

Appendix 1 Table H. Off-Label Comparative Study BMP-Related Adverse Events

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	No. adverse events (%) p-value	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 (40 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	1 of 22 (4.5) rhBMP2/CRM recipients had transient anti- rhBMP2 titer postsurgery	No adverse sequelae reported, nor complications attributable to rhBMP2/CRM
		rhBMP2/CRM alone n=11 (40 mg/pt)				
		ICBG plus TSRHSS n=5				
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)	single-level lumbar lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	Among 78 patients tested in the rhBMP2 group, none had elevated antibody response to the protein 7 (9) in the rhBMP2 group, and 4 (8) in ICBG group had uneventful elevated antibody reponse to bovine collagen	Origin of antibody responsiveness to bovine collagen unclear
		ICBG N=52				
Dimar et al., 2009 USA (86) Lumbar Spine Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006	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	None reported	
		ICBG n=224				

rec# 5480; Glassman et al., 2005, rec# 8040						
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	None reported	
Glassman et al., 2008 USA (87) Lumbar Spine	Multicenter nonblinded RCT	rhBMP2/ACS 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	None reported	
Haid et al., 2004 USA (88) Lumbar Spine	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4) ICBG N=33	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) interbody fusion cages plus rhBMP2 or ICBG	None reported 3 (9%) in the rhBMP2 group, and 5 (15%) in ICBG group had uneventful elevated antibody reponse to bovine collagen	No adverse sequelae reported
Johnsson et al., 2002 Sweden (92) Lumbar Spine	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	None reported	No adverse events of any type were reported
Kanayama et al., 2006 Japan, Cleveland (93) Lumbar Spine	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	None reported	
Mummaneni et al., 2004 USA (100) Lumbar Spine	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2	None reported	

				plus AGB or ICBG alone		
Pradhan et al., 2006 USA (101) Lumbar Spine	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	single-level lumbar DDD	single-level primary anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	None reported	
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	None reported	
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)	None reported	
Vaccaro et al., 2008 USA (94) Lumbar Spine	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG n=86	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Among pts tested for rhBMP7 antibody titers, 26% were positive for anti-rhBMP7 neutralizing antibodies versus 1.2% of ICBG recipients	No significant associations were observed between neutralizing antibody activity, clinical success, and safety parameters No other adverse events related to rhBMP7 were reported
Vaccaro et al., 2008 USA (95) Lumbar Spine Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184),	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	None reported	

and Vaccaro et al., 2005, (185)						
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	None reported	
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	None reported except cervical swelling	See table on perioperative complications for data on cervical swelling
Crawford et al., 2009 USA (105) Cervical Spine	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt) ICBG n=36	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	
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	Adjustment for demographic differences showed only rhBMP2 use was significantly associated with cervical swelling (OR 10.1, 95% CI 3.4, 29.7, p < 0.0001)	See table on perioperative complications for data on cervical swelling
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 with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	None reported except cervical swelling	See table on perioperative complications for data on cervical swelling
Boraiah et al., 2009 USA (108) Acute Tibial Fractures	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt) (2) n=23 no BMP	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	Development of HO BMP 10(59%) No BMP 1(4%)	
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	Soft tissue swelling BMP 12 (80%) Epidermal erythema BMP 5(33%) Infection	

					BMP 3(20%)	
					Heterotopic ossification BMP 1(7%)	
		(2) n=15 autogenous bone graft			Soft tissue swelling No BMP 9(60%)	
					Epidermal erythema No BMP 0	
					Infection No BMP 1(7%)	
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	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Pin track infection (discharge, redness, swelling pain, and positive bacterial culture) were found in 6 BMP patients (30%) and four in matched patients (20%)	
		Matched Zone 43 fracture (OREF) N=20			In BMP group 1 pt developed symptomless calcification of soft tissue	
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	None reported	
		rhBMP7/ALG n=6 (3.5 mg/pt)				
		ICBG n=6				
Dickinson et al., 2008 USA (91) Miscellaneous Off- Label Uses	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	None reported	
		ICBG n=12				
Ekrol et al., 2008 UK (97) Miscellaneous Off- Label Uses	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	rhBMP2 Non bridging external fixation: 2 pts. developed extensive osteolysis, 1 pt dorsal defect	
		Bone graft Non			Bone graft	

		bridging external fixation N=6			Non bridging external fixation: 1 pt had recurrence of deformity	
		RhBMP-7 internal fixation w/ pi-plate N=10			RhBMP-7 internal fixation w/ pi-plate 5 pts had dorsal defect, 2 pts had non-union, 1 rupture of extensor pollicis longus	
		Bone graft internal fixation w/ pi-plate N=10			Bone graft internal fixation w/ pi-plate: 5 donor site hematoma, 1 pt rupture all extensor tendons on the dorsum of wrist	
Geesink et al., 1999 Netherlands (98) Miscellaneous Off-Label Uses	Prospective double-blind randomized study	Untreated N=6 DMB N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductive materials	Positive antibody reaction in two pts for anti-collagen at 10 weeks in collagen type I group (33.3%) 1 pt in OP-1 group had pseudoarthrosis requiring resection 1.5 yrs post-op (16.6%)	
		Collagen type I N=6				
		OP-1 (2.5mg) with Collagen type I N=6				
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	None reported	
		Cups ALG n=10				
		Stems rhBMP7/ALG (1 g/pt) n=11				

		Stems ALG n=30				
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) ICBG n=32	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	None reported	