

Additional File 2

Table S1. Biomarker Analysis Kits

Biomarker	Matrix	Kit	Catalog N°	Manufacturer
βNGF; IL-1β; IL-6; TNF-α	Synovial fluid	Custom 4-plex U-PLEX Mesoscale Delivery System (MSD) kit	K151ACL-2	MESO SCALE DIAGNOSTICS, LLC, Maryland, USA
ADAMTS-5	Synovial fluid and serum	Cloud-Clone A Disintegrin and Metalloproteinase with Thrombospondin 5 (ADAMTS-5) ELISA kit	SEK205Hu	Cloud-Clone Corp, Texas, USA
ARGS	Synovial fluid and serum	Chemiluminescence immunoassay (CLIA) ARG_HP	1060DF01	Nordic Bioscience, Herlev, Denmark
CTX-I	Synovial fluid and serum	IBEX Pharmaceuticals C2C ELISA kit	AC-02F1;	Immunodiagnostic Systems (IDS), East Boldon, UK
CTX-II	Synovial fluid and urine	CartiLaps (CTX-II) ELISA kit (IDS)	AC-10F1	Immunodiagnostic Systems (IDS), East Boldon, UK
C2C	Synovial fluid and serum	IBEX Pharmaceuticals C2C ELISA kit	60-1001- 001	IBEX Pharmaceuticals, Montréal, QC
TIMP-1	Synovial fluid and serum	Abcam Human Tissue Inhibitor of Metalloproteinases 1 (TIMP-1) ELISA kit	Ab187394	Abcam, Cambridge, UK

Table S2. Participants from the Biomarker Analysis Set Who Underwent Lavage for Synovial Fluid Aspiration

	iPPS Once-weekly BAS n=19	iPPS Twice- weekly BAS n=15	Placebo BAS n=22
Baseline, n (%)	9 (47.4)	14 (93.3)	19 (86.4)
Day 56, n (%)	12 (63.2)	14 (93.3)	20 (90.9)
Day 168, n (%)	11 (57.9)	12 (80.0)	22 (100.0)

Participants within the biomarker analysis set who received synovial lavage at each time

point. Abbreviation: BAS, biomarker analysis set and includes all participants with a valid (non-missing) baseline and at least one post-baseline biomarker assessment.

Table S3. Summary of Change from Baseline in Synovial Fluid Biomarkers

LS means obtained from mixed model for repeated measures (MMRM) analysis of the biomarker analysis set (BAS), including factors for treatment group (iPPS once-weekly, iPPS twice-weekly, Placebo), KL grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. Lavage correction factors are not applied to synovial fluid biomarkers. There were no adjustments for Type I error inflation linked to the multiplicity of biomarkers tested due to the exploratory nature of the study.

Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid ADAMTS-5 (ng/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Baseline	Observed	n (missing)	8 (11)	2 (13)	10 (24)	2 (20)
		Mean (SD)	4.48 (3.829)	3.11 (1.837)	4.21 (3.480)	1.06 (0.610)
		Median	3.43	3.11	3.43	1.06
		Min ; Max	0.6 ; 10.8	1.8 ; 4.4	0.6 ; 10.8	0.6 ; 1.5
Day 56	Observed	n (missing)	8 (11)	2 (13)	10 (24)	2 (20)
		Mean (SD)	1.88 (1.129)	6.94 (6.519)	2.90 (3.203)	1.38 (1.072)
		Median	1.77	6.94	2.16	1.38
		Min ; Max	0.6 ; 3.8	2.3 ; 11.6	0.6 ; 11.6	0.6 ; 2.1
	CfB (abs.)	n (missing)	8 (11)	2 (13)	10 (24)	2 (20)
		Mean (SD)	-2.60 (3.651)	3.83 (4.682)	-1.31 (4.489)	0.33 (0.462)
		Median	-1.30	3.83	-0.62	0.33
		Min ; Max	-8.1 ; 2.0	0.5 ; 7.1	-8.1 ; 7.1	0.0 ; 0.7
	CfB (%)	Mean (SD)	-25.02 (64.901)	95.47 (94.204)	-0.92 (82.721)	21.96 (31.058)
		Median	-39.12	95.47	-15.72	21.96
		Min ; Max	-82.9 ; 113.3	28.9 ; 162.1	-82.9 ; 162.1	0.0 ; 43.9
	Adj. CfB (%) [1]	LS mean (95% CI)	7.87 (-68.65, 84.39)	44.12 (-62.06, 150.29)	20.73 (-33.06, 74.53)	-19.37 (-134.15, 95.41)
		LS mean diff.	27.24	63.49	49.52	
		[PPS - Placebo] (95% CI)	(-134.65, 189.13)	(-84.60, 211.58)	(-76.23, 175.27)	
		p-value for diff.	0.683	0.321	0.372	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid ADAMTS-5 (ng/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Day 168	Observed	n (missing)	0 (19)	0 (15)	0 (34)	0 (22)
		Mean (SD)	NE	NE	NE	NE
		Median	NE	NE	NE	NE
		Min ; Max	NE ; NE	NE ; NE	NE ; NE	NE ; NE
	CfB (abs.)	n (missing)	0 (19)	0 (15)	0 (34)	0 (22)
		Mean (SD)	NE	NE	NE	NE
		Median	NE	NE	NE	NE
		Min ; Max	NE ; NE	NE ; NE	NE ; NE	NE ; NE
	CfB (%)	Mean (SD)	NE	NE	NE	NE
		Median	NE	NE	NE	NE
		Min ; Max	NE ; NE	NE ; NE	NE ; NE	NE ; NE
	Adj. CfB (%) [1]	LS mean (95% CI)	NE	NE	NE	NE
		LS mean diff. [PPS - Placebo] (95% CI)	NE	NE	NE	
		p-value for diff.	NE	NE	NE	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid bNGF (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Baseline	Observed	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	3.73 (3.547)	5.43 (3.959)	4.50 (3.778)	4.17 (3.158)
		Median	2.32	3.85	3.41	3.19
		Min ; Max	0.5 ; 10.2	0.6 ; 13.5	0.5 ; 13.5	0.7 ; 12.6
Day 56	Observed	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	12.85 (28.165)	11.79 (24.536)	12.37 (26.158)	4.85 (2.332)
		Median	2.30	5.78	4.29	4.69
		Min ; Max	0.3 ; 96.4	0.1 ; 96.4	0.1 ; 96.4	0.9 ; 10.4
	CfB (abs.)	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	8.94 (27.531)	6.14 (26.168)	7.68 (26.513)	0.52 (4.081)
		Median	-0.14	-0.20	-0.17	1.20
		Min ; Max	-9.0 ; 86.7	-7.7 ; 95.8	-9.0 ; 95.8	-11.8 ; 5.1
	CfB (%)	Mean (SD)	463.65 (1657.690)	1131.03 (4165.473)	765.05 (3016.353)	90.00 (155.254)
		Median	-14.34	-2.92	-6.85	23.69
		Min ; Max	-88.8 ; 6836.4	-96.9 ; 15598.2	-96.9 ; 15598.2	-93.1 ; 490.1
	Adj. CfB (%) [1]	LS mean (95% CI)	431.98 (-697.31, 1561.26)	1374.97 (121.20, 2628.74)	856.64 (20.79, 1692.50)	79.29 (-931.19, 1089.78)
		LS mean diff.	352.68	1295.67	769.90	
		[PPS - Placebo] (95% CI)	(-1159.07, 1864.43)	(-318.53, 2909.87)	(-543.91, 2083.71)	
		p-value for diff.	0.641	0.113	0.245	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Follow Up Analysis at Day 168
Data Extraction Date: 20Jan2023

Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid bNGF (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Day 168	Observed	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	2.04 (2.152)	12.74 (35.012)	7.22 (24.575)	3.33 (2.061)
		Median	1.13	3.48	3.00	2.99
		Min ; Max	0.1 ; 8.1	0.3 ; 139.1	0.1 ; 139.1	0.9 ; 9.3
	CfB (abs.)	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	-1.99 (4.581)	7.31 (35.782)	2.51 (25.106)	-0.84 (3.285)
		Median	-0.26	0.07	-0.14	-0.27
		Min ; Max	-10.1 ; 3.9	-10.0 ; 135.7	-10.1 ; 135.7	-10.4 ; 5.2
	CfB (%)	Mean (SD)	12.51 (121.317)	260.58 (1030.308)	132.54 (720.155)	34.83 (164.618)
		Median	-16.50	1.39	-12.05	-17.34
		Min ; Max	-98.8 ; 308.4	-97.2 ; 3979.2	-98.8 ; 3979.2	-82.6 ; 709.9
	Adj. CfB (%) [1]	LS mean (95% CI)	70.05 (-218.10, 358.21)	344.77 (49.33, 640.21)	204.78 (-7.62, 417.18)	47.27 (-195.54, 290.08)
		LS mean diff.	22.79	297.50	151.37	
		[PPS - Placebo] (95% CI)	(-345.75, 391.32)	(-84.21, 679.22)	(-167.11, 469.86)	
		p-value for diff.	0.902	0.124	0.344	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid C2C (ng/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Baseline	Observed	n (missing)	10 (9)	3 (12)	13 (21)	4 (18)
		Mean (SD)	250.65 (244.798)	227.04 (110.276)	245.20 (216.976)	139.39 (42.688)
		Median	173.78	170.72	170.72	139.43
		Min ; Max	50.0 ; 878.7	156.3 ; 354.1	50.0 ; 878.7	99.3 ; 179.4
Day 56	Observed	n (missing)	11 (8)	2 (13)	13 (21)	3 (19)
		Mean (SD)	148.06 (52.424)	277.68 (260.752)	168.00 (101.616)	199.89 (90.037)
		Median	150.64	277.68	150.64	190.35
		Min ; Max	79.8 ; 225.7	93.3 ; 462.1	79.8 ; 462.1	115.0 ; 294.3
	CfB (abs.)	n (missing)	9 (10)	2 (13)	11 (23)	2 (20)
		Mean (SD)	-117.73 (232.149)	15.26 (131.080)	-93.55 (218.465)	13.25 (5.809)
		Median	-38.85	15.26	-38.85	13.25
		Min ; Max	-655.5 ; 123.5	-77.4 ; 108.0	-655.5 ; 123.5	9.1 ; 17.4
	CfB (%)	Mean (SD)	1.96 (99.977)	-7.43 (53.624)	0.25 (91.095)	9.33 (0.989)
		Median	-20.50	-7.43	-20.50	9.33
		Min ; Max	-77.5 ; 247.0	-45.4 ; 30.5	-77.5 ; 247.0	8.6 ; 10.0
	Adj. CfB (%) [1]	LS mean (95% CI)	-26.61 (-137.57, 84.36)	4.91 (-168.65, 178.46)	-9.80 (-110.81, 91.21)	72.65 (-96.47, 241.78)
		LS mean diff.	-99.26	-67.75	-86.78	
		[PPS - Placebo] (95% CI)	(-311.19, 112.67)	(-306.02, 170.53)	(-262.44, 88.88)	
		p-value for diff.	0.302	0.508	0.288	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Follow Up Analysis at Day 168
Data Extraction Date: 20Jan2023

Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid C2C (ng/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Day 168	Observed	n (missing)	6 (13)	5 (10)	11 (23)	10 (12)
		Mean (SD)	217.10 (161.731)	240.87 (119.455)	227.90 (137.624)	336.68 (154.685)
		Median	222.82	208.40	208.40	368.28
		Min ; Max	50.0 ; 482.0	120.6 ; 428.6	50.0 ; 482.0	140.1 ; 614.2
	CfB (abs.)	n (missing)	4 (15)	3 (12)	7 (27)	4 (18)
		Mean (SD)	-94.54 (501.622)	-60.72 (150.099)	-80.04 (365.580)	218.28 (222.363)
		Median	79.03	13.66	25.10	162.00
		Min ; Max	-828.7 ; 292.5	-233.5 ; 37.7	-828.7 ; 292.5	34.2 ; 514.9
	CfB (%)	Mean (SD)	46.19 (111.706)	-11.71 (47.431)	21.37 (89.144)	183.24 (229.870)
		Median	62.35	8.74	10.05	90.92
		Min ; Max	-94.3 ; 154.4	-65.9 ; 22.1	-94.3 ; 154.4	32.3 ; 518.8
	Adj. CfB (%) [1] LS mean (95% CI)		69.40	-1.07	42.31	126.70
			(-147.69, 286.49)	(-224.83, 222.70)	(-86.92, 171.54)	(-83.70, 337.09)
		LS mean diff.	-57.29	-127.76	-89.22	
		[PPS - Placebo] (95% CI)	(-381.18, 266.60)	(-431.21, 175.68)	(-329.34, 150.90)	
		p-value for diff.	0.616	0.306	0.403	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid COMP (ug/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Baseline	Observed	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	22.80 (10.184)	31.12 (10.892)	26.58 (11.168)	28.58 (10.768)
		Median	24.60	35.27	25.60	27.11
		Min ; Max	4.7 ; 41.8	12.0 ; 44.0	4.7 ; 44.0	9.1 ; 52.5
Day 56	Observed	n (missing)	18 (1)	15 (0)	33 (1)	21 (1)
		Mean (SD)	22.47 (14.075)	31.69 (11.007)	26.66 (13.415)	26.98 (11.028)
		Median	25.60	32.71	30.09	26.83
		Min ; Max	0.5 ; 46.2	3.0 ; 46.2	0.5 ; 46.2	5.7 ; 49.1
	CfB (abs.)	n (missing)	18 (1)	15 (0)	33 (1)	21 (1)
		Mean (SD)	-0.33 (18.674)	0.57 (12.196)	0.08 (15.828)	-1.75 (11.831)
		Median	-2.56	-0.41	-0.82	-1.61
		Min ; Max	-25.1 ; 41.6	-15.1 ; 34.2	-25.1 ; 41.6	-29.4 ; 27.1
	CfB (%)	Mean (SD)	57.68 (230.666)	15.29 (81.230)	38.41 (177.799)	8.67 (76.052)
		Median	-18.15	-0.96	-5.45	-5.06
		Min ; Max	-98.2 ; 890.8	-83.3 ; 283.7	-98.2 ; 890.8	-80.1 ; 298.2
	Adj. CfB (%) [1]	LS mean (95% CI)	40.33 (-23.83, 104.50)	45.13 (-22.84, 113.11)	43.55 (-1.99, 89.10)	21.18 (-35.59, 77.94)
		LS mean diff.	19.16	23.96	21.50	
		[PPS - Placebo] (95% CI)	(-66.58, 104.89)	(-64.00, 111.92)	(-50.47, 93.46)	
		p-value for diff.	0.656	0.587	0.551	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid COMP (ug/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Day 168	Observed	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	21.94 (20.760)	42.44 (24.695)	31.86 (24.668)	30.46 (16.421)
		Median	22.41	37.98	26.95	28.21
		Min ; Max	0.1 ; 82.3	11.1 ; 117.2	0.1 ; 117.2	5.0 ; 78.3
	CfB (abs.)	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	-1.36 (21.269)	11.31 (26.409)	4.77 (24.355)	1.87 (16.215)
		Median	-4.04	5.61	-1.96	-0.50
		Min ; Max	-32.7 ; 65.4	-14.9 ; 99.1	-32.7 ; 99.1	-19.4 ; 50.2
	CfB (%)	Mean (SD)	-4.88 (116.612)	55.88 (141.299)	24.52 (130.648)	19.90 (84.563)
		Median	-15.88	19.01	-6.08	-2.47
		Min ; Max	-98.0 ; 387.0	-41.5 ; 545.3	-98.0 ; 545.3	-78.5 ; 287.4
	Adj. CfB (%) [1]	LS mean (95% CI)	-4.29 (-61.54, 52.97)	72.71 (14.97, 130.45)	34.28 (-7.15, 75.71)	29.38 (-17.84, 76.60)
		LS mean diff.	-33.66	43.33	4.77	
		[PPS - Placebo] (95% CI)	(-107.57, 40.25)	(-30.74, 117.40)	(-58.51, 68.05)	
		p-value for diff.	0.365	0.245	0.880	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid CTX-I (ng/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Baseline	Observed	n (missing)	12 (7)	5 (10)	17 (17)	3 (19)
		Mean (SD)	0.68 (0.656)	0.40 (0.165)	0.60 (0.566)	0.43 (0.262)
		Median	0.44	0.47	0.47	0.31
		Min ; Max	0.1 ; 2.5	0.1 ; 0.5	0.1 ; 2.5	0.2 ; 0.7
Day 56	Observed	n (missing)	11 (8)	2 (13)	13 (21)	3 (19)
		Mean (SD)	0.33 (0.120)	0.98 (0.521)	0.43 (0.309)	0.46 (0.366)
		Median	0.37	0.98	0.38	0.50
		Min ; Max	0.1 ; 0.5	0.6 ; 1.3	0.1 ; 1.3	0.1 ; 0.8
	CfB (abs.)	n (missing)	9 (10)	2 (13)	11 (23)	2 (20)
		Mean (SD)	-0.47 (0.733)	0.51 (0.456)	-0.29 (0.780)	-0.20 (0.041)
		Median	-0.30	0.51	-0.16	-0.20
		Min ; Max	-2.2 ; 0.2	0.2 ; 0.8	-2.2 ; 0.8	-0.2 ; -0.2
	CfB (%)	Mean (SD)	-25.51 (75.792)	103.48 (82.877)	-2.06 (89.469)	-50.89 (27.403)
		Median	-46.81	103.48	-42.35	-50.89
		Min ; Max	-87.4 ; 150.3	44.9 ; 162.1	-87.4 ; 162.1	-70.3 ; -31.5
	Adj. CfB (%) [1]	LS mean (95% CI)	-19.66 (-120.69, 81.37)	162.95 (40.48, 285.41)	12.82 (-104.09, 129.73)	18.67 (-103.32, 140.67)
		LS mean diff.	-38.33	144.27	38.27	
		[PPS - Placebo] (95% CI)	(-199.80, 123.13)	(-19.16, 307.70)	(-203.16, 279.69)	
		p-value for diff.	0.615	0.080	0.651	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid CTX-I (ng/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Day 168	Observed	n (missing)	9 (10)	5 (10)	14 (20)	5 (17)
		Mean (SD)	0.49 (0.401)	1.10 (1.462)	0.71 (0.921)	0.74 (0.599)
		Median	0.34	0.61	0.35	0.45
		Min ; Max	0.1 ; 1.4	0.1 ; 3.7	0.1 ; 3.7	0.4 ; 1.8
	CfB (abs.)	n (missing)	8 (11)	4 (11)	12 (22)	3 (19)
		Mean (SD)	-0.42 (0.905)	0.82 (1.605)	-0.01 (1.263)	0.53 (0.827)
		Median	-0.17	0.11	-0.07	0.16
		Min ; Max	-2.4 ; 0.7	-0.2 ; 3.2	-2.4 ; 3.2	0.0 ; 1.5
	CfB (%)	Mean (SD)	-27.18 (58.948)	181.83 (336.936)	42.49 (209.197)	177.32 (257.385)
		Median	-44.15	37.03	-15.21	66.59
		Min ; Max	-94.2 ; 89.0	-31.6 ; 684.8	-94.2 ; 684.8	-6.2 ; 471.5
	Adj. CfB (%) [1] LS mean (95% CI)		33.14	161.40	56.26	156.21
			(-100.99, 167.27)	(-42.02, 364.82)	(-76.37, 188.90)	(-78.14, 390.56)
		LS mean diff.	-123.07	5.19	-93.97	
		[PPS - Placebo] (95% CI)	(-386.66, 140.52)	(-296.28, 306.66)	(-384.61, 196.67)	
		p-value for diff.	0.338	0.971	0.497	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid CTX-II (ng/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Baseline	Observed	n (missing)	15 (4)	13 (2)	28 (6)	21 (1)
		Mean (SD)	6.30 (13.464)	1.76 (0.954)	4.19 (9.986)	2.04 (1.474)
		Median	1.55	1.56	1.56	1.54
		Min ; Max	0.6 ; 53.7	0.8 ; 3.9	0.6 ; 53.7	0.6 ; 5.9
Day 56	Observed	n (missing)	15 (4)	13 (2)	28 (6)	21 (1)
		Mean (SD)	28.76 (105.060)	2.67 (2.518)	16.65 (76.822)	2.92 (2.593)
		Median	1.36	2.02	1.60	2.20
		Min ; Max	0.6 ; 408.5	0.6 ; 10.2	0.6 ; 408.5	0.6 ; 13.0
	CfB (abs.)	n (missing)	15 (4)	13 (2)	28 (6)	21 (1)
		Mean (SD)	22.46 (107.327)	0.91 (1.707)	12.45 (78.064)	0.88 (2.150)
		Median	0.00	0.61	0.00	0.26
		Min ; Max	-47.7 ; 407.9	-0.4 ; 6.3	-47.7 ; 407.9	-1.6 ; 9.1
	CfB (%)	Mean (SD)	4920.29 (19157.775)	36.67 (49.832)	2652.90 (14016.407)	63.48 (100.744)
		Median	0.00	28.85	0.00	19.32
		Min ; Max	-88.8 ; 74171.3	-41.2 ; 162.1	-88.8 ; 74171.3	-26.4 ; 363.9
	Adj. CfB (%) [1] LS mean (95% CI)		5441.32 (-3121.77, 14004.42)	2.06 (-8210.33, 8214.45)	NE	255.60 (-6336.19, 6847.39)
		LS mean diff. [PPS - Placebo] (95% CI)	5185.72 (-5463.13, 15834.58)	-253.54 (-10712.00, 10204.92)	NE	
		p-value for diff.	0.311	0.959	NE	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid CTX-II (ng/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Day 168	Observed	n (missing)	1 (18)	0 (15)	1 (33)	0 (22)
		Mean (SD)	1.18	NE	1.18	NE
		Median	1.18	NE	1.18	NE
		Min ; Max	1.2 ; 1.2	NE ; NE	1.2 ; 1.2	NE ; NE
	CfB (abs.)	n (missing)	1 (18)	0 (15)	1 (33)	0 (22)
		Mean (SD)	0.63	NE	0.63	NE
		Median	0.63	NE	0.63	NE
		Min ; Max	0.6 ; 0.6	NE ; NE	0.6 ; 0.6	NE ; NE
	CfB (%)	Mean (SD)	114.55	NE	114.55	NE
		Median	114.55	NE	114.55	NE
		Min ; Max	114.5 ; 114.5	NE ; NE	114.5 ; 114.5	NE ; NE
	Adj. CfB (%) [1]	LS mean (95% CI)	NE	NE	NE	NE
		LS mean diff. [PPS - Placebo] (95% CI)	NE	NE	NE	
		p-value for diff.	NE	NE	NE	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid huARGS (ng/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Baseline	Observed	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	428.75 (554.671)	235.01 (200.519)	340.69 (436.615)	240.33 (144.683)
		Median	126.43	198.11	175.54	231.19
		Min ; Max	37.4 ; 1776.2	76.1 ; 916.1	37.4 ; 1776.2	46.5 ; 537.6
Day 56	Observed	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	930.97 (2287.457)	800.36 (1991.182)	871.60 (2125.725)	305.04 (148.121)
		Median	150.58	240.71	200.97	266.49
		Min ; Max	22.5 ; 7950.8	75.8 ; 7950.8	22.5 ; 7950.8	97.2 ; 737.3
	CfB (abs.)	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	502.22 (2145.895)	565.35 (2022.927)	530.91 (2058.569)	64.71 (153.182)
		Median	-4.23	51.00	17.60	51.23
		Min ; Max	-1575.2 ; 6315.0	-39.8 ; 7874.7	-1575.2 ; 7874.7	-197.7 ; 437.4
	CfB (%)	Mean (SD)	499.12 (2058.291)	705.15 (2667.692)	592.77 (2318.411)	77.90 (163.742)
		Median	-4.35	13.18	7.08	28.45
		Min ; Max	-97.3 ; 8734.5	-26.7 ; 10347.8	-97.3 ; 10347.8	-39.8 ; 635.8
	Adj. CfB (%) [1] LS mean (95% CI)		658.87	778.23	723.42	56.85
			(-287.11, 1604.84)	(-195.86, 1752.32)	(44.82, 1402.03)	(-750.11, 863.82)
		LS mean diff.	602.02	721.38	660.53	
		[PPS - Placebo] (95% CI)	(-626.88, 1830.91)	(-531.97, 1974.72)	(-373.23, 1694.28)	
		p-value for diff.	0.330	0.253	0.205	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid huARGS (ng/mL)			PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Analysis Visit	Parameter	Statistics				
Day 168	Observed	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	177.97 (204.463)	4212.64 (15312.682)	2130.23 (10660.441)	305.50 (175.300)
		Median	100.53	217.15	168.14	286.08
		Min ; Max	8.6 ; 814.5	52.3 ; 59558.6	8.6 ; 59558.6	29.3 ; 732.7
	CfB (abs.)	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	-295.45 (618.471)	3977.64 (15330.924)	1772.17 (10704.548)	65.17 (176.023)
		Median	-36.63	43.76	-23.40	70.32
		Min ; Max	-1738.8 ; 276.0	-699.7 ; 59386.4	-1738.8 ; 59386.4	-252.2 ; 448.0
	CfB (%)	Mean (SD)	9.10 (140.205)	2328.29 (8898.921)	1131.29 (6193.025)	66.52 (119.384)
		Median	-37.40	17.41	-16.03	53.07
		Min ; Max	-99.5 ; 388.2	-79.2 ; 34494.5	-99.5 ; 34494.5	-83.4 ; 355.9
	Adj. CfB (%) [1]	LS mean (95% CI)	231.61 (-2255.56, 2718.78)	2415.83 (-62.69, 4894.35)	1331.48 (-410.00, 3072.97)	58.83 (-1991.54, 2109.21)
		LS mean diff.	172.77	2356.99	1305.46	
		[PPS - Placebo] (95% CI)	(-3091.46, 3437.01)	(-837.05, 5551.04)	(-1401.22, 4012.13)	
		p-value for diff.	0.916	0.144	0.337	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid IL-1 (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Baseline	Observed	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	7.72 (15.497)	2.21 (2.405)	5.22 (11.742)	2.58 (3.945)
		Median	1.03	1.48	1.47	1.45
		Min ; Max	0.5 ; 50.8	0.5 ; 10.2	0.5 ; 50.8	0.5 ; 19.4
Day 56	Observed	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	52.32 (144.445)	36.92 (127.771)	45.37 (135.139)	2.76 (2.451)
		Median	1.28	1.93	1.66	2.08
		Min ; Max	0.5 ; 480.8	0.5 ; 480.8	0.5 ; 480.8	0.5 ; 12.3
	CfB (abs.)	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	44.17 (137.974)	34.79 (128.236)	39.94 (131.535)	0.09 (4.063)
		Median	0.00	0.51	0.00	0.24
		Min ; Max	-45.1 ; 432.2	-6.1 ; 480.2	-45.1 ; 480.2	-15.3 ; 8.6
	CfB (%)	Mean (SD)	4396.01 (17982.101)	6631.78 (24671.746)	5405.71 (20916.587)	57.85 (105.661)
		Median	0.00	32.88	0.00	19.12
		Min ; Max	-88.8 ; 74171.3	-59.6 ; 92350.9	-88.8 ; 92350.9	-78.7 ; 363.9
	Adj. CfB (%) [1] LS mean (95% CI)		6613.59 (-1906.13, 15133.32)	6957.43 (-2046.30, 15961.15)	6856.09 (769.79, 12942.38)	135.42 (-7236.74, 7507.58)
		LS mean diff. [PPS - Placebo] (95% CI)	6478.17 (-4866.00, 17822.35)	6822.01 (-4728.27, 18372.28)	6672.45 (-2836.62, 16181.53)	
		p-value for diff.	0.257	0.241	0.165	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid IL-1 (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Day 168	Observed	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	3.99 (7.108)	49.19 (177.662)	25.86 (123.622)	4.01 (5.921)
		Median	1.08	2.01	1.41	2.22
		Min ; Max	0.6 ; 23.8	0.6 ; 691.3	0.6 ; 691.3	0.5 ; 29.6
	CfB (abs.)	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	-4.63 (19.211)	46.98 (178.042)	20.35 (125.159)	1.43 (6.588)
		Median	-0.48	0.50	0.07	0.68
		Min ; Max	-50.2 ; 23.3	-9.6 ; 690.4	-50.2 ; 690.4	-14.6 ; 25.9
	CfB (%)	Mean (SD)	500.63 (1409.897)	5280.04 (20149.589)	2813.25 (14012.789)	155.45 (307.267)
		Median	-12.12	57.29	13.38	44.18
		Min ; Max	-98.8 ; 4476.6	-94.2 ; 78115.0	-98.8 ; 78115.0	-75.0 ; 1292.7
	Adj. CfB (%) [1]	LS mean (95% CI)	2576.02 (-3235.09, 8387.12)	6076.66 (481.63, 11671.69)	4398.37 (366.94, 8429.81)	401.07 (-4233.05, 5035.19)
		LS mean diff.	2174.95	5675.59	4004.71	
		[PPS - Placebo] (95% CI)	(-5225.94, 9575.83)	(-1532.32, 12883.50)	(-2067.89, 10077.30)	
		p-value for diff.	0.557	0.120	0.191	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid IL-6 (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Baseline	Observed	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	48.09 (83.470)	40.76 (52.746)	44.76 (70.230)	65.48 (70.427)
		Median	15.15	18.30	17.26	33.70
		Min ; Max	1.0 ; 360.0	1.7 ; 181.4	1.0 ; 360.0	1.0 ; 201.3
Day 56	Observed	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	120.92 (272.633)	115.05 (236.774)	118.27 (252.872)	79.46 (106.447)
		Median	10.86	33.39	26.31	34.64
		Min ; Max	1.0 ; 920.9	2.3 ; 920.9	1.0 ; 920.9	2.9 ; 365.8
	CfB (abs.)	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	70.74 (265.924)	71.84 (246.404)	71.24 (253.032)	10.92 (73.845)
		Median	-2.06	7.72	0.39	3.49
		Min ; Max	-170.1 ; 828.0	-82.4 ; 918.7	-170.1 ; 918.7	-128.4 ; 217.0
	CfB (%)	Mean (SD)	134.44 (495.598)	3133.43 (11349.337)	1488.82 (7632.118)	66.03 (161.491)
		Median	-37.30	70.38	7.63	19.12
		Min ; Max	-88.8 ; 1840.2	-45.4 ; 42562.2	-88.8 ; 42562.2	-80.3 ; 525.7
	Adj. CfB (%) [1]	LS mean (95% CI)	464.76 (-2531.96, 3461.47)	3421.83 (178.75, 6664.92)	1830.92 (-440.35, 4102.19)	66.82 (-2608.53, 2742.16)
		LS mean diff.	397.94	3355.02	1721.47	
		[PPS - Placebo] (95% CI)	(-3590.32, 4386.19)	(-852.81, 7562.85)	(-1798.21, 5241.15)	
		p-value for diff.	0.842	0.115	0.330	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid IL-6 (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Day 168	Observed	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	20.77 (25.197)	146.55 (285.420)	81.63 (205.954)	52.99 (62.217)
		Median	10.45	40.87	21.60	36.03
		Min ; Max	1.0 ; 90.4	2.3 ; 1122.0	1.0 ; 1122.0	2.5 ; 247.6
	CfB (abs.)	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	-32.20 (94.166)	105.79 (295.784)	34.57 (223.999)	-12.48 (56.360)
		Median	-11.34	3.00	-4.69	-0.12
		Min ; Max	-338.4 ; 77.9	-108.5 ; 1120.3	-338.4 ; 1120.3	-150.4 ; 72.2
	CfB (%)	Mean (SD)	318.59 (971.738)	5131.43 (17038.168)	2647.38 (11913.133)	291.26 (965.683)
		Median	-60.58	39.45	-15.99	7.05
		Min ; Max	-99.0 ; 3778.2	-78.1 ; 66179.4	-99.0 ; 66179.4	-97.1 ; 4420.4
	Adj. CfB (%) [1]	LS mean (95% CI)	751.52 (-3813.13, 5316.17)	5435.71 (711.51, 10159.91)	3037.45 (-306.36, 6381.26)	362.57 (-3532.63, 4257.77)
		LS mean diff. [PPS - Placebo] (95% CI)	388.95 (-5583.72, 6361.62)	5073.14 (-1071.28, 11217.56)	2621.77 (-2530.55, 7774.08)	
		p-value for diff.	0.896	0.103	0.312	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid TIMP1 (ug/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Baseline	Observed	n (missing)	15 (4)	15 (0)	30 (4)	22 (0)
		Mean (SD)	0.49 (0.258)	0.68 (0.305)	0.58 (0.294)	0.73 (0.463)
		Median	0.41	0.58	0.54	0.73
		Min ; Max	0.1 ; 1.0	0.3 ; 1.3	0.1 ; 1.3	0.3 ; 2.5
Day 56	Observed	n (missing)	14 (5)	13 (2)	27 (7)	21 (1)
		Mean (SD)	0.54 (0.286)	0.73 (0.393)	0.63 (0.349)	0.67 (0.400)
		Median	0.52	0.73	0.61	0.60
		Min ; Max	0.1 ; 1.0	0.1 ; 1.7	0.1 ; 1.7	0.1 ; 1.9
	CfB (abs.)	n (missing)	14 (5)	13 (2)	27 (7)	21 (1)
		Mean (SD)	0.08 (0.294)	0.00 (0.213)	0.04 (0.256)	-0.06 (0.279)
		Median	0.07	0.03	0.03	0.01
		Min ; Max	-0.5 ; 0.7	-0.3 ; 0.3	-0.5 ; 0.7	-0.5 ; 0.5
	CfB (%)	Mean (SD)	51.67 (114.214)	-1.59 (39.308)	26.03 (89.282)	-0.99 (46.621)
		Median	9.52	3.39	3.39	2.68
		Min ; Max	-88.8 ; 280.7	-72.9 ; 68.4	-88.8 ; 280.7	-64.2 ; 133.1
	Adj. CfB (%) [1] LS mean (95% CI)		35.85	3.36	19.08	-0.36
			(-7.16, 78.87)	(-37.19, 43.91)	(-10.51, 48.68)	(-32.74, 32.03)
		LS mean diff.	36.21	3.72	19.12	
		[PPS - Placebo] (95% CI)	(-17.35, 89.77)	(-47.65, 55.08)	(-24.28, 62.52)	
		p-value for diff.	0.180	0.885	0.379	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid TIMP1 (ug/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Day 168	Observed	n (missing)	14 (5)	15 (0)	29 (5)	22 (0)
		Mean (SD)	0.48 (0.307)	1.68 (3.607)	1.10 (2.631)	0.69 (0.339)
		Median	0.54	0.81	0.72	0.62
		Min ; Max	0.0 ; 1.0	0.2 ; 14.7	0.0 ; 14.7	0.3 ; 1.6
	CfB (abs.)	n (missing)	13 (6)	15 (0)	28 (6)	22 (0)
		Mean (SD)	-0.02 (0.382)	1.00 (3.660)	0.53 (2.698)	-0.04 (0.361)
		Median	-0.02	0.08	0.05	-0.07
		Min ; Max	-0.9 ; 0.5	-0.2 ; 14.2	-0.9 ; 14.2	-0.9 ; 1.0
	CfB (%)	Mean (SD)	14.25 (82.772)	224.04 (830.254)	126.63 (609.773)	9.77 (61.116)
		Median	-2.29	12.12	7.43	-17.59
		Min ; Max	-98.0 ; 193.2	-51.2 ; 3222.2	-98.0 ; 3222.2	-57.1 ; 195.5
	Adj. CfB (%) [1] LS mean (95% CI)		-22.27	227.69	112.38	19.41
			(-284.49, 239.96)	(-11.31, 466.69)	(-65.47, 290.24)	(-179.81, 218.63)
		LS mean diff.	-41.68	208.28	97.03	
		[PPS - Placebo] (95% CI)	(-375.43, 292.08)	(-102.01, 518.58)	(-173.51, 367.58)	
		p-value for diff.	0.803	0.183	0.474	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid TNFa (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Baseline	Observed	n (missing)	18 (1)	15 (0)	33 (1)	22 (0)
		Mean (SD)	11.38 (19.386)	4.48 (4.304)	8.24 (14.829)	5.37 (5.983)
		Median	1.29	2.89	2.24	3.22
		Min ; Max	0.4 ; 61.2	0.7 ; 13.3	0.4 ; 61.2	0.4 ; 21.7
Day 56	Observed	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	47.62 (123.961)	38.89 (109.277)	43.68 (115.713)	10.43 (9.255)
		Median	1.55	6.38	4.41	9.01
		Min ; Max	0.4 ; 415.3	1.0 ; 415.3	0.4 ; 415.3	1.0 ; 30.6
	CfB (abs.)	n (missing)	17 (2)	14 (1)	31 (3)	21 (1)
		Mean (SD)	35.60 (120.698)	34.29 (110.181)	35.01 (114.152)	4.82 (10.082)
		Median	0.48	1.54	0.63	4.90
		Min ; Max	-42.5 ; 373.4	-5.2 ; 414.4	-42.5 ; 414.4	-16.3 ; 26.6
	CfB (%)	Mean (SD)	2124.49 (8372.754)	3303.73 (11706.186)	2657.05 (9855.247)	199.91 (271.560)
		Median	36.97	36.78	36.97	90.35
		Min ; Max	-96.6 ; 34603.3	-51.8 ; 43962.0	-96.6 ; 43962.0	-85.9 ; 882.9
	Adj. CfB (%) [1] LS mean (95% CI)		2870.06	3284.09	3074.84	178.56
			(-1038.45, 6778.56)	(-927.43, 7495.61)	(269.56, 5880.12)	(-3255.28, 3612.40)
		LS mean diff.	2691.50	3105.53	2890.97	
		[PPS - Placebo] (95% CI)	(-2555.97, 7938.96)	(-2294.47, 8505.54)	(-1525.79, 7307.74)	
		p-value for diff.	0.308	0.253	0.194	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Follow Up Analysis at Day 168
Data Extraction Date: 20Jan2023

Table 14.2.1.1.1: Summary of Change from Baseline in Synovial Fluid Biomarkers - Biomarker Analysis Set

Biomarker (Unit): Synovial Fluid TNFa (pg/mL)

Analysis Visit	Parameter	Statistics	PPS once-weekly N=19	PPS twice-weekly N=15	PPS pooled N=34	Placebo N=22
Day 168	Observed	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	2.49 (4.430)	30.66 (110.717)	16.12 (77.040)	2.50 (3.690)
		Median	0.68	1.25	0.88	1.39
		Min ; Max	0.4 ; 14.8	0.4 ; 430.8	0.4 ; 430.8	0.3 ; 18.4
	CfB (abs.)	n (missing)	16 (3)	15 (0)	31 (3)	22 (0)
		Mean (SD)	-10.26 (21.806)	26.17 (111.434)	7.37 (79.845)	-2.88 (7.063)
		Median	-1.08	-0.58	-0.94	-1.97
		Min ; Max	-60.8 ; 14.4	-12.9 ; 428.5	-60.8 ; 428.5	-20.6 ; 15.3
	CfB (%)	Mean (SD)	234.35 (850.961)	1267.03 (4937.725)	734.03 (3466.286)	27.79 (232.075)
		Median	-60.33	-46.77	-54.99	-64.86
		Min ; Max	-99.4 ; 3201.6	-97.2 ; 19111.8	-99.4 ; 19111.8	-94.8 ; 904.7
	Adj. CfB (%) [1] LS mean (95% CI)		744.17	1449.14	1105.46	119.43
			(-698.44, 2186.79)	(36.94, 2861.34)	(94.74, 2116.17)	(-1048.68, 1287.54)
		LS mean diff.	624.74	1329.71	986.27	
		[PPS - Placebo] (95% CI)	(-1216.13, 2465.61)	(-484.36, 3143.78)	(-532.33, 2504.86)	
		p-value for diff.	0.498	0.147	0.198	

[1] LS means obtained from Mixed Model for Repeated Measures (MMRM) analysis, including factors for treatment group (PPS once-weekly, PPS twice-weekly, Placebo), K-L grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. LS means for PPS Pooled are based on separate model where PPS once-weekly and PPS twice-weekly groups are combined.

CfB = Change from Baseline; abs. = Absolute; Adj. = Adjusted ; diff. = Difference; NE = Not Estimable.

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Table S4. Non-evaluable Biomarker Results

	iPPS Pooled	iPPS Once-Weekly	iPPS Twice-Weekly	Placebo
Synovial Fluid Biomarkers at Day 56				
ADAMTS-5 (ng/mL)				
Baseline, n (missing)	7 (27)	5 (14)	2 (13)	2 (20)
Observed mean (SD)	2.30 (1.512)	1.98 (1.459)	3.11 (1.837)	1.06 (0.610)
% below LOD	9.1	40.0	10.5	19.7
Correction factor mean (range)	3.73 (1.00, 7.05)	3.23 (1.00, 6.35)	4.97 (2.90, 7.05)	1.95 (1.51, 2.38)
Day 56, n (missing)	6 (28)	5 (14)	1 (14)	2 (20)
Observed mean (SD)	1.94 (1.242)	1.86 (1.372)	2.33 (NE)	1.38 (1.072)
Abs. CfB mean (SD)	-0.01 (1.239)	-0.12 (1.353)	0.52 (NE)	0.33 (0.462)
Adj. CfB (%) LS mean (95% CI)	44.98 (-63.86, 153.82)	25.44 (-77.71, 129.58)	107.45 (-78.45, 293.34)	-35.27 (-156.55, 56.02)
Adj. CfB (%) LS mean difference (95% CI)	83.14 (-127.55, 293.83)	60.70 (-124.76, 246.17)	142.71 (-91.61, 377.04)	--
p-value	NS	NS	NS	--
Day 56, % below LOD	9.1	40.0	10.5	19.7
Correction factor mean (range)	2.82 (1.21, 6.03)	2.74 (1.21, 6.03)	3.73 (3.73, 3.73)	3.39 (1.24, 5.49)
C2C (ng/mL)				
Baseline, n (missing)	10 (24)	7 (12)	3 (12)	4 (18)
Observed mean (SD)	170.40 (103.042)	146.12 (97.882)	227.04 (110.276)	139.39 (42.688)
% below LOD	10.0	20.0	0.0	4.5
Correction factor mean (range)	3.11 (1.00, 7.05)	3.02 (1.00, 6.35)	3.27 (1.54, 7.05)	3.45 (1.51, 7.18)
Day 56, n (missing)	8 (26)	7 (12)	1 (14)	3 (19)
Observed mean (SD)	140.24 (51.437)	146.94 (51.643)	93.30 (NE)	199.89 (90.037)
Abs. CfB mean (SD)	-11.53 (81.369)	-0.55 (83.258)	-77.42 (NE)	13.25 (5.809)
Adj. CfB (%) LS mean (95% CI)	NE	28.11 (-589.89, 646.10)	-48.42 (-1523.41, 1426.57)	3.14 (-1317.69, 1323.98)
Adj. CfB (%) LS mean difference (95% CI)	NE	24.96 (-1971.72, 2021.65)	-51.57 (-2158.63, 2055.50)	--
p-value	NE	NS	NS	--
Day 56, % below LOD	10.0	10.0	10.5	0.0
Correction factor mean (range)	2.82 (1.21, 6.03)	2.74 (1.21, 6.03)	3.73 (3.73, 3.73)	3.39 (1.24, 5.49)
CTX-I (ng/mL)				
Baseline, n (missing)	14 (20)	9 (10)	5 (10)	3 (19)
Observed mean (SD)	0.42 (0.240)	0.43 (0.282)	0.40 (0.165)	0.43 (0.262)
% below LOD	23.0	25.0	21.1	0.0
Correction factor mean (range)	3.13 (1.00, 7.05)	2.79 (1.00, 6.35)	3.63 (1.54, 7.05)	2.20 (1.51, 2.71)

Day 56, n (missing)	8 (26)	7 (12)	1 (14)	3 (19)
Observed mean (SD)	0.35 (0.168)	0.32 (0.142)	0.61 (NE)	0.46 (0.366)
Abs. CfB mean (SD)	-0.11 (0.325)	-0.16 (0.326)	0.19 (NE)	0.20 (0.041)
Adj. CfB (%) LS mean (95% CI)	NE	-0.11 (-326.37, 326.16)	91.12 (-331.88, 514.11)	-42.24 (-669.78, 585.30)
Adj. CfB (%) LS mean difference (95% CI)	NE	42.13 (-135.15, 219.42)	133.36 (-285.85, 552.56)	--
p-value	NE	NS	NS	--
Day 56, % below LOD	20.5	35	5.3	13.6
Correction factor mean (range)	2.82 (1.21, 6.03)	2.74 (1.21, 6.03)	3.73 (3.73, 3.73)	3.39 (1.24, 5.49)
CTX-II (ng/mL)				
Baseline, n (missing)	23 (11)	10 (9)	13 (2)	19 (3)
Observed mean (SD)	1.49 (1.027)	1.14 (1.061)	1.76 (0.954)	1.69 (1.014)
% below LOD	71.0	75.0	68.4	95.5
Correction factor mean (range)	2.88 (1.00, 7.05)	2.48 (1.00, 6.35)	3.20 (1.54, 7.05)	3.23 (1.16, 7.18)
Day 56, n (missing)	21 (13)	9 (10)	12 (3)	17 (5)
Observed mean (SD)	1.66 (1.176)	1.15 (1.027)	2.04 (1.174)	2.04 (0.832)
Abs. CfB mean (SD)	0.24 (0.733)	-0.06 (0.844)	0.46 (0.576)	0.48 (0.813)
Adj. CfB (%) LS mean (95% CI)	35.39 (2.82, 67.96)	27.28 (-22.24, 76.80)	40.22 (1.01, 79.44)	69.74 (36.44, 103.04)
Adj. CfB (%) LS mean difference (95% CI)	-34.50 (-78.83, 9.83)	-42.46 (-99.76, 14.83)	-29.51 (-79.03, 20.00)	--
p-value	NS	NS	NS	--
Day 56, % below LOD	71.0	75.0	68.4	95.5
Correction factor mean (range)	3.29 (1.21, 7.91)	2.80 (1.21, 6.03)	3.82 (1.87, 7.91)	3.95 (1.24, 7.94)
IL-1 (pg/mL)				
Baseline, n (missing)	27 (7)	12 (7)	15 (0)	20 (2)
Observed mean (SD)	1.67 (1.965)	0.99 (0.931)	2.21 (2.405)	1.64 (1.068)
% below LOD	82.0	90.0	73.7	90.9
Correction factor mean (range)	2.96 (1.00, 7.05)	2.47 (1.00, 6.35)	3.35 (1.54, 7.05)	3.21 (1.16, 7.18)
Day 56, n (missing)	22 (12)	10 (9)	12 (3)	17 (5)
Observed mean (SD)	1.69 (1.468)	1.06 (0.920)	2.21 (1.664)	1.93 (0.787)
Abs. CfB mean (SD)	0.03 (1.687)	-0.03 (0.757)	0.07 (2.227)	0.35 (0.880)
Adj. CfB (%) LS mean (95% CI)	30.65 (-1.58, 62.89)	20.77 (-29.38, 70.92)	36.62 (-5.27, 78.50)	59.24 (24.05, 94.42)
Adj. CfB (%) LS mean difference (95% CI)	-29.08 (-75.01, 16.85)	-38.47 (-98.08, 21.14)	-22.62 (-76.49, 31.25)	--
p-value	NS	NS	NS	--
Day 56, % below LOD	77.0	85.0	68.4	95.5
Correction factor mean (range)	3.22 (1.21, 7.91)	2.70 (1.21, 6.03)	3.82 (1.87, 7.91)	3.95 (1.24, 7.94)
Synovial Fluid Biomarkers at Day 168				

ADAMTS-5 (ng/mL)				
Baseline, n (missing)	7 (27)	5 (14)	2 (13)	2 (20)
Observed mean (SD)	2.30 (1.512)	1.98 (1.459)	3.11 (1.837)	1.06 (0.610)
% below LOD	9.1	40.0	10.5	19.7
Correction factor mean (range)	5.7 (1.00, 17.33)	6.59 (1.00, 17.33)	3.27 (1.54, 7.05)	2.20 (1.51, 2.71)
Day 168, n (missing)	0 (34)	0 (19)	0 (15)	0 (22)
Observed mean (SD)	NE	NE	NE	NE
Abs. CfB mean (SD)	NE	NE	NE	NE
Adj. CfB (%) LS mean (95% CI)	NE	NE	NE	NE
Adj. CfB (%) LS mean difference (95% CI)	NE	NE	NE	NE
p-value	NE	NE	NE	NE
Day 168, % below LOD	NE	NE	NE	NE
Correction factor mean (range)	NE	NE	NE	NE
C2C (ng/mL)				
Baseline, n (missing)	10 (24)	7 (12)	3 (12)	4 (18)
Observed mean (SD)	170.40 (103.042)	146.12 (97.882)	227.04 (110.276)	139.39 (42.688)
% below LOD	10.0	20.0	0.0	4.5
Correction factor mean (range)	3.11 (1.00, 7.05)	3.02 (1.00, 6.35)	3.27 (1.54, 7.05)	3.45 (1.51, 7.18)
Day 168, n (missing)	7 (27)	2 (17)	5 (10)	8 (14)
Observed mean (SD)	214.76 (121.656)	149.46 (140.665)	240.87 (119.455)	288.86 (124.789)
Abs. CfB mean (SD)	-12.30 (156.197)	132.96 (NE)	-60.72 (150.099)	47.96 (19.443)
Adj. CfB (%) LS mean (95% CI)	NE	105.05 (-318.73, 528.83)	27.13 (-1225.82, 1280.09)	33.78 (-1144.72, 1212.28)
Adj. CfB (%) LS mean difference (95% CI)	NE	71.28 (-331.68, 474.24)	-6.64 (-2133.01, 2119.73)	--
p-value	NE	NS	NS	--
Day 168, % below LOD	17	25	10.5	22.7
Correction factor mean (range)	3.37 (0.84, 6.84)	3.40 (2.32, 5.50)	3.36 (0.84, 6.84)	4.10 (0.79, 7.89)
CTX-I (ng/mL)				
Baseline, n (missing)	14 (20)	9 (10)	5 (10)	3 (19)
Observed mean (SD)	0.42 (0.240)	0.43 (0.282)	0.40 (0.165)	0.43 (0.262)
% below LOD	23.0	25.0	21.1	0.0
Correction factor mean (range)	3.13 (1.00, 7.05)	2.79 (1.00, 6.35)	3.63 (1.54, 7.05)	2.20 (1.51, 2.71)
Day 168, n (missing)	8 (26)	4 (15)	4 (11)	4 (18)
Observed mean (SD)	0.37 (0.199)	0.29 (0.096)	0.45 (0.255)	0.48 (0.139)
Abs. CfB mean (SD)	-0.13 (0.270)	-0.25 (0.290)	0.02 (0.175)	0.06 (0.147)
Adj. CfB (%) LS mean (95% CI)	NE	-36.28 (-215.11, 142.55)	14.55 (-207.93, 237.03)	37.24 (-228.17, 302.66)
Adj. CfB (%) LS mean difference (95% CI)	NE	-73.52 (-356.66, 209.62)	-22.69 (-347.97, 302.58)	--

p-value	NE	NS	NS	--
Day 168, % below LOD	30.7	40.0	21.1	18.2
Correction factor mean (range)	2.95 (0.84, 6.84)	2.71 (1.47, 5.50)	3.16 (0.84, 6.84)	3.89 (0.79, 7.89)
CTX-II (ng/mL)				
Baseline, n (missing)	23 (11)	10 (9)	13 (2)	19 (3)
Observed mean (SD)	1.49 (1.027)	1.14 (1.061)	1.76 (0.954)	1.69 (1.014)
% below LOD	71.0	75.0	68.4	95.5
Correction factor mean (range)	2.88 (1.00, 7.05)	2.48 (1.00, 6.35)	3.20 (1.54, 7.05)	3.23 (1.16, 7.18)
Day 168, n (missing)	1 (33)	1 (18)	0 (15)	0 (22)
Observed mean (SD)	1.18 (NE)	1.18 (NE)	NE	NE
Abs. CfB mean (SD)	0.63 (NE)	0.63 (NE)	NE	NE
Adj. CfB (%) LS mean (95% CI)	NE	NE	NE	NE
Adj. CfB (%) LS mean difference (95% CI)	NE	NE	NE	NE
p-value	NE	NE	NE	NE
Day 168, % below LOD	5.0	5.0	NE	NE
Correction factor mean (range)	2.32 (2.32, 2.32)	2.32 (2.32, 2.32)	NE	NE
IL-1 (pg/mL)				
Baseline, n (missing)	27 (7)	12 (7)	15 (0)	20 (2)
Observed mean (SD)	1.67 (1.965)	0.99 (0.931)	2.21 (2.405)	1.64 (1.068)
% below LOD	82.0	90.0	73.7	90.9
Correction factor mean (range)	2.96 (1.00, 7.05)	2.47 (1.00, 6.35)	3.35 (1.54, 7.05)	3.21 (1.16, 7.18)
Day 168, n (missing)	18 (16)	7 (12)	11 (4)	17 (5)
Observed mean (SD)	1.34 (0.926)	0.86 (0.381)	1.65 (1.052)	2.22 (0.966)
Abs. CfB mean (SD)	-0.44 (2.554)	-0.32 (0.823)	-0.51 (3.266)	0.76 (0.931)
Adj. CfB (%) LS mean (95% CI)	47.49 (1.53, 93.45)	23.37 (-50.74, 97.48)	61.78 (3.19, 120.36)	84.87 (37.48, 132.27)
Adj. CfB (%) LS mean difference (95% CI)	-37.83 (-103.46, 27.81)	-61.50 (-148.42, 25.42)	-23.10 (-98.71, 52.52)	--
p-value	NS	NS	NS	--
Day 168, % below LOD	79.4	80.0	78.9	100.0
Correction factor mean (range)	2.73 (0.84, 6.84)	2.61 (1.47, 5.50)	2.85 (0.84, 6.84)	3.89 (0.79, 7.89)
Serum Biomarkers at Day 56				
ADAMTS-5 (ng/mL)				
Baseline, n (missing)	32 (2)	17 (2)	15 (0)	22 (0)
Observed mean (SD)	0.78 (0.000)	0.78 (0.000)	0.78 (0.000)	2.69 (7.788)
Baseline, % below LOD	82.0	85.0	78.9	86.4

Day 56, n (missing)	32 (2)	17 (2)	15 (0)	22 (0)
Observed mean (SD)	0.78 (0.000)	0.78 (0.000)	0.78 (0.000)	2.81 (8.725)
Abs. CfB mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)	0.12 (1.002)
Adj. CfB (%) LS mean (95% CI)	0.49 (-2.37, 3.34)	0.62 (-3.30, 4.53)	0.34 (-3.74, 4.43)	-2.97 (-6.40, 0.46)
Adj. CfB (%) LS mean difference (95% CI)	3.46 (-0.90, 7.81)	3.58 (-1.52, 8.68)	3.31 (-2.00, 8.62)	--
p-value	NS	NS	NS	--
Day 56, % below LOD	82.0	85.0	78.9	90.9
Serum Biomarkers at Day 168				
ADAMTS-5 (ng/mL)				
Baseline, n (missing)	32 (2)	17 (2)	15 (0)	22 (0)
Observed mean (SD)	0.78 (0.000)	0.78 (0.000)	0.78 (0.000)	2.69 (7.788)
% below LOD	82.0	85.0	78.9	86.4
Day 168, n (missing)	30 (4)	15 (4)	15 (0)	22 (0)
Observed mean (SD)	0.78 (0.000)	0.78 (0.000)	0.78 (0.000)	1.73 (3.563)
Abs. CfB mean (SD)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)	-0.96 (4.297)
Adj. CfB (%) LS mean (95% CI)	-1.08 (-3.76, 1.61)	-0.96 (-4.65, 2.73)	-1.21 (-5.01, 2.60)	-3.43 (-6.62, -0.23)
Adj. CfB (%) LS mean difference (95% CI)	2.35 (-1.71, 6.41)	2.47 (-2.30, 7.24)	2.22 (-2.72, 7.16)	--
p-value	NS	NS	NS	--
Day 168, % below LOD	77.0	75.0	78.9	90.9

LS means obtained from mixed model for repeated measures (MMRM) analysis of the biomarker analysis set (BAS), including factors for treatment group (iPPS once-weekly, iPPS twice-weekly, Placebo), KL grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. There were no adjustments for Type I error inflation linked to the multiplicity of biomarkers tested due to the exploratory nature of the study. Abs. = absolute; Adj. = adjusted; CfB = change from baseline; CI = confidence interval; LOD = limit of detection; NE = not estimable; SD = standard deviation.

Table S5. Percentage of Results Below the Limit of Detection for Evaluable Biomarkers

		SF COMP	SF ARGS	SF TIMP-1	SF IL-6	SF TNF- α	SF β NGF	Serum COMP	Serum ARGS	Serum TIMP-1	Serum C2C	Serum CTX-I	Urine CTX-II
Baseline	% below LOD	5.1	0.0	5.0	28.0	48.7	7.606	0.0	0.0	0.0	0.0	12.8	2.5
iPPS Pooled													
Baseline	% below LOD	10.0	0.0	10.0	30.0	65.0	15.0	0.0	0.0	0.0	0.0	5.0	5.0
iPPS Once- Weekly													
Baseline	% below LOD	0.0	0.0	0.0	26.3	31.6	0.0	0.0	0.0	0.0	0.0	21.1	0.0
iPPS Twice- Weekly													
Baseline	% below LOD	0.0	0.0	0.0	31.8	36.4	9.1	0.0	0.0	0.0	0.0	0.0	13.6
Placebo													
D56	% below LOD	7.66	0.0	5.0	23.0	35.8	12.0	0.0	0.0	0.0	0.0	2.5	2.5
iPPS Pooled													
D56	% below LOD	10.0	0.0	5.0	35.0	45.0	15.0	0.0	0.0	0.0	0.0	5.0	0.0
iPPS Once- Weekly													
D56	% below LOD	5.33	0.0	5.3	10.5	26.3	10.5	0.0	0.0	0.0	0.0	0.0	5.3
iPPS Twice- Weekly													
D56	% below LOD	0.00	0.0	4.5	27.3	36.4	9.1	0.0	0.0	0.0	0.0	18.2	9.1
Placebo													
D168	% below LOD	10.0	0.0	10.0	30.7	79.0	20.0	0.0	0.0	0.0	0.0	0.0	17.9
iPPS Pooled													
D168	% below LOD	15.0	0.0	10.0	35.0	80.0	25.0	0.0	0.0	0.0	0.0	0.0	20.0
iPPS Once- Weekly													
D168	% below LOD	5.3	0.0	10.5	26.3	78.9	15.8	0.0	0.0	0.0	0.0	0.0	15.8
iPPS Twice- Weekly													
D168	% below LOD	4.5	0.0	4.5	40.9	100.0	18.2	0.0	0.0	0.0	0.0	4.5	22.7
Placebo													

Abbreviations: LOD, limit of detection; SF, synovial fluid.

Table S6. Lavage Correction Factor Distribution for Evaluable Biomarkers

		SF COMP	SF ARGS	SF TIMP-1	SF IL-6	SF TNF- α	SF β NGF
Baseline iPPS Pooled	Correction factor mean (range)	2.90 (1.00, 7.05)	2.86 (1.00, 7.05)	2.95 (1.00, 7.05)	2.88 (1.00, 7.05)	2.85 (1.00, 7.05)	2.86 (1.00, 7.05)
Baseline iPPS Once-Weekly	Correction factor mean (range)	2.47 (1.00, 6.35)	2.47 (1.00, 6.35)	2.64 (1.00, 6.35)	2.47 (1.00, 6.35)	2.47 (1.00, 6.35)	2.47 (1.00, 6.35)
Baseline iPPS Twice-Weekly	Correction factor mean (range)	3.20 (1.13, 7.05)	3.11 (1.13, 7.05)	3.11 (1.13, 7.05)	3.15 (1.13, 7.05)	3.12 (1.13, 7.05)	3.11 (1.13, 7.05)
Baseline Placebo	Correction factor mean (range)	3.21 (1.16, 7.18)	3.21 (1.16, 7.18)	3.21 (1.16, 7.18)	3.21 (1.16, 7.18)	3.21 (1.16, 7.18)	3.21 (1.16, 7.18)
Day 56 iPPS Pooled	Correction factor mean (range)	3.19 (1.21, 7.91)	3.19 (1.21, 7.91)	3.19 (1.21, 7.91)	3.22 (1.21, 7.91)	3.22 (1.21, 7.91)	3.22 (1.21, 7.91)
Day 56 iPPS Once-Weekly	Correction factor mean (range)	2.68 (1.21, 6.03)	2.68 (1.21, 6.03)	2.61 (1.21, 6.03)	2.70 (1.21, 6.03)	2.70 (1.21, 6.03)	2.70 (1.21, 6.03)
Day 56 iPPS Twice-Weekly	Correction factor mean (range)	3.82 (1.87, 7.91)	3.82 (1.87, 7.91)	3.82 (1.87, 7.91)	3.82 (1.87, 7.91)	3.82 (1.87, 7.91)	3.82 (1.87, 7.91)
Day 56 Placebo	Correction factor mean (range)	3.95 (1.24, 7.94)	3.95 (1.24, 7.94)	3.95 (1.24, 7.94)	3.95 (1.24, 7.94)	3.95 (1.24, 7.94)	3.95 (1.24, 7.94)
Day 168 iPPS Pooled	Correction factor mean (range)	2.73 (0.84, 6.84)	2.73 (0.84, 6.84)	2.73 (0.84, 6.84)	2.73 (0.84, 6.84)	2.73 (0.84, 6.84)	2.73 (0.84, 6.84)
Day 168 iPPS Once-Weekly	Correction factor mean (range)	2.61 (1.47, 5.50)	2.61 (1.47, 5.50)	2.61 (1.47, 5.50)	2.61 (1.47, 5.50)	2.61 (1.47, 5.50)	2.61 (1.47, 5.50)
Day 168 iPPS Twice-Weekly	Correction factor mean (range)	2.85 (0.84, 6.84)	2.85 (0.84, 6.84)	2.85 (0.84, 6.84)	2.85 (0.84, 6.84)	2.85 (0.84, 6.84)	2.85 (0.84, 6.84)
Day 168 Placebo	Correction factor mean (range)	3.89 (0.79, 7.89)	3.89 (0.79, 7.89)	3.89 (0.79, 7.89)	3.89 (0.79, 7.89)	3.89 (0.79, 7.89)	3.89 (0.79, 7.89)

Correction factors are only applicable to synovial fluid biomarker measures. Abbreviation: SF, synovial fluid.

Table S7. Clinical Outcomes at Day 365

	iPPS Pooled n=39	iPPS Once-Weekly n=20	iPPS Twice-Weekly n=19	Placebo n=22
WOMAC and PGIC Measures – Day 365				
WOMAC Pain				
n (missing)	26 (13)	15 (5)	11 (8)	18 (4)
abs. CfB mean (SD)	-1.72 (1.906)	-1.37 (1.432)	-1.72 (1.906)	-1.50 (2.223)
adj. CfB% LS mean (95% CI)	-29.09 (-42.02, -16.16)	-16.78 (-33.85, 0.29)	-43.42 (-62.06, -24.77)	-19.86 (-35.59, -4.12)
LS mean difference (95% CI)	-9.24 (-29.57, 11.09)	2.84 (-19.91, 25.59)	-23.80 (-48.03, 0.44)	--
p-value	NS	NS	NS 0.054	--
WOMAC Function				
n (missing)	26 (13)	15 (5)	11 (8)	18 (4)
abs. CfB mean (SD)	-1.88 (2.171)	-1.67 (1.632)	-2.17 (2.809)	-1.20 (2.296)
adj. CfB% LS mean (95% CI)	-29.86 (-43.05, -16.66)	-20.98 (-39.01, -2.95)	-41.14 (-60.47, -21.82)	-15.15 (-31.27, 0.97)
LS mean difference (95% CI)	-14.70 (-35.48, 6.07)	-5.12 (-28.97, 18.74)	-25.28* (-50.34, -0.22)	--
p-value	NS	NS	0.048	--
WOMAC Stiffness				
n (missing)	26 (13)	15 (5)	11 (8)	18 (4)
abs. CfB mean (SD)	-1.46 (2.375)	-1.10 (1.454)	-1.95 (3.267)	-1.50 (2.437)
adj. CfB% LS mean (95% CI)	-21.80 (-35.92, -7.67)	-12.50 (-31.63, 6.62)	-32.22 (-52.79, -11.65)	-15.17 (-32.52, 2.18)
LS mean difference (95% CI)	-6.63 (-28.92, 15.67)	2.50 (-22.96, 27.95)	-17.22 (-44.17, 9.73)	--
p-value	NS	NS	NS	--
Total WOMAC				
n (missing)	26 (13)	15 (5)	11 (8)	18 (4)
abs. CfB mean (SD)	-1.81 (2.071)	-1.56 (1.501)	-2.16 (2.709)	-1.29 (2.268)
adj. CfB% LS mean (95% CI)	-28.96 (-41.95, -15.97)	-19.17 (-36.70, -1.64)	-41.05 (-59.94, -22.16)	-16.52 (-32.39, -0.66)
LS mean difference (95% CI)	-12.44 (-32.88, 8.01)	-2.20 (-25.42, 21.01)	-24.08 (-48.62, 0.46)	--
p-value	NS	NS	NS 0.054	--
PGIC				
n (missing)	26 (13)	15 (5)	11 (8)	18 (4)
mean (SD)	3.19 (1.86)	2.93 (1.67)	3.55 (2.11)	2.06 (1.70)
LS mean (95% CI)	3.23 (2.57, 3.89)	2.84 (1.94, 3.74)	3.74 (2.78, 4.70)	1.96 (1.16, 2.75)
LS mean difference (95% CI)	1.27* (0.24, 2.30)	0.93 (-0.26, 2.12)	1.82** (0.58, 3.07)	--
p-value	0.016	NS	0.005	--

LS means obtained from mixed model for repeated measures (MMRM) analysis of the full

analysis set (FAS), including factors for treatment group (iPPS once-weekly, iPPS twice-weekly, Placebo), KL grade (2, 3, 4), visit, age (continuous), treatment-by-visit interaction, baseline value of the outcome variable, and baseline-by-visit interaction. Abbreviations:

abs. = absolute; adj. = adjusted; CfB = change from baseline; CI = confidence interval;

PGIC = patient global impression of change; SD = standard deviation; WOMAC = Western

Ontario and McMaster Universities Osteoarthritis Index. Significance is indicated with

asterisks, where * $p \leq 0.05$ and ** $p \leq 0.01$ when LS mean is compared to placebo.

Table S8. Pain Response Duration

	iPPS Pooled	iPPS Once- Weekly	iPPS Twice- Weekly	Placebo
Pain responders Day 56 only	3	1	2	2
Pain responders Day 168 only	1	0	1	0
Pain responders Day 365 only	4	4	0	0
Pain responders Days 56 and 168	4	1	3	5
Pain responders Days 56, 168, and 365	6	1	5	4

Pain responders are classified as those with greater than or equal to 30% improvement in

WOMAC pain adjusted percentage change from baseline LS mean values. Of the three iPPS

twice-weekly participants with pain responses at both Days 56 and 168, two withdrew or

were lost to follow-up at Day 365.