

# RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2 IN OPEN TIBIAL FRACTURES

## A SUBGROUP ANALYSIS OF DATA COMBINED FROM TWO PROSPECTIVE RANDOMIZED STUDIES

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**Background:** The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) to improve the healing of open tibial shaft fractures has been the focus of two prospective clinical studies. The objective of the current study was to perform a subgroup analysis of the combined data from these studies.

**Methods:** Two prospective, randomized clinical studies were conducted. A total of 510 patients with open tibial fractures were randomized to receive the control treatment (intramedullary nail fixation and routine soft-tissue management) or the control treatment and an absorbable collagen sponge impregnated with one of two concentrations of rhBMP-2. The rhBMP-2 implant was placed over the fracture at the time of definitive wound closure. For the purpose of this analysis, only the control treatment and the Food and Drug Administration-approved concentration of rhBMP-2 (1.50 mg/mL) were compared. Patients who anticipated receiving planned bone-grafting as part of a staged treatment were excluded from enrollment.

**Results:** Fifty-nine trauma centers in twelve countries participated, and patients were followed for twelve months postoperatively. Two subgroups were analyzed: (1) the 131 patients with a Gustilo-Anderson type-IIIA or IIIB open tibial fracture and (2) the 113 patients treated with reamed intramedullary nailing. The first subgroup demonstrated significant improvements in the rhBMP-2 group, with fewer bone-grafting procedures ( $p = 0.0005$ ), fewer patients requiring invasive secondary interventions ( $p = 0.0065$ ), and a lower rate of infection ( $p = 0.0234$ ), compared with the control group. The second subgroup analysis of fractures treated with reamed intramedullary nailing demonstrated no significant difference between the control and the rhBMP-2 groups.

**Conclusions:** The addition of rhBMP-2 to the treatment of type-III open tibial fractures can significantly reduce the frequency of bone-grafting procedures and other secondary interventions. This analysis establishes the clinical efficacy of rhBMP-2 combined with an absorbable collagen sponge implant for the treatment of these severe fractures.

**Level of Evidence:** Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Despite improvements in surgical techniques, internal fixation, and a better understanding of fracture biology, the treatment of open tibial fractures continues to be associated with high rates of nonunion. In many patients, multiple additional surgical treatments (i.e., secondary interventions) may also be required to finally achieve healing. A recent, large observational study (Lower Extremity Assessment Project; LEAP), conducted at eight level-I trauma centers in the United States, found the rate of nonunion among

severe leg fractures (Gustilo-Anderson type-IIIB tibial fractures) to be as high as 28.9%<sup>1</sup>. The LEAP study found that 19.1% of the reconstruction patients required at least one additional operation during their treatment and that 10.9% of patients still had an unhealed fracture even after twenty-four months of treatment.

Bone morphogenetic proteins (BMPs) are the family of osteoinductive proteins in bone matrix first identified by Marshall Urist in 1965<sup>2</sup>. Osteoinduction is defined as the ability of a protein to mediate bone formation in an extraosseous site. The first publications on the clinical use of extracts of human BMP from allograft bone matrix began appearing in the late 1980s<sup>3,4</sup>. This was followed in 1988 by the isolation of an indi-



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vidual protein, BMP-2, from a purified extract and its recombinant production<sup>5</sup>. The recombinant process allows for reproducible production of a single BMP, at a known concentration and purity.

The osteoinductive potential of recombinant human bone morphogenetic protein-2 (rhBMP-2) has been widely studied. Preclinical and clinical research has demonstrated that rhBMP-2 carried on an absorbable collagen sponge (ACS) can induce new bone formation when implanted surgically. For example, rhBMP-2/ACS has been shown in animal models to heal critical-size bone defects and accelerate fracture-healing<sup>6,7</sup>. Clinical studies have also demonstrated the equivalence of rhBMP-2/ACS to autogenous iliac bone-grafting in spine fusion<sup>8-11</sup>. Those prospective, randomized studies led to the approval by the United States Food and Drug Administration, in July 2002, of the 1.50 mg/mL concentration of rhBMP-2/ACS (INFUSE Bone Graft [marketed in Europe under the trade name InductOs]; Medtronic Sofamor Danek, Memphis, Tennessee) for use with certain metallic cages in spine fusion procedures<sup>12</sup>. That same year, the BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) study group published a prospective, randomized study of 450 patients with open tibial fractures treated with two different concentrations of rhBMP-2 on an absorbable collagen sponge<sup>13</sup>. That study found the 1.50 mg/mL concentration of rhBMP-2/ACS to be substantially superior to intramedullary nail fixation alone in reducing the frequency of secondary interventions, accelerating fracture-healing, and improving the chance for clinical success. Based on the BESTT study results, the Food and Drug Administration, in April 2004, granted approval for the 1.50 mg/mL concentration of rhBMP-2/ACS in the treatment of acute, open tibial fractures that have been stabilized with an intramedullary nail<sup>14</sup>.

Between 1996 and 1999, two concurrent prospective, randomized, multicenter clinical studies were conducted to evaluate the potential of rhBMP-2 in the treatment of open tibial fractures. Both used the same study design and protocol, which has already been described in detail<sup>13</sup>. The first clinical study involved 450 patients and was conducted by the BESTT study group<sup>13</sup>. The second, previously unpublished, study was conducted at ten level-I trauma centers in the United States and included a total of sixty patients (the United States study group). Neither clinical study was sized with the intention of conducting a subgroup analysis, but review of the BESTT study data suggested a significant reduction in the rate of infection in the type-III open fractures treated with rhBMP-2 ( $p = 0.0219$ )<sup>13</sup>. The results from that study also implied that the rate of secondary intervention was reduced with the addition of rhBMP-2 in patients treated with reamed as well as unreamed intramedullary nailing. Criticism has been voiced that these two outcomes were not described in enough detail in the original publication, and it has been suggested that the BESTT study was not representative of a United States population. Many surgeons are unaware that a sixty-patient trial was conducted in the United States at the same time as the BESTT trial and that the United States study found similar outcomes. The goal of this paper was to combine the raw patient data from these two clinical trials

and conduct a subgroup analysis of the effect of rhBMP-2 on the clinical outcomes for the type-III open fractures and reamed intramedullary nailing groups individually. A secondary goal was to provide a head-to-head demographic, treatment, and outcome comparison between the BESTT and the United States study groups.

### Materials and Methods

Both studies used identical designs, with the patients prospectively randomized to one of three groups: (1) standard treatment only, which included intramedullary nail fixation and routine soft-tissue management (the control group), (2) standard treatment and an implant containing a 0.75-mg/mL concentration of rhBMP-2, or (3) standard treatment and an implant containing 1.50 mg/mL of rhBMP-2. To ensure a balanced distribution of fracture severity across the three groups, the patient assignments were stratified on the basis of the Gustilo-Anderson classification of open wounds<sup>15,16</sup>. Gustilo-Anderson type-I through IIIB fractures were studied. Patients were followed for twelve months, with assessments at six, ten, fourteen, twenty, twenty-six, thirty-nine, and fifty-two weeks after treatment.

The clinical investigators determined fracture-healing. A fracture was considered to be healed when there was radiographic evidence of fracture union and the patient was able to bear full weight on the limb and had a lack of tenderness at the fracture site on palpation. A recommendation for secondary intervention by the investigator and/or the performance of such intervention to promote fracture union was considered a failure of treatment. All procedures with the potential to promote fracture-healing (or events such as screw breakage, resulting in dynamization of the intramedullary nail) were counted as treatment failures. An independent radiology panel that was blinded to the treatment also evaluated fracture union. A fracture was considered to be united when at least two of the three radiologists reported cortical bridging and/or disappearance of the fracture lines on at least three of the four cortices on the anteroposterior and lateral radiographs.

### Preparation and Implantation of rhBMP-2/ACS

An absorbable collagen sponge of type-I bovine collagen (Helistat; Integra Life Sciences, Plainsboro, New Jersey) was used as a carrier because of its handling properties and ability to retain and deliver rhBMP-2 at the implantation site<sup>12,14</sup>. The combination of the absorbable collagen sponge and rhBMP-2 protein, referred to as the rhBMP-2 implant in this paper, was prepared with a standardized protocol. A sterile water solution containing either 6 or 12 mg of rhBMP-2 was applied to a 7.5 × 10-cm absorbable collagen sponge, resulting in a final implant concentration of either 0.75 mg/mL or 1.50 mg/mL of rhBMP-2. Following wound irrigation and the achievement of hemostasis, the rhBMP-2 implant was placed as an onlay covering the fracture and bridging the area of comminution, just prior to soft-tissue closure.

### Combined Demographic Data on the Patients

Patient demographics (Table I) were similar across the treat-

**TABLE I Demographic Data on the Patients from the Two Studies According to Treatment Group**

	Control Groups		Groups Treated with 1.50 mg/mL of rhBMP-2	
	United States Study	BESTT Study	United States Study	BESTT Study
No. of patients	19	150	20	149
Mean age (yr)	33.6	36.8	35.2	33.4
Male patients (%)	89.5	78.7	85.0	84.6
Mean weight (kg)	80.2	75.4	87.9	75.6
Smokers (%)	52.6	44.9	40.0	51.7

ment groups. A detailed statistical analysis of the two study populations showed that the patients were comparable across geographic areas and treatment centers<sup>17</sup>. The two groups had similar distributions of injury patterns and treatment methods (Tables II and III). The study protocol required that definitive fracture fixation with intramedullary nailing (with or without reaming) be performed no later than fourteen days after the injury. The majority of patients underwent definitive fracture fixation within forty-eight hours after the injury (Table III). All patients received routine soft-tissue management, including wound irrigation and débridement, followed by definitive wound closure, within an average of four days.

The choice of reamed and unreamed intramedullary nailing was left to the individual investigator or center. In the BESTT study group, reamed intramedullary nailing was used more often in the group treated with 1.50 mg/mL of rhBMP-2

than in the control group (Table III). The imbalance was due to the central randomization method used, which resulted in more patients being randomly allocated to the rhBMP-2 treatment at centers that predominantly used reamed nailing. Multiple regression analysis in that study showed that rhBMP-2 affected the outcome of the fractures independent of reaming, indicating the efficacy of rhBMP-2 in patients treated with reamed as well as with unreamed intramedullary nailing<sup>13</sup>.

Combining the data from the two completed studies, a total of 510 patients with open tibial fractures were randomized at fifty-nine trauma centers in twelve countries. For the purpose of this review, only the commercially approved concentration of 1.50 mg/mL of rhBMP-2/ACS was compared with the control group. Both the control and the rhBMP-2 groups consisted of a total of 169 patients each. Two subgroup analyses were performed: (1) Gustilo-Anderson type-

**TABLE II Distribution of Injury Between the Control and rhBMP-2 Treatment Groups**

	Control Groups (% of patients)		Groups Treated with 1.50 mg/mL of rhBMP-2 (% of patients)	
	United States Study	BESTT Study	United States Study	BESTT Study
Isolated tibial injury	78.9	55.8	50.0	55.9
Injury related to a motor-vehicle accident	68.4	60.5	65.0	57.2
Type of fracture				
I	15.8	23.3	15.0	22.1
II	31.6	36.7	45.0	33.6
IIIA and IIIB	52.6	40.6	40.0	44.0

**TABLE III Treatment Methods Between the Control and rhBMP-2 Treatment Groups**

	Control Groups		Groups Treated with 1.50 mg/mL of rhBMP-2	
	United States Study	BESTT Study	United States Study	BESTT Study
Mean days to definitive fixation	1.4	1.6	1.5	1.9
Mean no. of irrigation and débridement procedures per patient	2.4	2.0	2.1	1.9
Mean days to definitive wound closure	4	4	4	3
Percentage of patients who had reamed nailing	52.6	26.0	50.0	39.6

IIIA or IIIB open tibial fractures (131 patients) and (2) fractures treated with reamed intramedullary nailing (113 patients). These subgroups included only patients who had received treatment according to the protocol and had completed the twelve-month period of follow-up. Four patients in the rhBMP-2 group did not receive the randomized treatment, and one patient received the rhBMP-2 implant, but two days later the implant site underwent an additional irrigation and débridement that, in the surgeon's opinion, had the potential of removing the implant; these five patients were excluded from the analysis. Two patients (one in the control group and one in the rhBMP-2 group) underwent a below-the-knee amputation during the follow-up period and were excluded from the subgroup analysis (see Appendix). Neither amputation was the result of a failure of union of the original fracture; both were the result of wound infections. This per-protocol comparison was chosen instead of an intent-to-treat analysis, since our intent was to measure the effect of rhBMP-2. Patients who did not receive the correct randomized treatment because of technical error (during implantation) were not included.

Overall efficacy and pairwise category comparisons were tested with use of a two-sided Fisher exact test (QuickCalcs; GraphPad Software, San Diego, California). Outcome data were entered into  $2 \times 2$  contingency tables for each group, and then two-tailed p values were calculated. The relative risk reduction of adding the rhBMP-2 and the 95% confidence interval of that reduction were calculated. The cumulative probability that patients would achieve full weight-bearing and have radiographic evidence of union was estimated with use of Kaplan-Meier curves and two-sided log-rank tests. Data on the patients who were unable to achieve full weight-bearing or those with fractures judged not to be united were censored at the time of the last follow-up for these probability analyses. Statistical significance was judged to be a p value of  $\leq 0.05$ .

## Results

### Gustilo-Anderson Type-III Fractures Subgroup

From the combined data set, 131 patients with a type-IIIA or IIIB open tibial fracture were analyzed; this included sixty-five patients in the control group and sixty-six patients in the rhBMP-2 group. The injury date spanned from December 1996 to December 1998, and the demographics were similar between the two treatment groups, with no significant difference in regard to gender distribution or the percentage of smokers (see Appendix). Type-IIIB fractures were more common in the rhBMP-2 patients (38%) than in the control patients (26%), but this difference was not found to be significant ( $p = 0.19$ ). The distribution of patients treated with reamed or unreamed intramedullary nailing was similar between the groups ( $p = 0.14$ ), with forty-seven patients in the control group and thirty-nine patients in the rhBMP-2 group managed with unreamed intramedullary nailing. The distribution of the intramedullary nail diameter used for the type-III subgroup is shown in a table in the Appendix.

The most important finding in this subgroup analysis was the reduction in the number of patients receiving secondary autologous bone-grafting procedures to treat delayed union or nonunion of the type-III fractures (Table IV). More patients in the control group (thirteen [20%] of sixty-five patients) required an invasive autologous bone-grafting procedure than in the rhBMP-2 group (one [2%] of sixty-six patients). This translates into a relative risk reduction in the need for a bone graft to treat a delayed union of 90% (95% confidence interval, 41% to 98%) when rhBMP-2 was added to the treatment of type-III tibial fractures ( $p = 0.0005$ ). The average time from the initial injury to the performance of the secondary bone-grafting procedure was twenty-five weeks (range, thirteen to forty-nine weeks).

The use of the rhBMP-2 implant also significantly decreased the number of invasive secondary interventions (bone-

**TABLE IV Comparison of Patient Outcomes in the Control Group and rhBMP-2 Treatment Group for the Gustilo-Anderson Type-III Open Fracture Subgroup**

Outcome Criteria	Control Group (n = 65)	rhBMP-2 Group (n = 66)	P Value*	Risk Reduction (95% Confidence Intervals)†
No. (%) of patients receiving bone graft	13 (20)	1 (2)	0.0005	90% (41% to 98%)
No. (%) of patients receiving invasive secondary procedure‡	18 (28)	6 (9)	0.0065	68% (24% to 86%)
Time to achievement of full weight-bearing§ (days)	126 ± 61	95 ± 38	NA	NA
No. (%) of patients who had infection	26 (40)	13 (21)	0.0234	48% (8% to 70%)
No. (%) of patients who had dynamization	14 (22)	14 (21)	1.0000	5% (-84% to 50%)
No. (%) of patients who had dynamization subsequent to screw breakage	16 (25)	7 (11)	0.0407	56% (1% to 80%)
Total no. (%) of patients who had dynamization	30 (46)	21 (32)	0.1085	30% (-8% to 55%)

\*Fisher exact test (two-tailed value). †Relative risk reduction calculation =  $(1 - \text{rate in rhBMP-2 group}/\text{rate in control group}) \times 100$ , as described by Bhandari et al.<sup>21</sup> ‡Invasive secondary procedures were defined as one or more of the following: bone-grafting to treat delayed union or nonunion, fibular osteotomy, and/or exchange nailing. §The values are given as the mean and the standard deviation. NA = not available.

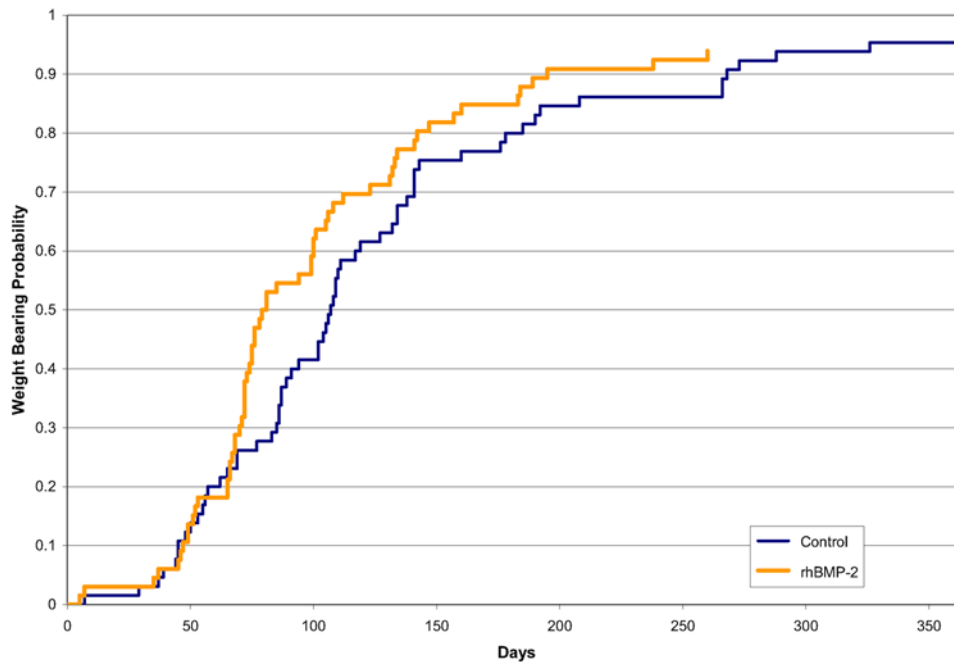


Fig. 1  
Cumulative probability of patients being able to bear full weight as a function of time from definitive wound closure for the type-III fracture subgroup ( $p = 0.20$ ).

grafting, fibular osteotomy, and/or exchange nailing) that were performed to promote fracture-healing (Table IV). There was a risk reduction of 68% (95% confidence interval, 24% to 86%) in the number of patients who received invasive secondary interventions, with 28% (eighteen) of the sixty-five patients in the control group compared with only 9% (six) of the sixty-six patients in the rhBMP-2 group who needed such a procedure ( $p = 0.0065$ ). Three control patients received two simultaneous invasive secondary procedures (bone-grafting and exchange nailing) to treat a delayed union. No difference was observed between the two treatment groups with respect to the incidence of nail dynamization (Table IV). However, the locking screws broke twice as often in the control group as in the rhBMP-2 group ( $p = 0.04$ ).

Patients who received the implant with 1.50 mg/mL of rhBMP-2 achieved fracture-healing sooner than did those in the control group. The average time to full weight-bearing was 95.1 days for the rhBMP-2 group and 126.6 days for the control group. The cumulative probability of a patient being able to bear full weight is estimated in Figure 1 ( $p = 0.20$ ). For the first two months, the probability of patients with a type-III fracture being able to achieve full weight-bearing was similar between the two groups. After two months, the probability of rhBMP-2-treated patients being able to achieve full weight-bearing was slightly higher than that for the controls. For the type-III subgroup, the average time to radiographic union as judged by the blinded radiologist was 277 days for the control patients and 271 days for the rhBMP-2-treated patients ( $p = 0.43$ ). The rate of infection was significantly lower in the patients treated with rhBMP-2 than it was in the control patients

( $p = 0.02$ ), which was similar to the findings reported in the BESTT study<sup>13</sup>. This represents a risk reduction in the rate of infection of 48% (95% confidence interval, 8% to 70%) when rhBMP-2 is added to the treatment of type-III tibial fractures.

#### Reamed Intramedullary Nailing Subgroup

From the combined dataset, 113 patients treated with reamed intramedullary nailing were analyzed; this included forty-eight patients in the control group and sixty-five patients in the rhBMP-2 group. It should be noted that this subgroup includes open tibial fractures of type I through type IIIB and may or may not include patients from the previous subgroup. Variations in the use of reamed nailing across countries highlight the ongoing debate regarding the relative benefits of this procedure taking place during study enrollment (see Appendix). The demographic data were similar for the two groups, with no significant difference with regard to gender distribution, number of smokers, or distribution of fracture grade (see Appendix). No difference was observed between the two groups with respect to nail dynamization ( $p = 0.8251$ , Table V).

With use of the same outcome criteria as with the previous subgroup analysis, no significant difference was observed between the control and the rhBMP-2 groups in the reamed intramedullary nailing subgroup. Fewer events were observed for rhBMP-2-treated patients, but that difference was not found to be significant (Table V). Both the mean time to full weight-bearing (83.8 days compared with 80.4 days) and the time to radiographic evidence of union (251 days compared with 234 days) were slightly, but not significantly, shorter in the rhBMP-2 treatment group. The cumulative probability of

**TABLE V Comparison of Patient Outcomes in Control Group and rhBMP-2 Treatment Group for the Reamed Nailing Subgroup**

Outcome Criteria	Control Group (n = 48)	rhBMP-2 Group (n = 65)	P Value*	Risk Reduction (95% Confidence Intervals)†
No. (%) of patients receiving bone graft	3 (6)	1 (2)	0.3100	67% (-201% to 96%)
No. (%) of patients receiving invasive secondary procedure‡	7 (15)	5 (8)	0.3549	47% (-64% to 83%)
Time to achievement of full weight-bearing§ (days)	84 ± 43	80 ± 37	NA	NA
No. (%) of patients who had infection	13 (27)	12 (18)	0.3597	30% (-43% to 65%)
No. (%) of patients who had dynamization	10 (21)	11 (17)	0.6311	19% (-77% to 63%)
No. (%) of patients who had dynamization subsequent to screw breakage	2 (4)	3 (5)	1.0000	-25% (-594% to 77%)
Total no. (%) of patients who had dynamization	12 (25)	14 (22)	0.8251	12% (-74% to 55%)

\*Fisher exact test (two-tailed value). †Relative risk reduction calculation =  $(1 - \text{rate in rhBMP-2 group} / \text{rate in control group}) \times 100$ , as described by Bhandari et al.<sup>21</sup>. ‡Invasive secondary procedures were defined as one or more of the following: bone-grafting to treat delayed union or non-union, fibular osteotomy, and/or exchange nailing. §The values are given as the mean and the standard deviation. NA = not available.

patients being full weight-bearing ( $p = 0.41$ ) and having radiographic evidence of union ( $p = 0.64$ ) were similar. The percentage of patients who had an infection was found to be higher in the control group, but the difference was not significant (27% compared with 18%;  $p = 0.36$ ).

## Discussion

Clinical evidence has always been an essential part of the surgeon's decision-making process in planning individual patient treatment. The purpose of this study was to combine the data from two level-I randomized controlled trials and conduct a subgroup analysis of the combined data set. A comparison of the control group and a group that had treatment with use of an implant containing the clinically available concentration of rhBMP-2 was performed. As neither clinical study was originally sized with the intention of conducting a subgroup analysis, these statistical comparisons therefore are at greater risk of producing a false-positive result and these data alone should be viewed with caution until further studies are performed.

The first subgroup analysis involved the most severe open tibial fractures studied (type IIIA and IIIB) and demonstrated significant clinical improvements when the rhBMP-2 implant was added to the treatment, as only one patient from the rhBMP-2 group required bone-grafting to treat a delayed union compared with thirteen patients from the control group. It should be noted that one of the exclusion criteria in the original study was the surgeon's anticipated need to perform a staged bone-grafting procedure as part of the patient's treatment plan. Thus, the bone-grafting procedures identified in this review were not planned; the procedure was performed to treat an unexpected delayed union or nonunion.

The decreased need for invasive surgical procedures, the finding that patients in the rhBMP-2 group were bearing weight an average of thirty-two days sooner than the con-

trols, and the reduced rate of infection all demonstrate the advantage of adding an rhBMP-2 implant to the treatment of a severe open tibial fracture (Gustilo-Anderson type IIIA and IIIB). These benefits have the potential to reduce the treatment costs of this subgroup of open fractures. A recent economic model based on the BESTT study results revealed a cost savings to the payer when rhBMP-2 was reserved for only type-IIIA and IIIB tibial fractures<sup>18</sup>.

A comparison of the average time for radiographic union and full weight-bearing highlights the inherent difficulty in judging fracture-healing solely with radiographs. It also reinforces the need to judge healing with use of a combination of clinical and radiographic factors, as was highlighted in a recent survey of orthopaedic surgeons. Bhandari et al.<sup>19</sup> found that the majority of surgeons assess fracture-healing on the basis of radiographic evidence of cortical continuity and loss of the fracture line in combination with the ability of the patient to bear weight. Typically, the radiographic changes indicative of fracture union occur later in the fracture repair process (soft callus lacks substantial mineral content and is not easily detected). A blinded radiology panel must assess union on the basis of radiographs alone, without any knowledge of patient and treatment characteristics, resulting in a judgment of union later than that of the treating surgeon and well after the patient is fully weight-bearing. The results in this study show that the patients were fully weight-bearing an average of six months before the blinded radiology panel judged them to have union at the fracture site.

The subgroup analysis of patients treated with reamed intramedullary nailing did not appear to have sufficient power to reveal significant differences, but it showed a trend in favor of the rhBMP-2 implant, suggesting that larger randomized studies that involve reamed intramedullary nailing and the rhBMP-2 implant may confirm the differences observed.

In the present study, we evaluated the addition of the

rhBMP-2 implant to the treatment of open tibial fractures as an adjunct to intramedullary nail fixation. We did not compare the healing of rhBMP-2 treatment with that of autologous bone-grafting. Therefore, if a patient presents with an open tibial fracture, for which the planned treatment does not involve staged bone-grafting and only includes intramedullary nail fixation, then the rhBMP-2 implant would be used acutely and have the potential to improve patient outcome. A prospective, randomized study in which autograft bone was compared with the rhBMP-2 implant combined with allograft bone for the treatment of tibial fractures with traumatic bone loss has been conducted<sup>20</sup>. The authors of that study concluded that the rhBMP-2 implant combined with allograft may be a reasonable alternative to autogenous bone-grafting in patients with tibial fractures with traumatic diaphyseal bone loss that require staged bone-grafting in addition to fixation.

In conclusion, the use of the rhBMP-2 implant significantly reduced the frequency of bone-grafting procedures and invasive secondary interventions in Gustilo-Anderson type-III open tibial fractures. This study supports the addition of this implant at a concentration of 1.50 mg/mL of rhBMP-2 in the treatment of these severe fractures.

### Appendix

**eA** Several tables presenting additional data determined from the analysis are available with the electronic versions of this article, on our web site at [jbjs.org](http://jbjs.org) (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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