Appendix 1 Table A. On-Label BMP Comparative Studies

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Surgical intervention	Inclusion/exclusion criteria	Outcomes measured	Duration of F/U (rng)	Withdrawal or loss to F/U (%)	USPSTF quality rating	Comment
Boden et al., 2000 USA (71) **Lumbar spine**	Multicenter, nonblinded RCT	rhBMP2 n=11 (4.2-8.4 mg/pt) ICBG n=3	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	Inclusion: primary symptomatic single-level anterior lumbar fusion, DDD, age 18-65 yrs, grade I spondylolisthesis, symptoms unresponsive to minimum 6 mos. nonoperative therapies Exclusion: spinal condition other than DDD, use of drugs that inhibit bone healing, osteopenia, BMI > 40%, tobacco use, endocrine bone disorder	Radiographic fusion using plain film radiographs and CT analysis, SF-36, Oswestry Low Back Pain Disability Index, neurological functional status, pain medication use, perioperative data, second surgeries, work status, complications and adverse events	24 mos.	0	FAIR	Pilot study using rhBMP2 soaked absorbable collagen sponges (ACS) as carrier inside tapered lumbar interbody fusion cages
Burkus et al., 2002 USA (72) **Lumbar spine**	Multicenter, nonblinded RCT	rhBMP2 n=143 (4.2-8.4 mg/pt) ICBG n=136	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	Inclusion: primary symptomatic single-level anterior lumbar fusion, DDD, symptoms unresponsive to minimum 6 mos. nonoperative therapies Exclusion: NR	Radiographic fusion using plain film radiographs and CT analysis, Oswestry Low Back Pain Disability Index, neurologic functional status, back, leg and graft site pain numerical rating scales, perioperative	24 mos.	rhBMP2 20 (14%) ICBG 27 (20%)	FAIR	Pivotal trial using rhBMP2 soaked absorbable collagen sponges (ACS) as carrier inside tapered lumbar interbody fusion cages

					data, second surgeries, return to work, complications and adverse events				
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 primary anterior lumbar fusion with interbody fusion cages	Same as Burkus et al., 2002 (72)	Radiographic fusion using plain film radiographs and CT analysis, SF-36, Oswestry Low Back Pain Disability Index, perioperative data, second surgeries, work status, complications and adverse events	24 mos.	rhBMP2 30 (11%) ICBG 75 (19%)	POOR	Analysis of combined data from 2 published studies (Burkus et al., 2002, [72], and Kleeman et al., 2001, [183]) plus unpublished data from a third study. rhBMP2 soaked absorbable collagen sponges (ACS)
Dawson et al., 2009 USA (73) **Lumbar spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt) ICBG n=21	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	Inclusion: primary symptomatic single-level lumbar DDD, low back pain or radicular leg pain unresponsive to minimum 6 mos. nonoperative therapies, grade I or less spondylolisthesis Exclusion: NR	Radiographic fusion using plain film radiographs and CT analysis, Oswestry Low Back Pain Disability Index, SF-36 physical component and physical function subscales, neurological functional status, back, leg and graft site pain numerical rating scales, perioperative data, second	24 mos.	rhBMP2/CRM 3 (12%) 1 death, 2 second-surgery failures ICBG 3 (14%) 1 pt without 24 mos. visit, 2 second-surgery failures	GOOD	Pilot study for Infuse/Mastergraft device,which has received FDA marketing approval Infuse/Mastergraft comprises rhBMP2, an osteoconductive, compression-resistant matrix (CRM) composed of 15% hydroxyapatite and 85% tricalcium phosphate ceramic bulking agent, plus

					surgeries, work status, complications and adverse events Overall success defined as combination of successful fusion, improvement in ODI score > 15%, absence of severe device-related adverse events, no second surgical procedure involving the index level, maintenance or improvement of neurological status				absorbable collagen sponge (ACS)
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multicenter, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient) (2) n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue management)	IM nail fixation and soft tissue management	Inclusion: Open tibial fracture of which the major component was diaphyseal.	Radiographic evidence of fracture fusion and full weight bearing and lack of tenderness at the fracture site on palpation. Failure was determined by a recommendation of secondary intervention by the investigators.	12 mos. (0-73 weeks)	(1) 9 (6%) (2) 8 (5%) (3) 12 (8%)	FAIR	rhBMP2 soaked absorbable collagen sponges (ACS)

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)	IM nail fixation and soft tissue management	Type III open tibial fractures and reamed IM nailing groups Had to complete full 12 months of follow-up in parent study.	Radiographic evidence of fracture fusion and full weight bearing and lack of tenderness at the fracture site on palpation.	12 mos.	0	FAIR	rhBMP2 soaked absorbable collagen sponges (ACS)
Boyne et al., 2005 USA (75) **Maxillofacial Defects**	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	staged bilateral or unilateral maxillary sinus floor augmentation	Inclusion: age 18 and older, inadequate alveolar bone height (< 6 mm confirmed on CT scan) in th epostedrior maxilla Exclusion: acute or chronic sinus disease or pathology, untreated periodontal disease, caries, or oral infection, onlay ridge augmentation to achieve adequate bone for endosseous dental implant placement, use of nicotine-containing product within 2 wks of surgery, pregnancy, insulin-dependent diabetes mellitus, medications or treatments	New bone formation sufficient for endosseous dental implant placement, dental implant success rate following functional loading, perioperative and device-related complications and adverse events	36 mos.	0	GOOD	Randomized dose-comparison and efficacy study of rhBMP2/ACS versus AGB with or without ALG

				known to affect bone turnover, disease affecting bone metabolism					
Fiorellini et al., 2005 USA (76) **Maxillofacial Defects**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (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	extraction socket augmentation	Inclusion: necessity for local alveolar ridge preservation or augmentation of buccal wall defects (≥ 50% buccal bone loss of the extraction socket) followng extraction of maxillary teeth (bicuspids forward) Exclusion: NR	Bone induction, bone volume for dental implant placement, bone density, adverse events and complications	4 mos.	0	FAIR	Randomized dose-comparison and efficacy study of rhBMP2/ACS versus placebo or no treatment
Triplett et al., 2009 USA (77) **Maxillofacial Defects**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	staged bilateral or unilateral maxillary sinus floor augmentation	Inclusion: age 18 and older, inadequate alveolar bone height (< 6 mm confirmed on CT scan) in the posterior maxilla Exclusion: acute or chronic sinus disease or pathology, untreated periodontal disease, caries, or oral infection, onlay ridge augmentation to achieve adequate bone for endosseous dental implant placement, history of cancer within 5 years (except basal cell	New bone formation sufficient for endosseous dental implant placement, dental implant success rate following functional loading, patient success, perioperative complications and device-related adverse events	24 mos.	9 (6)	GOOD	Randomized comparison of rhBMP2/ACS versus AGB with or without ALG

				or squamous cell carcinoma or in situ cervical cancer), use of nicotine-containing product within 3 wks of surgery, lactation, insulin-dependent diabetes mellitus, medications or treatments known to affect bone turnover (except estrogen/progesterone), disease affecting bone metabolism (excluding idiopathic osteoporosis), autoimmune disease, allergies to components of the device, prior exposure to components of the device, tetracycline allergy, plans to be treated with an investigational drug					
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial Defects**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	maxillary sinus floor augmentation	Inclusion: general good condition (excluding ASA class III and IV), age 18-60 years, inadequate native alveolar process and bone Exclusion: mental retardation, smoking, pregnancy, collagen allergy, diabetes mellitus, metabolic bone disease, cancer, rheumatoid arthritis or	New bone formation	6 mos.	0	POOR	Open label pilot study of rhBMP7/ACS

				other autoimmune disease, prior radiotherapy or immunosuppression, history of chronic paranasal sinus inflammation or Caldwell-Luc operations					
Calori et al., 2008 Italy (78) **Long Bone Nonunions**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	Inclusion: post-traumatic atrophic nonunion for ≥ 9 mos., with no signs of healing over the last 3 mos., considered as non-treatable only by means of fixation revision Exclusion: skeletal immaturity, insufficient skin to cover fracture site, systemic infection or infected nonunion, pathological fracture, autoimmune or active neoplastic disease, previous treatment with any growth factor, need for autologous bone graft	Radiographic fusion, pain-free weight-bearing or movement, perioperative complications	minimum 9 mos. mn 12 (9-43)	0	POOR	rhBMP7 (Osigraft, EU) was compared to platelet rich plasma (PRP), both interventions applied with or without adjuvant bone graft extender(s) such as homologous bone, xenograft, or composites such as hydroxyapatite
Dahabreh et al., 2008 UK, Italy (83) **Long Bone Nonunions**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7/ACS	Inclusion: patients who received ICBG or rhBMP7/ACS treatment to enhance healing following declaration of tibial fracture nonunion Exclusion: infected nonunion,	Radiographic fusion, painless full-weight bearing, perioperative complications, second surgeries	29-34 mos.	NR	POOR	rhBMP7 (Osigraft, EU) compared to ICBG in a retrospective cohort of patients selected for the cost study on the basis of successful treatment

			or ICBG	skeletal immaturity, presence of tumor, chronic debilitation, previous treatment of nonunion					
Friedlaender et al., 2001 USA (79) **Long Bone Nonunions**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt) AGB n=61	IM rod fixation with rhBMP7/ACS or AGB	Inclusion: tibial nonunion for ≥ 9 mos. with no signs of healing over previous 3 mos Exclusion: skeletal immaturity, unable to complete F/U, severely compromised soft-tissue coverage at nonunion site, pathological nonunions, radiation, chemotherapy, immunosuppressant or chronic steroid therapy, pregnancy or lactation, systemic or local infection at nonunion site, other investigational therapy, congenital or synovial tibial pseudarthrosis, neuropathy that interferes with walking or pain sensation, multiple nonunions other than tibia, autoimmune disease, immune sensitivity to collagen	Radiographic fusion, pain (none, mild, moderate, severe) at fracture site and ability to bear weight (none, partial or full), surgeon's satisfaction with healing, perioperative outcomes, adverse events	minimum 9 mos., up to 24 mos.	0	FAIR	IDE study for rhBMP7/ACS (OP-1) versus autograft bone (AGB) in treatment of tibial nonunions