

Appendix 1 Table G. On-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., 2000 USA (71) Lumbar Spine	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	rhBMP2 3 of 11 (27) had increased antibovine collagen Type I titers	No adverse sequelae reported
		ICBG n=3				
Burkus et al., 2002 USA (72) Lumbar Spine	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	0.7% and 0.8% of each group had anti-rhBMP2 titers 3mos. postsurgery	No adverse sequelae reported
		ICBG n=136				
Burkus et al., 2003 USA (182) Lumbar Spine Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages	None reported	
		ICBG n=402				
Dawson et al., 2009 USA (73) Lumbar Spine	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	None reported	
		ICBG n=21				
Govender et al. for the BESTT study group 2002 South Africa (74) Open Tibial Fractures	Multi-center, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	None reported except for BMP-2 antibodies (1) 2%	
		(2)rhBMP2/CRM n=149 (12 mg/patient)			(2) 6%	
		(3) n=150 Standard care (IM nail fixation and soft tissue			(3) 1%	

		management)				
Swiontkowski et al., 2006 USA (81) Open Tibial Fractures Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient) (2) n=169 Standard care (IM nail fixation and soft tissue management)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR	
Boyne et al., 2005 USA (75) Maxillofacial and Dental	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Facial edema rhBMP2/ACS 0.75 mg/mL 7 (39%)	Most (67%) immune responses were transient No clinical manifestations of an immune response or neutralizing effect toward rhBMP2 were identified
					Immune sensitization to rhBMP2 0.75 mg/mL 0	
					Immune sensitization to collagen rhBMP2/ACS 0.75 mg/mL 2 (11%)	
					Facial edema 1.50 mg/mL 14 (82%)	
					Immune sensitization to rhBMP2 1.50 mg/mL 2 (12%)	
					Immune sensitization to collagen 1.50 mg/mL 4 (24%)	
					Facial edema AGB 5 (38%)	
	rhBMP2/ACS (15-48 mg/pt) n=17					
	AGB n=13					

					(p=0.0227, 0.0152, 1.50 mg/mL vs AGB and 0.75 mg/mL groups)	
					Immune sensitization to rhBMP2 AGB 0	
					Immune sensitization to collagen AGB 3 (23%)	
Fiorellini et al., 2005 USA (76) Maxillofacial and Dental	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22	≥ 50% buccal bone loss of the extraction socket(s)	extraction socket augmentation	None reported	
		rhBMP2/ACS(mn dose 1.9 mg/pt) n=21				
		Placebo n=17				
		No Tx n=20				
Triplett et al., 2009 USA (77) Maxillofacial and Dental	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt)	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Facial edema occurred at a significantly higher rate (p=0.048) in rhBMP2/ACS recipients than in AGB recipients (data not reported in paper)	No clinical manifestations of an immune response or neutralizing effect toward rhBMP2 were identified
		AGB n=80				
					Immune sensitization to rhBMP7 2 (2%)	
					Immune sensitization to collagen rhBMP7/ACS 24 (29%)	
					Immune sensitization to rhBMP7 AGB 0	
					Immune sensitization to collagen	

					AGB 25 (32%)	
van den Bergh et al., 2000 Netherlands (82) Maxillofacial and Dental	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	partly edentulous	maxillary sinus floor augmentation	None reported	
Calori et al., 2008 Italy (78) Long Bone Nonunion	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	post-traumatic atrophic nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	None reported	Did not perform immunological analysis for antibodies to rhBMP7
Dahabreh et al., 2008 (83) Long Bone Nonunion	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9 mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	None reported	
Friedlaender et al., 2001 (79) Long Bone Nonunion	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt) AGB n=61	tibial nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	IM rod fixation with rhBMP7/ACS or AGB	Transient, low titers of anti-rhBMP7 antibodies reported in 6 patients (10%) Anticollagen antibodies reported in 3 patients treated with rhBMP7/ACS	No adverse events were related to sensitization