

**Appendix 1 Table N. Off-Label Comparative Study Functional Outcomes**

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score (p-value)	Outcome measure % improved or success (p-value)	Comment
Boden et al., 2002 USA (84) <b>Lumbar Spine</b>	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	SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ~1, ~0, ~5, ~4	NR	Both rhBMP2/CRM groups showed statistically significant improvements over baseline, the ICBG group did not
		(40 mg/pt) rhBMP2/CRM alone n=11			rhBMP2/CRM alone ~1, ~9, ~11, ~16		
		(40 mg/pt) ICBG plus TSRHSS n=5			ICBG/TSRHSS ~1, ~3, ~2, ~17		
Burkus et al., 2005 USA (85) <b>Lumbar Spine</b>	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	single-level lumbar lumbar DDD	primary single- level anterior lumbar fusion with a pair of threaded allograft	SF-36 physical component subscale Mean score improvement (points) 6, 12, 24 mos rhBMP2 43, 45, 45	NR	SF-36 scores in both groups showed steady improvement from 6 to 24 mos. postsurgery

Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640		ICBG N=52		cortical bone dowels (CBD) plus rhBMP2 or ICBG	Average days to return to work rhBMP2 89		
					SF-36 physical component subscale Mean score improvement (points) 6, 12, 24 mos ICBG 37, 39, 39 (p=0.001, 0.003, 0.015)		
					Average days to return to work ICBG 96 (p=not significant)		
Dimar et al., 2009 USA (86) <b>Lumbar Spine</b> Note: contains pts in Glassman et al., 2007,	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/CRM ~4, ~9, ~13, ~13, ~13	Work status at 24 mos rhBMP2/CRM 87 of 207 (42) working	SF-36 physical component scale mean score improvements at 24 mos. exceeded a 5.41 point threshold proposed to be clinically significant (Ware

rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040		ICBG n=224			ICBG ~4, ~8, ~9, ~10, ~10	ICBG 89 of 184 (48) working	et al., 1994)
Glassman et al., 2007 USA (99) <b>Lumbar Spine</b>	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt)	single- and multi-level lumbar DDD, degenerativ e scoliosis, postdissect omy instability, spinal stenosis, adjacent level degeneratio n	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	NR	NR	Study only reported fusion data
		ICBG n=35					
Glassman et al., 2008 USA (87) <b>Lumbar</b>	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not reported)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral	SF-36 physical component subscale Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 7, 8, 10, 7	NR	Both groups showed substantial improvements over baseline, with

<b>Spine</b>		ICBG n=52		lumbar fusion plus rhBMP2 or ICBG	ICBG 7, 9, 10, 7		no significant intergroup differences
Haid et al., 2004 USA (88) <b>Lumbar Spine</b>	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4)	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) interbody fusion cages plus rhBMP2 or ICBG	<p>SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 ~5, ~10, ~12, ~14, ~14</p> <hr/> <p>Motor function Mean score improvement (points) 24 mos rhBMP2 4.5</p> <hr/> <p>Sensory function Mean score improvement (points) 24 mos rhBMP2 8.0</p> <hr/> <p>Reflex function Mean score improvement (points) 24 mos rhBMP2 7.0</p>	Overall neurological success 24 mos rhBMP2 100	Overall neurological success rate represents a combination of the four neurological measurements

					<p>Straight leg raise Mean score improvement (points) 24 mos rhBMP2 48</p>		
					<p>Median days to return to work rhBMP2 43</p>		
		ICBG N=33			<p>SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG ~2, ~6, ~6, ~6, ~11</p>	ICBG 100	
					<p>Motor function Mean score improvement (points) 24 mos ICBG 2.8</p>		
					<p>Sensory function Mean score improvement (points) 24 mos ICBG 2.8</p>		

					<p>Reflex function Mean score improvement (points) 24 mos ICBG 5.4</p>		
					<p>Straight leg raise Mean score improvement (points) 24 mos ICBG 39</p>		
					<p>Median days to return to work ICBG 137 (p=NSD)</p>		
<p>Johnsson et al., 2002 Sweden (92) <b>Lumbar Spine</b></p>	<p>Multicenter nonblinded RCT</p>	<p>rhBMP7 n=10 (7 mg/pt)</p>	<p>single-level lumbar DDD</p>	<p>single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG</p>	<p>NR</p>	<p>NR</p>	
		<p>ICBG n=10</p>					
<p>Kanayama et al., 2006 Japan, Cleveland</p>	<p>Multicenter nonblinded RCT</p>	<p>rhBMP7 n=9 (7 mg/pt)</p>	<p>single-level lumbar DDD</p>	<p>single-level primary instrumented posterolateral</p>	<p>NR</p>	<p>NR</p>	

(93) <b>Lumbar Spine</b>		AGB/CRM n=10		lumbar fusion with rhBMP7 or AGB/CRM			
Mummaneni et al., 2004 USA (100) <b>Lumbar Spine</b>	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	Prolo Scale Functional status subscale Mean score at F/U rhBMP2/AGB 3.8±0.9	NR	No statistical analysis
		ICBG N=19			ICBG 4.0±0.7		
Pradhan et al., 2006 USA (101) <b>Lumbar Spine</b>	Prospective consecutive patient single- center cohort study	rhBMP2 n=9 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	NR	NR	Study only reported fusion data
		ICBG n=27					
Singh et al., 2006 USA (102) <b>Lumbar</b>	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral	NR	NR	

<b>Spine</b>		ICBG N=11		lumbar fusion with rhBMP2 plus ICBG or ICBG alone			
Slosar et al., 2007 USA (103) <b>Lumbar Spine</b>	Prospective consecutive patient single- center cohort study	rhBMP2 n=45 (3-9 mg/pt)	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)	NR	NR	
		ALG N=30					
Vaccaro et al., 2008 USA (94) <b>Lumbar Spine</b>	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	Neurological success 36+ mos rhBMP7 84	Neurological success is a composite outcome comprising muscle strength, reflexes, sensation, and straight leg raise
		ICBG n=86				ICBG 80	



Vaccaro et al., 2008 USA (95) <b>Lumbar Spine</b> 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)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	Patients in both groups displayed increases in the SF-36 physical component subscale, increasing from the 25th percentile, reaching age-matched normative values at 48 mos. (data not shown)	
		ICBG n=12					
Baskin et al., 2003 USA (89) <b>Cervical Spine</b>	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 9, 13, 14, 14, 17	SF-36 physical component subscale 24 mos rhBMP2/ALG 92	No significant differences between group
					SF-36 mental component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 19, 16, 22, 22, 22	SF-36 mental component subscale 24 mos rhBMP2/ALG 92	

						Neurological status 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 94, 100, 88, 100, 100	
		ICBG/ALG n=15				SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG/ALG 7, 12, 14, 16, 16	SF-36 physical component subscales 24 mos ICBG/ALG 100
						SF-36 mental component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG/ALG 10, 5, 12, 8, 7	SF-36 mental component subscales 24 mos ICBG/ALG 75
							Neurological status 1.5, 3, 6, 12, 24 mos ICBG/ALG 100, 100, 100, 93, 100
Butterman et al., 2008 (104) <b>Cervical Spine</b>	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt)	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented	NR	Neurological deficits manifested as weakness and altered sensation rhBMP2/CRA 100	

		ICBG n=36		d ACDF with rhBMP2/CRA or ICBG		ICBG 100	
Crawford et al., 2009 USA (105) <b>Cervical Spine</b>	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt)	single- or multi-level posterior cervical stenosis, ACDF nonunion, or unstable spondylosis	single- or multi-level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG	NR	NR	
		ICBG n=36					
Smucker et al., 2006 (106) <b>Cervical Spine</b>	Retrospective case-control	rhBMP2/CRA n=69 (dose NR)	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	NR	
		CRA n=165					
Vaidya et al., 2007 (107) <b>Cervical Spine</b>	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt)	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	NR	NR	
		ALG/DBM n=24					

Boraiah et al., 2009 USA (108) <b>Acute Tibial Fractures</b>	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt)	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	NR	NR	
		(2) n=23 no BMP					
Jones et al., 2006 USA (90) <b>Acute Tibial Fractures</b>	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	NR only in a graph	SMFA performance index Mean change from baseline to 12 months BMP -23.9	
						SMFA bother indec BMP -24.6	
		(2) n=15 autogenous bone graft				SMFA performance index Mean change from baseline to 12 months No BMP -22.2	
		SMFA bother indec No BMP -20.3					
Ristiniemi et al., 2007 Finland (110) <b>Acute Tibial Fractures</b> (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Mean duration of external fixation in weeks: BMP: 15(9 to 37)	NR	
Mean length of sick leave in months: BMP: 6.3 (3 to 13)							

					<p>Restriction in range of movement dorsiflexion: BMP: 12 (-42 to 5)</p>		
					<p>Restriction in range of movement plantar flexion: BMP: 13 (50 to 5)</p>		
					<p>Secondary intervention due to delayed healing: BMP: 2</p>		
		Matched Zone 43 fracture (OREF) N=20			<p>Mean duration of external fixation in weeks: Matched 21.4 (10 to 40) P=.037</p>		
					<p>Mean length of sick leave in months: Matched 9 (4 to 15) P= .018</p>		
					<p>Restriction in range of movement dorsiflexion: Matched 10 (-33 to 6) P=.71</p>		
					<p>Restriction in range of movement plantar flexion: Matched: 7 (20 to 8) P=.3</p>		

					Secondary intervention due to delayed healing: Matched 7 P=.13		
Bilic et al., 2006 Croatia, Netherlands (96) <b>Miscellaneous Off-Label Uses</b>	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG	symptomatic proximal pole scaphoid nonunion	revision of nonunion	Mean grip strength (kg) 4, 12 mos rhBMP7/AGB 36±4, 41±5	NR	Patients in all 3 groups showed improvement of all functional measures and clinical outcomes throughout the 24 mos. F/U
					Mean pinch strength (kg) 4, 12 mos rhBMP7/AGB 8±2, 10±2		
		n=6 (3.5 mg/pt)			Mean grip strength (kg) 4, 12 mos rhBMP7/ALG 31±3, 37±3		
					Mean pinch strength (kg) 4, 12 mos rhBMP7/ALG 6±1, 9±2		
		ICBG n=6			Mean grip strength (kg) 4, 12 mos ICBG 28±4, 35±4		

					Mean pinch strength (kg) 4, 12 mos ICBG 6±1, 9±2			
Dickinson et al., 2008 USA (91) <b>Miscellaneous Off-Label Uses</b>	Single-center RCT	rhBMP2/ACS n=9 (dose not given)	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR	NR		
		ICBG n=12						
Ekrol et al., 2008 UK (97) <b>Miscellaneous Off-Label Uses</b>	Prospective randomized cohort	rhBMP2 Non bridging external fixation N=4	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	Pre-op, 52-wks, % change Ability to undertake daily living activities: rhBMP2 Non bridging external fixation 77,85,10%	P values all non significant for outcome measures.		
					Grip strength: rhBMP2 Non bridging external fixation 69,78,13%			Ability to undertake daily living activities: rhBMP2 Non bridging external fixation 10%
					Pronation: rhBMP2 Non bridging external fixation 81,85,5%			Grip strength: rhBMP2 Non bridging external fixation 13%

				Supination rhBMP2 Non bridging external fixation 74,58,-22%	Pronation: rhBMP2 Non bridging external fixation 5%
				Flexion rhBMP2 Non bridging external fixation 40,48,20%	Supination rhBMP2 Non bridging external fixation -22%
				Extension rhBMP2 Non bridging external fixation 57,53,-7%	Flexion rhBMP2 Non bridging external fixation 20%
				Ulnar deviation rhBMP2 Non bridging external fixation 24,23,-4%	Extension rhBMP2 Non bridging external fixation -7%
				Radial deviation rhBMP2 Non bridging external fixation 20,28,40%	Ulnar deviation rhBMP2 Non bridging external fixation -4%
				No significant P values	Radial deviation rhBMP2 Non bridging external fixation 40%



		Bone graft Non bridging external fixation N=6			Pre-op, 52-wks, % change Ability to undertake daily living activities: Bone graft Non bridging external fixation 65,100,54%	Ability to undertake daily living activities: Bone graft Non bridging external fixation 54%	
					Grip strength: Bone graft Non bridging external fixation 38,69,82%	Grip strength: Bone graft Non bridging external fixation 82%	
					Pronation: Bone graft Non bridging external fixation 86,82,-5%	Pronation: Bone graft Non bridging external fixation -5%	
					Supination Bone graft Non bridging external fixation 68,82,21%	Supination Bone graft Non bridging external fixation 21%	
					Flexion Bone graft Non bridging external fixation 42,60,43%	Flexion Bone graft Non bridging external fixation 43%	
					Extension Bone graft Non bridging external fixation 46,49,7%	Extension Bone graft Non bridging external fixation	

				Ulnar deviation Bone graft Non bridging external fixation 22,30,36%	Ulnar deviation Bone graft Non bridging external fixation 36%	
				Radial deviation Bone graft Non bridging external fixation 22,25,14%	Radial deviation Bone graft Non bridging external fixation 14%	
		RhBMP-7 internal fixation w/ pi-plate N=10		Pre-op, 52-wks, % change  Ability to undertake daily living activities: RhBMP-7 internal fixation w/ pi-plate 49, 91, 86%	Ability to undertake daily living activities: RhBMP-7 internal fixation w/ pi-plate 86%	
				Grip strength: RhBMP-7 internal fixation w/ pi-plate 37, 81,119%	Grip strength: RhBMP-7 internal fixation w/ pi-plate 119%	
				Pronation: RhBMP-7 internal fixation w/ pi-plate 66,81, 23%	Pronation: RhBMP-7 internal fixation w/ pi-plate 23%	
				Supination RhBMP-7 internal fixation w/ pi-plate 60,79,32%	Supination RhBMP-7 internal fixation w/ pi-plate 32%	

					Flexion RhBMP-7 internal fixation w/ pi-plate 35,38,9%	Flexion RhBMP-7 internal fixation w/ pi-plate 9%	
					Extension RhBMP-7 internal fixation w/ pi-plate 50,43,-14%	Extension RhBMP-7 internal fixation w/ pi-plate -14%	
					Ulnar deviation RhBMP-7 internal fixation w/ pi-plate 18,25,39%	Ulnar deviation RhBMP-7 internal fixation w/ pi-plate 39%	
					Radial deviation RhBMP-7 internal fixation w/ pi-plate 16,23,44%	Radial deviation RhBMP-7 internal fixation w/ pi-plate 44%	
		Bone graft internal fixation w/ pi-plate N=10			Pre-op, 52-wks, % change  Ability to undertake daily living activities: Bone graft internal fixation w/ pi-plate 61,84, 38%	Ability to undertake daily living activities: Bone graft internal fixation w/ pi-plate 38%	
					Grip strength: Bone graft internal fixation w/ pi-plate 48,73,52%	Grip strength: Bone graft internal fixation w/ pi-plate 52%	

					Pronation: Bone graft internal fixation w/ pi-plate 67,82,22%	Pronation: Bone graft internal fixation w/ pi-plate 22%	
					Supination Bone graft internal fixation w/ pi-plate 63,78,24%	Supination Bone graft internal fixation w/ pi-plate 24%	
					Flexion Bone graft internal fixation w/ pi-plate 24,31,29%	Flexion Bone graft internal fixation w/ pi-plate 29%	
					Extension Bone graft internal fixation w/ pi-plate 43,37,-14%	Extension Bone graft internal fixation w/ pi-plate -14%	
					Ulnar deviation Bone graft internal fixation w/ pi-plate 17,28,65%	Ulnar deviation Bone graft internal fixation w/ pi-plate 65%	

					Radial deviation Bone graft internal fixation w/ pi-plate 19,25,32%	Radial deviation Bone graft internal fixation w/ pi-plate 32%	
Geesink et al., 1999 Netherlands (98) <b>Miscellaneous Off-Label Uses</b>	Prospective double-blind randomized study	Untreated N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductive materials	Mean BMD (g/cm <sup>2</sup> ) of the fibular defect at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, 12 mths: (untreated, dmb, collagen type I, OP-1 on collagen type I): .44, .48, .47, .46, .43, .44	Untreated and collagen groups BMD stayed approximately the same while OP-1 and DMB group increased by about 80%. Untreated + collagen vs. DMB p=.001, Untreated + collagen vs OP-1 p=.0038	
		DMB N=6			.51, .51, .57, .70, .80, 1.01		
		Collagen type I N=6			.38, .43, .42, .43, .43, .44		
		OP-1 (2.5mg) with Collagen type I N=6			.45, .47, .53, .64, .69, .82		
Karrholm et al., 2006 UK (111) <b>Miscellaneous Off-Label Uses</b>	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	Harris hip score is a composite that measures pain and activities of daily living, including walking, sitting, ability to dress oneself, presence of a limp (see table on pain outcomes for HHS results)	NR	
		Cups ALG n=10					
		Stems rhBMP7/ALG (1 g/pt) n=11					
		Stems ALG n=30					

Maeda et al., 2009 USA, Japan (109) <b>Miscellaneous Off-Label Uses</b>	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	NR	NR	
		ICBG n=32					