Appendix 1 Table K. On-Label Comparative Study Pain Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score (p-value)	Percent improved or success (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	Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 9, 12, 22, 25	Oswestry DI ≥ 15% improvement 3, 6, 12, 24 mos rhBMP2 55, 64, 91, 91	Success for ODI defined as ≥ 15% improvement over baseline score
		ICBG n=3			Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos ICBG 35, -18, 7, 8, 15	ICBG 0, 67, 67, 67	
					Iliac crest pain postharvest NR		
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	Oswestry DI Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 12, 20, 25, 28, 30	Oswestry DI 12, 24 mos rhBMP2 85, 84	Success for ODI defined as ≥ 15% improvement over baseline score Both groups showed significant improvements from baseline, but there were no significant differences between groups in mean score or rates
					Back pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 6.5, 7.1, 7.2, 7.8, 8.5	Back pain (> 3 point improvement) 1.5, 3, 6, 12, 24 mos rhBMP 77, 74, 78, 79, 75	
					Leg pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 5.0, 5.7, 6.2, 6.2, 6.2	Leg pain (> 3 point improvement if baseline score > 10 points, or maintenance of score if < 10) 12, 24 mos rhBMP2 72, 80	
		ICBG n=136			Oswestry DI Mean score improvement (points)	Oswestry DI 12, 24 mos	

					1.5, 3, 6, 12, 24 mos ICBG 55, 14, 21, 26, 29, 31	ICBG 86, 82	
					Back pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG 7.3, 7.1, 7.2, 7.7, 8.2	Back pain (> 3 point improvement) 1.5, 3, 6, 12, 24 mos ICBG 76, 78, 72, 73, 79	
					Leg pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG 4.1, 5.7, 6.2, 5.9, 6.2	Leg pain (> 3 point improvement if baseline score > 10 points, or maintenance of score if < 10) 12, 24 mos ICBG 73, 74	
					Iliac crest pain postharvest Mean score (20 point VAS) 0, 24 mos 12.7, 1.8	Iliac crest pain postharvest % at 24 mos 32	
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	Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 31, 26, 30, 31	NR	Both groups improved over time
					SF-36 pain index subscale Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 27, 32, 36, 39		
		ICBG n=402			Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos ICBG 5, 20, 23, 26 (p=0.0041, 0.0053, 0.0013, 0.0023 rhBMP2 vs ICBG)		

					SF-36 pain index subscale Mean score improvement (points) 3, 6, 12, 24 mos ICBG 20, 24, 29, 33 (p=0.0002 at 3, 6, 12 mos. and 0.0008 at 24 mos, rhBMP2 vs ICBG)		
					Iliac crest pain postharvest NR		
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	Oswestry DI Mean score improvement (points) 24 mos rhBMP2/CRM 28	Oswestry DI > 20% improvement 24 mos rhBMP2/CRM 91	Overall success rate was 81% in rhBMP2/CRM group and 55% in the ICBG group (p NSD)
					Back pain Mean score improvement (points) 24 mos rhBMP2/CRM 9.6		
					Leg pain Mean score improvement (points) 24 mos rhBMP2/CRM 9.3		
		ICBG n=21			Oswestry DI Mean score improvement (points) 24 mos ICBG 23	ICBG 70	
					Back pain Mean score improvement (points) 24 mos ICBG 7.2		
					Leg pain Mean score improvement (points) 24 mos		

					ICBG 7.2 Iliac crest pain postharvest NR		
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) rhBMP2 (2) n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue management)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	Overall pain (1) 67% (2) 68% (3) 79% (0.0389 for comparison with 1, and 2) Iliac crest pain postharvest NR	NR	
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 Iliac crest pain postharvest NR	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 rhBMP2/ACS (15-48 mg/pt) n=17 AGB n=13	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	NR Iliac crest pain postharvest 4 mos 38	NR	
Fiorellini et al.,	Double-blind,	rhBMP2/ACS	≥ 50% buccal	extraction	NR	NR	

2005 USA (76) **Maxillofacial and Dental**	multicenter randomized, placebo-control dose-comparison, safety and efficacy study	(mn dose 0.9 mg/pt) n=22 rhBMP2/ACS (mn dose 1.9 mg/pt) n=21 Placebo n=17 No Tx n=20	bone loss of the extraction socket(s)	socket augmentation			
Triplett et al., 2009 USA (77) **Maxillofacial and Dental**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Iliac crest pain postharvest Reported to have occurred in "many" patients Intraoral harvest site pain % at 6 mos 17	NR	
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	Iliac crest pain postharvest NR	NR	
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	Time to reach clinical union rhBMP7 md 3.5±0.5 mos PRP md 4±0.6 mos	Clinical union rhBMP7 87 Proportion pain-free 9 mos rhBMP7 upper extremity 97 lower extremity 80 Clinical union PRP 68 (p=0.016) Proportion pain-free	Clinical union: pain-free full-weight bearing for lower extremity fractures, pain-free movement for upper extremity fractures

						9 mos PRP upper extremity 91	
						lower extremity 81	
Dahabreh et al., 2008 (83) **Long Bone Nonunion**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt)	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	Patient-controlled analgesia for iliac crest pain postharvest % postoperative 33	Clinical union rhBMP7/ACS 100	Clinical union defined as painless full-weight bearing
		ICBG n=12				ICBG 100	
Friedlaender et al., 2001 (79) **Long Bone Nonunion**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt)	tibial nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	IM rod fixation with rhBMP7/ACS or AGB	Autograft harvest site pain 0, 6, 12 mos 100 (80% moderate or severe), 20, 13	Pain on weight-bearing 9 mos rhBMP7/ACS 89	Clinical success defined as full-weight bearing with les than severe pain at the fracture site, and no further surgical intervention fo rth epurpose of enhancing repair
						Combined clinical success 9 mos rhBMP7/ACS 81	
		AGB n=61				Pain on weight-bearing 9 mos AGB 90	
						Combined clinical success 9 mos AGB 85	