0	1 (0.5%), 0.48	2 (1.1%), 0.94
GI perforation	0	1 (0.5%), 0.48	0
Treatment-emergent infection	58 (31.2%), 33.38	62 (33.3%), 38.79	59 (31.6%), 35.90
SAE of infection	4 (2.2%), 1.85	14 (7.5%), 6.97	5 (2.7%), 2.36

a Includes patients randomized to adalimumab who continued adalimumab 40 mg q2wk or escaped to adalimumab 40 mg q1wk
b Includes patients randomized to sirukumab 50 mg q4wk who continued sirukumab 50 mg q4wk or escaped to sirukumab 100 mg q2wk
c Includes patients randomized to sirukumab 100 mg q2wk (this group did not have the option to escape)
d Incudes non-fatal MI, non-fatal stroke, and cardiovascular death
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Data through 120 day safety update (cutoff date July 29, 2016)
Abbreviations: IR=incidence rate per 100 patient years; SAE=serious adverse event; AE=adverse event; MACE=major adverse cardiovascular event; GI=gastrointestinal
Source: IR response, Table 1, page 4, submitted 7/24/17

Table 7: Number of Subjects with Post-baseline Increases in Total Bilirubin by Maximum Toxicity through Week 24 in ARA3005

	Combined adalimumab[1]	Combined Sirukumab 50 mg[2]	Sirukumab 100 mg[3]
N	186	186	187
Total bilirubin (increased)			
Grade 0 (≤ULN)	180 (96.8%)	163 (87.6%)	164 (87.7%)
Grade 1 (>ULN-1.5xULN)	6 (3.2%)	17 (9.1%)	17 (9.1%)
Grade 2 ((>1.5-3xULN)	0	5 (2.7%)	6 (3.2%)
Grade 3 (>3-10xULN)	0	1 (0.5%)	0
Grade 4 (>10xULN)	0	0	0

1 Includes patients randomized to adalimumab who continued adalimumab 40 mg q2 w or escaped to adalimumab 40mg q1w
2 Includes patients randomized to sirukumab 50 mg q4w who continued sirukumab 50 mg q4w or escaped to sirukumab 100 mg q2w
3 Includes patients randomized to sirukumab 100 mg q2w (this group did not have the option to escape)
Sirukumab doses: sirukumab 50 mg every 4 weeks and sirukumab 100 mg every 2 weeks
Source: Study report ARA3005, Table 53, page 214, submitted 9/22/16