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 isoluded in	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	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
included in Govender et al., 2002 (74) 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	(2) 251 NR	NR	

and Dental efficacy study
Fiorellini et al., 2005 Double-blind, n=13 rhBMP2/ACS (15-48 mg/pt) n=17 ≥ 50% extraction socket In:0 mg/mL 10.16±4.7 NR Adequate alveolar Biorellini et al., 2005 multicenter randomized, placebo- socket rhBMP2/ACS (mn dose 0.9 mg/pt) ≥ 50% extraction socket Implant positions with adequate bone formation NR Adequate alveolar USA (76) control dose- control dose- maxilofacial and Dental mg/pt) n=22 extraction socket(s) socket(s) augmentation 25, 50, 75% ESL rhBMP2/ACS narrowest point (buccal to palatal) Maxillofacial and Dental efficacy study (m dose 1.9 mg/pt) rhBMP2/ACS (m dose 1.9 mg/pt) rhBMP2/ACS (m dose 1.9 mg/pt) rhBMP2/ACS (m dose 1.9 mg/pt) rhBMP2/ACS (m dose 1.9 mg/pt) Three independent masked CT scan reviewers Placebo n=17 No Tx n=20 No Tx No tx No tx
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I riplett et al., Multicenter, rhBMP2/ACS < 6 mm staged bilateral Mean bone height NR NR Significant overall bone
2009 nonblinded n=80 alveolar or unilateral change from baseline at height gain occurred in
USA RC1 (12-24 mg/pt) bone height maxillary sinus 6 mos. (mm) both groups
(77) In the Tioor InBMP2/ACS
maxilioracial posterior augmentation 7.83±3.52
n=80 9.46±4.11
(p=0.009)
Parde at al apply the short study p=2 and adaptulate floar formation at 6 map
2000 (2.5 mg/pt) augmentation rbRMP7/ACS
Netherlands
(82)
and Dental

					5.8±1.6			
		ICBG			Good quality bone			
		n=3			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.,	Single-center,	rhBMP7/ACS	post-	open reduction	9 mos	rhBMP7	Radiological union:	Successful completion
2008	nonblinded	n=60	traumatic	internal fixation	rhBMP7	md 8±0.5	presence and staging	of treatment was
Italy	RCT	(3.5-7.0	atrophic	(ORIF), external	87	mos	of callus at 3 of 4	defined as the
(78)		mg/pt)	nonunion for	fixation (EF), or			cortices on both	accomplishment of
Long Bone			≥ 9 mos, with	reamed			anteroposterior and	both radiological and
Nonunio		PRP	no signs of	intramedullary	PRP	PRP	lateral plain film	clinical union
		n=60	healing over	nailing (IM) with	68	md 9±0.5	views, as well as the	
			the last 3	rhBMP7 or PRP	(p=0.016)	mos	type of	4 (7%) in rhBMP7
			mos				osseointegration	group and 5 (8%) in
							(undefined)	PRP group were
								complicated by
								infection and failed to
								progress to union
Dahabreh et	Retrospective	rhBMP7/ACS	tibial fracture	open reduction	Radiological union	rhBMP7/AC	Radiological evidence	
al.,	cohort study	n=15	nonunion	internal fixation	rhBMP7ACS	S	of bridging callus of	
2008		(3.5 mg/pt)	with clinical	(ORIF),	100	5.5	all cortices in the two	
(83)			and	exchange		(4.7-6.2)	standard planes of	
Long Bone		ICBG	radiographic	intramedullary	ICBG	ICBG	plian film radiographs	
Nonunio		n=12	failure to	nailing (IM), or	100	6.9	(radiological union)	
			progress to	llizarov, with		(6.1-7.6)		
			union for ≥ 9	rhBMP7 or		(p < 0.001)		
			mos.	ICBG				
			following					
			initial fracture					
			stabilization					
Friedlaender	Multicenter,	rhBMP7/ACS	tibial	IM rod fixation	9, 24 mos	NR	Combination of the	Prior autograft
et al.,	partially	n=61	nonunion for	with	rhBMP7/ACS		presence of bridging	procedure had no

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