Appendix 1 Table I. On-Label Comparative Study Radiographic Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Successful outcome (%) (p-value)	Time to successful outcome mn ± SD (rng) (p-value)	Definition of successful outcome	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11 ICBG n=3	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	3, 6, 12, 24 mos. rhBMP2 91, 100, 100, 100 ICBG 67 at all times	NR	Plain radiograph: < 5 degrees of angular motion on flexion-extension film, and absence of radiolucent lines covering 50% or more of implant surfaces CT: presence of continuous trabecular bone growing through both cages Fusion success required agreement among all 5 independent readers unaware of treatment	No evidence of clinically significant (1 mm) graft subsidence in either group, no anteroposterior migration or rotation
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143 ICBG n=136	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	6, 12, 24 mos rhBMP2 97, 97, 94 ICBG 96, 93, 89	NR	Plain radiograph: < 3mm translation, < 5 degrees angular motion on flexion-extension film, and absence of radiolucent lines covering 50% or more of implant surfaces CT: presence of	Secondary surgeries were classified as fusion failures regardless of independent radiologic assessment

							continuous trabecular bone growing through both cages Fusion evaluated by two independent radiologists who were unaware of treatment, a third was consulted for adjudication of disagreement	
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) ICBG n=402	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages	6, 12, 24 mos rhBMP2 95, 96, 94 ICBG 96, 93, 89 (p=0.022 at 24 mos)	NR	Same as Burkus et al., 2002 (rec#11620)	Fusion success difference at 24 mos. statistically significant by ANCOVA
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt) ICBG n=21	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	6, 12, 24 mos rhBMP2/CRM 91, 89, 95 ICBG 58, 65, 67 (p=0.032 at 6 mos)	NR	Presence of bridging trabecular bone between the transverse processes, absence of motion, defined as 3 mm or less of translation and < 5 degrees of angular motion on flexion-extension views, and absence of radiolucent lines through the fusion mass Fusion evaluated by two independent	Thin-cut CT showed progressive formation of bridging bone across the transverse processes and incorporation of the ceramic component

							radiologists who were unaware of treatment, a third was consulted for adjudication of disagreement	
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	(1) 54% (2) 65% P-value 0.0028 in comparison to (3) control group (3) 47%	50% union by (1) 187 days (2) 145 days (3) 184 days	Radiographic evidence of union and fulfillment of clinical criteria including full weight bearing and lack of tenderness at the fracture site.	
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	Type III subgroup (1) 271 days Reamed nailing subgroup (1) 234 Type III subgroup (2) 277 days Reamed nailing subgroup (2) 251	Radiographic evidence of union	Data was analyzed only for two subgroups those with type III open tibial fractures and those who received IM reamed nailing
Boyne et al., 2005 USA (75)	Multicenter randomized dose-comparison,	rhBMP2/ACS (6-24 mg/pt) n=18	< 6 mm alveolar bone height in the	staged bilateral or unilateral maxillary sinus floor	Mean bone height change from baseline at 4 mos. (mm) rhBMP2/ACS	NR	NR	

Maxillofacial and Dental	safety and efficacy study		posterior maxilla	augmentation	0.75 mg/mL 9.47±5.72			
		rhBMP2/ACS (15-48 mg/pt) n=17			1.50 mg/mL 10.16±4.7			
		AGB n=13			AGB 11.29±4.12			
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	Implant positions with adequate bone formation 25, 50, 75% ESL rhBMP2/ACS 0.75 mg/mL 25, 30, 30	NR	Adequate alveolar bone defined as > 6mm in width at narrowest point (buccal to palatal) based on CT scans Three independent masked CT scan reviewers	
		rhBMP2/ACS (mn dose 1.9 mg/pt) n=21			1.50 mg/mL 56, 41, 32			
		Placebo n=17			Placebo 6, 20, 21			
		No Tx n=20			No tx 12, 9, 14			
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	Mean bone height change from baseline at 6 mos. (mm) rhBMP2/ACS 7.83±3.52	NR	NR	Significant overall bone height gain occurred in both groups
		AGB n=80			AGB 9.46±4.11 (p=0.009)			
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial and Dental**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt)	partly edentulous	maxillary sinus floor augmentation	Good quality bone formation at 6 mos rhBMP7/ACS 33	NR	Based on histological analysis, visual bone appearance	
					Mean vertical alveolar process height increase (mm) at 6 mos rhBMP7/ACS			

					5.8±1.6			
		ICBG n=3			Good quality bone formation at 6 mos ICBG 100			
					Mean vertical alveolar process height increase (mm) at 6 mos rhBMP7/ACS ICBG 9.8±2.3			
Calori et al., 2008 Italy (78) **Long Bone Nonunio**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt)	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	9 mos rhBMP7 87	rhBMP7 md 8±0.5 mos	Radiological union: presence and staging of callus at 3 of 4 cortices on both anteroposterior and lateral plain film views, as well as the type of osseointegration (undefined)	Successful completion of treatment was defined as the accomplishment of both radiological and clinical union 4 (7%) in rhBMP7 group and 5 (8%) in PRP group were complicated by infection and failed to progress to union
		PRP n=60			PRP 68 (p=0.016)	PRP md 9±0.5 mos		
Dahabreh et al., 2008 (83) **Long Bone Nonunio**	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	Radiological union rhBMP7ACS 100	rhBMP7/ACS 5.5 (4.7-6.2)	Radiological evidence of bridging callus of all cortices in the two standard planes of plian film radiographs (radiological union)	
		ICBG n=12			ICBG 100	ICBG 6.9 (6.1-7.6) (p < 0.001)		
Friedlaender et al.,	Multicenter, partially	rhBMP7/ACS n=61	tibial nonunion for	IM rod fixation with	9, 24 mos rhBMP7/ACS	NR	Combination of the presence of bridging	Prior autograft procedure had no

2001 (79) **Long Bone Nonunio**	blinded RCT	(3.5-7.0 mg/pt)	≥ 9 mos, with no signs of healing over the last 3 mos	rhBMP7/ACS or AGB	81, 82 Radiographic bridging in at least 1 view rhBMP7/ACS 75		by new bone across the fracture site and on how many of the 4 views this bridging was apparent Consensus of at least 2 of 3 musculoskeletal radiologists unaware of treatment and time following surgery independently assessed anteroposterior, lateral and 2 oblique projection radiographs	influence on clinical and radiographic success rates
					Radiographic bridging in at least 3 views rhBMP7/ACS 62			
		AGB n=61			9, 24 mos AGB 85, 82			
					Radiographic bridging in at least 1 view AGB 84			
					Radiographic bridging in at least 3 views AGB 74			