

**Appendix 1 Table E. On-Label Comparative Study Surgery and Perioperative Outcomes**

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Mean OR time (hr)	Mean estimated blood loss (mL)	Mean hospital LOS (days)	Perioperative complications (n)	Second surgeries (n)	Comment
Boden et al., 2000 USA (71) <b>Lumbar Spine</b>	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11	single-level DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	rhBMP2 1.9±0.2 (2.3-4.2)	rhBMP2 95±31 (25-400)	rhBMP2 2.0±0.6 (0-6)	rhBMP2 wound dehiscence (1)	ICBG 1 (supplemental instrumentation on fusion at 18 mos)	Besides OR time, no other significant differences reported
		ICBG n=3			ICBG 3.3±0.6 (1.0-3.2) p=0.006	ICBG 167±117 (50-400)	ICBG 3.3±1.4 (1-6)	ICBG urinary retention (1)		
Burkus et al., 2002 USA (72) <b>Lumbar Spine</b>	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	rhBMP2 1.6	rhBMP2 110	rhBMP2 3.1	rhBMP2 vascular (6)	rhBMP2 11 (2 implant removals, 7 supplemental posterior fixations for pseudarthrosis, 2 others for pain)	No significant differences reported
		ICBG n=136			ICBG 2.0	ICBG 153	ICBG 3.3	ICBG vascular (5) iliac crest pain (8)		
Burkus et al., 2003 USA	Retrospective combined comparative	rhBMP2 n=277 (dose NR)	single-level lumbar DDD	single-level primary anterior	rhBMP2 1.8±0.8	rhBMP2 127±295	rhBMP2 2.2±1.7	NR	rhBMP2 75 (8 revisions, 7	Significantly more reoperations

(182) <b>Lumbar Spine</b>  Note: may include pts in Burkus et al., 2003, (80)	analysis			lumbar fusion with interbody fusion cages					removals, 28 supplemental fixations, 32 reoperations)	were reported in ICBG group than rhBMP2 group (p=0.0036)
		ICBG n=402			ICBG 2.7±1.3 p< 0.001	ICBG 193±414 p=0.024	ICBG 3.1±3.2 p < 0.001	ICBG 30 (1 revision, 2 removals, 7 supplemental fixations, 2 reoperations)		
Dawson et al., 2009 USA (73) <b>Lumbar Spine</b>	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	rhBMP2/CRM 2.4±0.7 (95% CI, 2.1, 2.7)	rhBMP2/CRM 329±212 (95% CI, 241, 417)	rhBMP2/CRM 4.0±1.4 (95% CI, 3.4, 4.6)	rhBMP2/CRM incidental durotomy (1)	rhBMP2/CRM 2 (failures at index site)	No significant differences reported between groups
		ICBG n=21			ICBG 2.8±0.8 (95% CI, 2.2, 3.0)	ICBG 452±210 (95% CI, 357, 548)	ICBG 4.1±1.1 (95% CI, 3.6, 4.6)	ICBG incidental durotomy (1) wound infection (1)		
Govender et al. for the BESTT study group 2002 South Africa (74) <b>Open Tibial Fractures</b>	Multicenter, 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	NR	NR	NR	Infection (1) Types I and II 12 (15%) Types IIIA and IIIB 19 (29%) Hardware Failure (1) 25 (17%) Pain all body (1) 97 (67%)	(1) 47	

								Death One per group		
								Antibodies to BMP-2 (1) 3, 2%		
								Antibodies to Type I collagen (1) 22, 15%		
		rhBMP2 (2) n=149 (12 mg/patient)						Infection (2) Types I and II 15 (21%) Types IIIA and IIIB 15 (24%)	(2) 30	
								Hardware Failure (2) 16 (11%)		
								Pain all body (2) 98 (68%)		
								Antibodies to BMP-2 (2) 9, 6%		
								Antibodies to Type I collagen (2) 29, 20%		
		(3) n=150 Standard care (IM nail fixation and soft tissue management						Infection (3) Types I and II 13 (15%) Types IIIA and IIIB 26 (44%)	(3) 58	
								Hardware Failure		

								(3) 90 (65%)		
								Pain all body (3) 116 (79%)		
								Antibodies to BMP-2 (3) 1, 1%		
								Antibodies to Type I collagen (3) 9, 6%		
Swiontkowski et al., 2006 USA (81) <b>Open Tibial Fractures</b>  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)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR	NR	NR	Type III subgroup Infection (1) 13 (21%)	Type III subgroup (1) 6 (9%)	Data was analyzed only for two subgroups Type III and reamed nailing
		(2) n=169 Standard care (IM nail fixation and soft tissue management )						Reamed nailing subgroup (1) 12(18%)	Reamed nailing subgroup (1) 5 (8%)	
								Type III subgroup Infection (2) 26 (40%)	Type III subgroup Infection (2) 18 (28%)	
								Reamed nailing subgroup (2) 13(27%)	Reamed nailing subgroup (2) 7 (15)	
Boyne et al., 2005 USA (75) <b>Maxillofacial and Dental</b>	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	NR	NR	NR	Total 546, of which 261 occurred during first 4 mos, 56% were mild, 38% moderate,	rhBMP2/ACS 0.75 mg/mL 3 (11%) (additional augmentation )	Perioperative complications were generally consistent with the surgical procedures,
rhBMP2/ACS (15-48 mg/pt)	rhBMP2/ACS 1.50 mg/mL									

		n=17						transient	2 (12%) (additional augmentation )	distributed equally between groups except for edema (AGB> rhBMP2/ACS ), face edema (rhBMP2 > AGB), and skin rash (AGB > rhBMP2/ACS )
		AGB n=13							AGB 0	
Fiorellini et al., 2005 USA (76) <b>Maxillofacial and Dental</b>	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	NR	NR	NR	Total 250 for 78 of 80 pts but not specified except for facial edema in pts who received rhBMP2/ACS	Secondary sugmentation for dental implant rhBMP2/ACS 0.75 mg/mL 10 (45%)	
		rhBMP2/ACS (mn dose 1.9 mg/pt) n=21							rhBMP2/ACS 1.50 mg/mL 3 (14%)	
		Placebo n=17							Placebo 7 (41%)	
		No Tx n=20							No Tx 11 (55%) (p < 0.01 vs no tx)	
Triplett et al., 2009 USA	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB	< 6 mm alveolar bone height in the posterior	staged bilateral or unilateral maxillary	NR	NR	NR	NR	NR	Perioperative complications were generally

(77) <b>Maxillofacial and Dental</b>		n=80	maxilla	sinus floor augmentation						consistent with the surgical procedures
van den Bergh et al., 2000 Netherlands (82) <b>Maxillofacial and Dental</b>	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	partly edentulous	maxillary sinus floor augmentation	NR	NR	NR	NR	NR	
Calori et al., 2008 Italy (78) <b>Long Bone Nonunion</b>	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt)	post-traumatic atrophic nonunion for $\geq 9$ 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	NR	NR	NR	NR	rhBMP7 3 (2 had no radiologically visible callus formation)	None of the patients who did not form callus reached a state of union
		PRP n=60							PRP 13 (9 had no callus formation)	
Dahabreh et al., 2008 (83) <b>Long Bone Nonunion</b>	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt)	tibial fracture nonunion with clinical and radiographic failure to progress to union for $\geq 9$ mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	NR	NR	rhBMP7/ACS 8.7 (7-11)	rhBMP7/ACS wound infection 1	rhBMP7/ACS 1 (nail dynamization)	
		ICBG n=12					ICBG 10.7 (9-13)	ICBG wound infection 1	ICBG 3 (2 exchange IM nailing, 1 nail dynamization)	
Friedlaender et al.,	Multicenter, partially	rhBMP7/ACS n=61	tibial nonunion for	IM rod fixation with	rhBMP7/ACS 2.8	rhBMP7/ACS 254	rhBMP7/ACS 3.7	rhBMP7/ACS arthralgia,	rhBMP7/ACS 1 (1.6%)	Second surgeries not

2001 (79) <b>Long Bone Nonunion</b>	blinded RCT		≥ 9 mos, with no signs of healing over the last 3 mos	rhBMP7/ACS or AGB	(0.97-7)	(10-1150)	(0-18)	lower leg 8 (13%)		described
							pain, multiple sites 8 (13%)	osteomyelitis lower leg 2 (3%)		
		AGB (3.5-7.0 mg/pt) n=61			AGB 2.97 (0.97-7)	AGB 345 (35-1200)	AGB 4.1 (1-24)	AGB arthralgia, lower leg 5 (%)	AGB 6 (9.8%)	
								pain, multiple sites 9 (15%)		
								osteomyelitis lower leg 13 (21%) (p=0.002)		
								pyrexia 28 (46%)		
								vomiting 19 (31%)		
								leg edema 7 (11%)		

								hardware complication 34 (56%)		
								hematoma 8 (13%)		
								infection 12 (20%)		