Appendix 1 Table D. Off-Label Comparative Studies Patient Characteristics

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Defect severity and characteristics (%)	Age mean ± SD yrs (rng)	≥ 65 yrs (%)	Males (%)	Weight mean ± SD lbs (rng)	Comorbidities (%)	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	grade I spondylo-listhesis	rhBMP2/CRM /TSRHSS 58±4	NR	rhBMP2/CRM /TSRHSS 27	NR	Tobacco use rhBMP2/CRM /TSRHSS 0 Alcohol use rhBMP2/CRM /TSRHSS 54 Diabetes rhBMP2/CRM /TSRHSS 0 Previous back surgery rhBMP2/TSRHSS 27%	Other than diabetes, no significant differences between groups
		(40 mg/pt) rhBMP2/CRM alone n=11				rhBMP2/CRM alone 52±6		rhBMP2/CRM alone 56		Tobacco use rhBMP2/CRM alone 12 Alcohol use rhBMP2/CRM alone 25 Diabetes rhBMP2/CRM alone 0 Previous back surgery rhBMP2 alone 12%	

		(40 mg/pt) ICBG plus TSRHSS n=5				ICBG/TSRHSS 53±10		ICBG/TSRHSS 40		Tobacco use ICBG/TSRHSS 20 Alcohol use ICBG/TSRHSS 40 Diabetes ICBG/TSRHSS 40 (p=0.036 for diabetes) Previous Surgery?	
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt) ICBG N=52	single-level lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	grade I spondylo-listhesis	rhBMP2 40 ICBG 44	NR	rhBMP2 40 ICBG 36	rhBMP2 172 ICBG 173	Tobacco use rhBMP2 33 Previous back surgery rhBMP2 37 Tobacco use ICBG 33 Previous back surgery ICBG 33	No significant differences between groups
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec#	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt) ICBG	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	grade I spondylo-listhesis	rhBMP2/CRM 53 (20-82) ICBG	NR	rhBMP2/CRM 45 ICBG	rhBMP2/CRM 187 (103-361) ICBG	Tobacco use rhBMP2/CRM 26 Alcohol use rhBMP2/CRM 38 Previous back surgery rhBMP2 30 Tobacco use	No significant differences between groups

5480; Glassman et al., 2005, rec# 8040		n=224				52 (18-86)		42	189 (99-312)	ICBG 26 Alcohol use ICBG 35 Previous back surgery ICBG 28	
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability, spinal stenosis, adjacent level degeneration	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	Not reported	rhBMP2 60 (27-84) ICBG 53 (33-80)	NR	rhBMP2 40 ICBG 43	NR	Tobacco use rhBMP2 15 ICBG 23	No statistically significant differences between primary single-level pts in rhbMP2 or ICBG group
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2 n=50 (dose not reported) ICBG n=52	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	Not reported	rhBMP2 69±6 ICBG 70±6	NR all > 60	rhBMP2 30 ICBG 33	NR BMI rhBMP2 29±6 ICBG 28±6	Tobacco use rhBMP2 22 ICBG 17	No significant differences between groups, including mean number of surgical levels (rhBMP2=1.96, ICBG=1.98)
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4 mg/pt)	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) with interbody fusion cages plus rhBMP2 or ICBG	grade I spondylo-listhesis	rhBMP2 46 (26-66)	NR	rhBMP2 50	rhBMP2 180±38	Tobacco use rhBMP2 53 Alcohol use rhBMP2 44 Previous back surgery rhBMP2 35	No significant differences between groups

		ICBG N=33				ICBG 46 (28-71)		ICBG 46	ICBG 173±36	Tobacco use ICBG 46 Alcohol use ICBG 27 Previous back surgery ICBG 39	
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	rhBMP7 43±11	0	rhBMP7 30	NR	rhBMP7 40	Poorly described patients samples
		ICBG n=10				ICBG 40±10		ICBG 70		ICBG 30	
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	grade I spondylo-listhesis	rhBMP7 70±8	NR	rhBMP7 56	NR	NR	Poorly described patient samples, significantly older pts in rhBMP7 group
		AGB/CRM n=10				AGB/CRM 59±9 ($p < 0.05$)		AGB/CRM 60			
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	grade I spondylo-listhesis	rhBMP2/AGB 56±12 (33-76)	rhBMP2/AGB 24	rhBMP2/AGB 68	NR	Tobacco use rhBMP2/AGB 12 Prior surgery rhBMP/AGB 40 Tobacco use ICBG 5 Prior surgery ICBG 67	More older pts and males in the rhBMP2/AGB group than ICBG group, but small numbers limit comparison
		ICBG N=19				ICBG 49±10 (33-64)	ICBG 0 ($p < 0.01$)	ICBG 47			
Pradhan et al., 2006	Prospective consecutive	rhBMP2 n=9	single-level lumbar DDD	single-level primary	grade I spondylo-	rhBMP2 51	3 (1 of 36)	rhBMP2 33	NR	NR	Patient sample demographics

USA (101) **Lumbar Spine**	patient single-center cohort study	(dose NR) ICBG n=27		aAAnterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	listhesis	 ICBG 53		 ICBG 18			not well described
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	grade I-II spondylo-listhesis	rhBMP2/ICBG 65 ICBG 54	NR	rhBMP2/ICBG 44 ICBG 46	NR	NR	Patients in rhBMP2/ICBG group appear to be older, but no statistical analysis was done to confirm
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	grade I-II spondylo-listhesis	rhBMP2 45 ALG 44	NR	rhBMP2 60 ALG 51	NR	Tobacco use rhBMP2 18 Previous back surgery rhBMP2 46 Tobacco use ALG 8 Previous back surgery ALG 37	Both groups were similar in demographics and number of levels fused
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	grade I-II spondylo-listhesis	rhBMP7 68±10 ICBG	at least 50% in both groups rhBMP7 med=68 ICBG	rhBMP7 34 ICBG	NR NSD reported	NR	No significant differences between groups

		n=86				69±8	med=71	30			
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	grade I-II spondylo-listhesis	rhBMP7 63 (43-80) ICBG 67 (51-79)	NR	rhBMP7 46 ICBG 42	rhBMP7 198 (125-299) ICBG 176 (130-220)	NR	Patients in rhBMP7 group appear to be younger and heavier than in ICBG group, but no statistical analysis was done
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt) ICBG/ALG n=15	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	NR	rhBMP2/ALG 51 ICBG/ALG 47	NR	rhBMP2/ALG 44 ICBG/ALG 47	rhBMP2/ALG 170 ICBG/ALG 174	Tobacco use rhBMP2/ALG 28 ICBG/ALG 47	No significant differences between groups
Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt) ICBG n=36	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	NR	rhBMP2/CRA 49±10 ICBG 48±9	NR	rhBMP2/CRA 50 ICBG 33	NR	Tobacco use rhBMP2/CRA 37 Adjacent level DDD rhBMP2 63 Tobacco use rhBMP2/CRA ICBG 53 Adjacent level DDD ICBG 64	No significant differences between pt groups except a greater number of levels were treated in the rhBMP2/CRA group compared to the ICBG group (mn 1.6 vs. 2.2, p=0.003)
Crawford et al.,	Retrospective	rhBMP2/BGE	single- or multi-	single- or multi-	NR	rhBMP2/BGE	NR	rhBMP2/BGE	NR	Tobacco use	No significant

2009 USA (105) **Cervical Spine**	cohort of consecutive patients	n=41 (4.2-12 mg/pt) ICBG n=36	level posterior cervical stenosis, ACDF nonunion, or unstable spondylosis	level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG		56±11 ICBG 54±12		32 ICBG 42		rhBMP2/BGE 24 ICBG 36	differences between groups
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	rhBMP2/CRA 52 CRA 50	NR	rhBMP2/CRA 49 CRA 49	NR	Tobacco use rhBMP2/CRA 29 Prior ACDF rhBMP2/CRA 28 ≥ 3 levels fused rhBMP2/CRA 13 Tobacco use CRA 14 (p=0.02) Prior ACDF CRA 10 (p=0.001) ≥ 3 levels fused CRA 2 (p=0.003)	Patients in rhBMP2/CRA (cortical ring allograft) group had significantly higher rates of comorbidities that can adversely affect fusion
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	NR	rhBMP2 50 (29-70) ALG/DBM 48 (30-69)	NR	rhBMP2 32 ALG/DBM 45	NR	NR	No significant differences between groups
Boraiah et al.,	Retrospective	rhBMP2	Complex tibial	Surgery for	NR	53 years	NR	22 (55%)	NR	NR	

2009 USA (108) **Acute Tibial Fractures**	case series	(1) n=17 (12 mg/pt) (2) n=23 no BMP	plateau fractures	Acute traumatic tibial plateau fractures		(17-83)					
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	Open BMP 14 (93%) Closed BMP 1 (7%) Defect location Proximal third BMP 3 (20%) Middle third BMP 8 (53%) Distal third BMP 4 (27%) Gustilo-Anderson I or II BMP 1 (7%) IIIA BMP 9 (64%) IIIB BMP 4(29%) OTA classification Simple fracture BMP 1(7%)	BMP 36 (18-51)	NR	BMP 14 (93%)	NR	Tobacco use BMP 6(40%)	

					Wedge Fracture BMP 5(33%)					Diabetes BMP 3(30%)	
					Complex Fract BMP 9(60%)					Cardiovascular disease BMP 1 (7%)	
		(2) n=15 autogenous bone graft			No BMP 13(87%)	Non BMP 38 (18-71)		No BMP 13 (87%)		Tobacco use No BMP 4 (27%)	
					No BMP 2(13%)						
					No BMP 5(33%)						
					No BMP 7(47%)						
					No BMP 3(23%)						
					No BMP 2(15%)						
					No BMP 8(62%)						
					No BMP 3(23%)						
					No BMP 0						
					No BMP 8(53%)					Diabetes No BMP 1 (7%)	
					No BMP					Cardiovascular	

					7(47%)					disease No BMP 3 (20%)	
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Inclusion: Zone 43 tibial fracture, fixation with two-ring hybrid external fixation, treatment with rhBMP7 (controls matched from other patients undergoing Zone 43 external fixation)	BMP: High energy injury 10(50%) Bone defects: BMP: 6(30%)	BMP: 41.3 (23 to 79)	NR	BMP: 11 (55%)	nr	Smokers (1) 10 (50%)	
		Matched Zone 43 fracture (OREF) N=20			Matched: high energy injury 11 (55%) Boney defects: Matched: 2(10%)	Matched: 47.2 (28 to 78)		Matched: 10 (50%)		(2) 8 (40%)	
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt)	symptomatic proximal pole scaphoid nonunion	revision of nonunion	≥ 9 mos. duration, no evidence of healing over past 3 mos	rhBMP7/AGB 23±5	0	100	BMI (kg/m2) rhBMP7/AGB 20.1±1.5	Tobacco use rhBMP7/AGB 50 Nonunion duration (mos) rhBMP7/AGB 15±5	No significant differences between groups
		rhBMP7/ALG n=6 (3.5 mg/pt)				rhBMP7/ALG 19±4			rhBMP7/ALG 21.3±2.1	Tobacco use rhBMP7/ALG 50 Nonunion duration (mos) rhBMP7/ALG 14±5	
		ICBG n=6				ICBG 22±5			ICBG 19.8±1.3	Tobacco use ICBG 33 Nonunion	

										duration (mos) ICBG 13±4	
Dickinson et al., 2008 USA (91) **Miscellaneous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR	rhBMP2/ACS 16±1 ICBG 16±2	0	43	NR	NR	
Ekrol et al., 2008 UK (97) **Miscellaneous Off-Label Uses**	Prospective randomized cohort	RhBMP2 Non bridging external fixation N=4 Bone graft Non bridging external fixation N=6 RhBMP-7 internal fixation w/ pi-plate N=10 Bone graft internal fixation w/ pi-plate N=10	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	Inclusion: malunion of distal radius (more than 10 degrees of dorsal angulation, more than 2 mm of radial shortening, carpal malalighnment or a combination of these)		Internal fixation w/ pi plate bone graft: 57(49-68) Internal fixation w/ pi plate rhBMP-7: 62(35-78) External fixation rhBMP7: 58(41-81) External fixation bone graft: 61(25-79)	NR	Internal fixation w/ pi plate bone graft: 3(30%) Internal fixation w/ pi plate rhBMP-7: 0(0%) External fixation rhBMP7: 1(25%) External fixation bone graft: 1(16.6%)	NR	NR	
Geesink et al., 1999 Netherlands (98) **Miscellaneous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6 DMB N=6 Collagen type I N=6 OP-1 (2.5mg)	High tibial osteotomy with three osteoinductive materials	Pts with high tibial osteotomy who complied with study criteria	15.6mm in untreated, 13.4 mm in DMB 14.2 mm in collagen only 16.4mm in	50 years (25 to 73)	NR	11 (45%)	NR	NR	

		with Collagen type I N=6			OP-1						
Karrholm et al., 2006 UK (111) **Miscellaneous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	NR	Cups rhBMP7/ALG 68 (51-78)	NR	Cups rhBMP7/ALG 50	Cups rhBMP7/AKG 152 (128-187)	Osteoarthritis 100% both groups	No significant differences between groups
		Cupss ALG n=10				Cups ALG 65 (48-75)		Cups ALG 50	Cups ALG 158 (106-216)		
		Stems rhBMP7/ALG (1 g/pt) n=11				Stems rhBMP7/ALG 68 (51-77)		Stems rhBMP7/ALG 54	Stems rhBMP7/ALG 154 (119-187)		
		Stems ALG n=30				Stems ALG 67 (37-79)		Stems ALG 60	Stems ALG 165 (128-220)		
Maeda et al., 2009 USA, Japan (109) **Miscellaneous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt)	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	preoperative major curve Cobb angle (mn ± SD degrees) rhBMP2/BGE 54±20	rhBMP2/BGE 56±10	NR	NR	BMI rhBMP2/BGE 26±10	Tobacco use rhBMP2/BGE 13	No significant differences between groups
		ICBG n=32			ICBG 58±13	ICBG 53±10			ICBG 25±4	ICBG 12	