Response to FDA Deficiency letter of 03 September 2010 regarding P100006 for Augment™ Bone Graft

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Table of Contents

Table of In-Text Tables 3
Table of Figures 5
Introduction 6
Non Clinical 7
Question 1 7
Question 2 9
Question 3 20
Question 4 20
Question 5 21
Clinical 23
Question 6 23
Question 7 29
Question 8 47
Question 9 67
Question 10 69
Question 11 84
Question 12 87
Question 13 95
Statistical 96
Question 14 96
Question 15 96
Question 16 101
Question 17 102
Question 18 104
Question 19 112
Question 20 112
Epidemiological Issues 114

Question 21 114
Question 22 119
Question 23 126
Question 24 127
Question 25 127
Question 26 128
Minor Deficiencies 130
Question 27 130
Question 28 132
Question 29 133
Question 30 134
List of Exhibits 136

Table of In-Text Tables

Table 1: Microscopic Findings at Implantation Site 8
Table 2: Plate IDs that contain pre-treatment outliers 9
Table 3: Bootstrap sample analyst-specific and pooled cut-points 10
Table 4: Millipore and analyst-specific pre-treatment positive and negative declaration comparison 11
Table 5: Millipore and pooled pre-treatment positive and negative declaration comparison 12
Table 6: Millipore and analyst-specific post-treatment positive and negative declaration comparison 12
Table 7: Millipore and pooled post-treatment positive and negative declaration comparison 13
Table 8: Subjects with suspect declarations 14
Table 9: Incidence of Cancer 24
Table 10: Comparison of rhPDGF-BB in Augment versus Regranex 26
Table 11: Subject Performance Composite 31
Table 12 Subject Performance Composite Endpoint plus CT ≥ 50% 32
Table 13: Categorization of Secondary Procedures 34
Table 14: Subjects Screened But Never Randomized or Treated 39
Table 15: Summary of Subject Exclusion from mITT Population* 40
Table 16: ELISA Tier 3 titration results from confirmed positive BMTI-2006-01 serum samples analyzed for the presence of anti-rhPDGF-BB antibody 59

Table 17: Subject Positive Serum Antibody Titers and Adverse Events 63
Table 18: Comparison of Analyses 70
Table 19: Radiographic Observations with Treatment and Adverse Events 77
Table 20: Distribution of Age of Injury / Deformity 84
Table 21: Distribution of Subject Age 85
Table 22: Age of Injury / Deformity Quartile Fusion Rates 85
Table 23: Age of Subject Quartile Fusion Rates 86
Table 24: Age of Subject plus Age of Injury / Deformity Fusion Rates 87
Table 25: Clinical Healing Change by Visit (patient level) 89
Table 26: Clinical Union Per Joint Change by Visit (full complement of joints) 89
Table 27: Clinical Success Change by Visit 90
Table 28: Weight Bearing Pain Change by Visit 90
Table 29: Fusion Site Pain Change by Visit 91
Table 30: Composite Success Change by Visit 92
Table 31: Osseous Bridging ≥ 50% via CT Change by Visit 93
Table 32: Graft Harvest Site Pain Change by Visit 93
Table 33: SF-12 PCS Score Change by Visit 94
Table 34: Foot Pain and Disability Index Score Change by Visit 94
Table 35: AOFAS Score Change by Visit 94
Table 36: Breslow-Day Test 97
Table 37: Subject Success by Site 97
Table 38: Pooling of Affected Sites with Small Sites 98
Table 39: Pooling of Affected Sites as Single Site 99
Table 40: Breslow-Day Results by Strategy 99
Table 41 Type III Wald Chi-square p-values 100
Table 42 Site specific estimates of the odds ratio within each site 100
Table 43: Summary of Subject/ Investigator Requests for Early Withdrawal 101
Table 44: Subject Early Withdrawals by Treatment Assignment 102
Table 45: List of Treated Subject Early Withdrawals 103
Table 46: Model 1 Correlation Matrix of Joint Within Subject 105
Table 47: Model 2 Correlation Matrix of Joint Within Subject 106
Table 48: Model 2 Wald Type 3 GEE Analysis of Variance 106
Table 49: Model 3 Correlation Matrix of Joint Within Subject 109

Table 50: Model 3 Wald Type 3 GEE Analysis of Variance 109
Table 51: Model 3 Correlation Matrix of Joint Within Subject 110
Table 52: Model 3 Wald Type 3 GEE Analysis of Variance 111
Table 53: Patient Demographics for mITT Population 114
Table 54: Model 2 Wald Type 3 GEE Analysis of Variance 121
Table 55: Model 3 Wald Type 3 GEE Analysis of Variance 124
Table 56: Model 4 Wald Type 3 GEE Analysis of Variance 125
Table 57: Fibrinogen Values by All Animals and Segregated by Sex 131

Table of Figures

Figure 1: Composite Endpoints 31
Figure 2: Subject Populations 37
Figure 3: Description of Excluded Subjects 38
Figure 4: CT Scan Specificity and Sensitivity 46
Figure 5: Model 2 odds ratios and corresponding confidence intervals 107
Figure 6: Model 3 odds ratios and corresponding confidence intervals 110
Figure 7: Model 4 odds ratios and corresponding confidence intervals 111
Figure 8: Model 2 odds ratios and corresponding confidence intervals 123
Figure 9: Model 3 odds ratios and corresponding confidence intervals 124
Figure 10: Model 4 odds ratios and corresponding confidence intervals 126
Figure 11: Fibrinogen levels as a function of time in the three treatment groups 131

Response to FDA Deficiency letter of 03 September 2010 regarding P100006 for Augment™ Bone Graft

Introduction

BioMimetic Therapeutics, Inc. (BMTI) has developed responses to the questions posed in the FDA deficiency letter dated 03 Sep 2010 regarding P100006 for Augment™ Bone Graft. The original questions from FDA are restated, with BMTI's response following each question. For ease of review, data displays and discussion have been incorporated into the response wherever possible. In cases where additional data or information is required, this additional data is included in an exhibit numbered in reference to the original question.

BMTI is submitting with this response an updated clinical study report for the Augment pivotal study, Protocol BMTI-2006-01, containing final follow-up for all subjects through the end of the 52-week study period. This report is included in Exhibit 6 (with electronic versions of the study data tables, figures and listings) supporting responses to the clinical questions.

BMTI is also completing final review of data for a safety study of Augment conducted in the European Union. The results of this study are undergoing final internal audit, and will be provided separately. The safety data from the EU is analogous to those data presented herein; with no unusual adverse event occurrences, trends or signals. Also of note, no cancers were reported.

Non Clinical

Question 1

1) *You have provided a draft interim report, "Recombinant Human Platelet-Derived Growth Factor-BB (rhPDGF-BB): An Intravenous Injection Teratology Study in Rat" (Exhibit 7-1, RD-072809-01P), for the evaluation of the chronic toxicity and carcinogenicity of rhPDGF-BB mixed with β-TCP matrix (Augment bone graft) implanted in a rat model study. Please provide the final report for the intravenous rhPDGF-BB teratology in rats study to address the recovery of injection site pathology that was observed six months after treatment, as presented in your preliminary study report and as used to help develop the labeling of your product. In addition, a single dose toxicity study with Augment Bone Graft in rats with a one year observation period was scheduled to be completed in May of 2010 (Study number 1524-003). Although this study was requested as a postmarketing commitment, the final study report should be submitted for review prior to marketing to address the recovery of injection site pathology.*

Response

BMTI is submitting the final reports of two non-clinical studies (Exhibit 1):

- Teratology study in pregnant rats "Recombinant Human Platelet-Derived Growth Factor-BB (rhPDGF-BB): An Intravenous Injection Teratology Study in Rat"
- Carcinogenicity study in rats "Evaluation of the Chronic Toxicity and Carcinogenicity of Recombinant Human Platelet-Derived Growth Factor-BB (rhPDGF-BB) Mixed with β-Tricalcium Phosphate (β-TCP) Matrix (Augment Bone Graft) Implanted in a Rat Model"

The teratology study results are addressed as a response to Question #29.

The pathology findings observed at the implantation site in the study "*Evaluation of the Chronic Toxicity and Carcinogenicity of Recombinant Human Platelet-Derived Growth Factor-BB (rhPDGF-BB) Mixed with β-Tricalcium Phosphate (β-TCP) Matrix (Augment Bone Graft) Implanted in a Rat Model*" (Study number 1524-003) occurred in both the Control Article group and in the Test Article group, and they were likely related to the β-TCP matrix and thus not considered test article-related. Importantly, the incidence of both the granulation tissue and the hyperostosis decreased from Day 180 to Day 365 without signs of worsening or progression. Below BMTI summarizes the narrative on these findings, which can be found in the Final Study Report (Exhibit 1).

Minimal to mild granulation tissue was noted at the implant site in animals from the Control Article and the Test Article groups (no animals from the Sham Surgery group displayed this change) on Day 30 (50 and 75% of the animals in the Control Article and Test Article groups respectively), Day 180 (90 and 100% of the animals in the Control Article and Test Article groups respectively) and Day 365 (60 and 45% of the animals in the Control Article and Test Article

groups respectively). Because these findings occurred in both the Control Article group and in the Test Article group, they were likely related to the β-TCP matrix.

Table 1: Microscopic Findings at Implantation Site

Microscopic Findings at Implantation Site												
Study Day	**Day 30**				**Day 180**				**Day 365**			
Group	**Control Article**		**Test Article**		**Control Article**		**Test Article**		**Control Article**		**Test Article**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Granulation	4/10	6/10	6/10	9/10	9/10	9/10	10/10	10/10	16/30	20/30	9/30	18/30
Minimal	1/10	2/10	2/10	3/10	3/10	6/10	3/10	3/10	10/30	11/30	6/30	13/30
Mild	3/10	4/10	4/10	3/10	6/10	3/10	7/10	7/10	6/30	9/30	3/30	5/30
Hyperostosis	0/10	0/10	0/10	0/10	5/10	7/10	5/10	5/10	6/30	7/30	12/30	6/30
Minimal	0/10	0/10	0/10	0/10	1/10	2/10	3/10	4/10	6/30	6/30	10/30	5/30
Mild	0/10	0/10	0/10	0/10	4/10	5/10	2/10	1/10	0/30	1/30	2/30	1/30

Control Article = β-TCP + 20 mM sodium acetate, pH 6.0 ± 0.5

Test Article = β-TCP + 0.3 mg/mL rhPDGF-BB in 20 mM sodium acetate, pH 6.0 ± 0.5

The granulation tissue was present along the periosteal surface of the femur or within the adjacent skeletal muscle. On Day 30, it was characterized by a cavitating space surrounded by a loose fibrovascular tissue that contained occasional mononuclear cells and rare giant cells. On Day 180, the fibrovascular tissue was denser and more organized. On Day 365, the cavitating space was surrounded by a dense well-organized fibrovascular tissue with occasional mononuclear cells and rare giant cells; less frequently, the granulation tissue was compact with no evidence of cavitating space. Compared to the changes noted on Day 180, this finding was less frequent and the granulation tissue looked more mature and somewhat reduced in size (as evidenced by the overall lower severity).

A finding present on Day 180 and on Day 365 but absent on Day 30 was minimal to mild hyperostosis. The hyperostosis occurred on the periosteal surface of the femur where the granulation tissue was present. On Day 180 it was present in 60% of the animals in the Control Article group and in 50% of the animals in the Test Article group and it consisted of well differentiated bone that was undistinguishable from the normal femoral bone. On Day 365, the hyperostosis had lower incidence; it was present in 22% of the animals in the Control Article group and in 30% of the animals in the Test Article group. It was similar to what was noted on Day 180 with no evidence of progression. Because it was found in both the Control Article group and the Test Article group, it was considered secondary to the effect of the bone graft matrix (in this case β-TCP) on the periosteal surface of the femur.

Question 2

2) *You have validated the ELISA method for the screening of anti-rhPDGF-BB antibodies in human sera using only normal human sera. However, you did not provide confirmatory data for the cut-point in the target patient population. Serum samples from different populations (e.g. healthy control vs. disease) have been found to perform differently in some immunoassays. Therefore, although it is acceptable to use serum samples from healthy controls to develop and validate immunogenicity assays, the cut-point should be confined using serum samples from treatment naive target population subjects. If a target population specific cut-point needs to be established then please re-evaluate the sensitivity, specificity and selectivity of the assay using target population sera. Please provide supporting raw data for the estimation of the cut point value of the ELISA screening method in the target patient population.*

Response

Per FDA request, a cut-point confirmation based on treatment-naive target population subjects was carried out as follows.

Optical density (OD) values from tier 1 testing for 414 subjects prior to treatment in the study were available for analysis. These 414 readings were generated by three analysts over a multitude of days. Each day witnessed as many as six plates being run, as many as two plates per analyst per day. In total, 106 plates were used to generate the 414 OD values.

OD values within each plate were checked for outlier values via a single pass of Grubb's test. Plates with fewer than three pre-treatment samples present could not have Grubb's test computed and were thus tautologically free of outliers. Five outliers were detected and flagged as such. These outliers were not considered when computing the percentile estimates below.

The five outlier values were found on five plates. The plates with the outliers are shown below. Inspection of the OD values on the plates with outliers readily reveals the suspect values.

Table 2: Plate IDs that contain pre-treatment outliers

Plate ID	Subject number	Screening number	OD value	Outlier
071609MLW01	[redacted]	54S17	0.0715	No
071609MLW01	[redacted]	55S22	0.0639	No
071609MLW01	[redacted]	56S28	0.0813	No
071609MLW01	[redacted]	56S29	1.1276	Yes
071609MLW01	[redacted]	56S31	0.0684	No
072009MLW01	[redacted]	67S12	0.0928	No
072009MLW01	[redacted]	68S33	0.0040	Yes
072009MLW01	[redacted]	68S36	0.0510	No
072009MLW01	[redacted]	68S42	0.0431	No
072009MLW01	[redacted]	69S97	0.0957	No

Plate ID	Subject number	Screening number	OD value	Outlier
072109HH02	[redacted]	72S15	0.0461	No
072109HH02	[redacted]	72S18	0.2836	Yes
072109HH02	[redacted]	72S20	0.0375	No
072109HH02	[redacted]	72S24	0.0511	No
072309MLW01	[redacted]	72S28	0.1079	No
072309MLW01	[redacted]	72S30	0.2721	Yes
072309MLW01	[redacted]	72S31	0.1093	No
072309MLW01	[redacted]	72S33	0.1096	No
091808MW01	[redacted]	44S06	0.0868	No
091808MW01	[redacted]	67S03	0.0810	No
091808MW01	[redacted]	67S04	0.3721	Yes
091808MW01	[redacted]	69S21	0.0918	No

A bootstrap sample of size 414 was taken from the original sample of 414 pre-treatment tier 1 OD values. This sample was used to produce non-parametric estimates of the 95th percentile point of the distribution OD values on both an overall level (based on the 414 OD values) and on an individual analyst level (based on the number of observations in the bootstrap sample from the respective analysts). If outliers were included in the bootstrap sample, they were not used in the computations of the percentile points.

Each OD value was then compared to the two bootstrap estimates of the 95th percentile point ("cut-point") of the OD value distribution and subsequently declared "positive" if the OD value exceeded the cut-point and "negative" if the value fell less than the cut-point.

The positive and negative declarations were then compared to the declarations made based on the cut-point based on the normal human serum samples as described in Millipore Cut-point Determination report (R2007-06). (For future reference, a cut-point developed according to the procedure described in this report will be referred to as a "Millipore" cut-point.)

The bootstrap sampling was carried out 10 times in an effort to understand the variation present in the process. The analyst-specific and overall 95th percentile cut-points are shown in the table below. Also included are the numbers of non-outliers belonging to each analyst, the expected number of data points upon which the percentiles are based.

Table 3: Bootstrap sample analyst-specific and pooled cut-points

Sample number	Analyst 1 (n=134)	Analyst 2 (n=80)	Analyst 3 (n=195)	Pooled (n=409)
1	0.674	0.221	0.224	0.276
2	0.674	0.345	0.233	0.299
3	0.371	0.276	0.209	0.299
4	0.674	0.345	0.190	0.276
5	0.371	0.221	0.221	0.249
6	0.371	0.337	0.182	0.299
7	0.299	0.276	0.233	0.276

Sample number	Analyst 1 (n=134)	Analyst 2 (n=80)	Analyst 3 (n=195)	Pooled (n=409)
8	0.816	0.221	0.256	0.301
9	0.371	0.292	0.224	0.276
10	0.260	0.330	0.233	0.260

For purposes of comparison, the non-parametric Millipore cut-points were 0.234 and 0.278 for the two analysts under consideration in that study, and 0.255 for the pooled estimate. The bootstrap-based cut-points presented in the table above are generally (but not always) larger than the corresponding Millipore cut-points, implying that the Millipore cut-points will be more conservative than those in the table above, as they will flag more values as positive.

A direct comparison of the outcome of the use of the cut-points from the bootstrap-based estimates and the Millipore cut-point is shown in the following tables. For each bootstrap sample, the joint distribution of positive/negative declarations under the Millipore and bootstrap samples is shown. Both the analyst-specific and grand percentiles are considered.

The first table shows the joint positive/negative declarations for the Millipore and analyst-specific cut-points.

Table 4: Millipore and analyst-specific pre-treatment positive and negative declaration comparison

	Millipore declaration / bootstrap analyst-specific declaration			
Sample number	Negative / Negative	Negative / Positive	Positive / Negative	Positive / Positive
1	365	2	25	22
2	367	0	29	18
3	366	1	20	27
4	366	1	25	22
5	365	2	20	27
6	365	2	20	27
7	367	0	21	26
8	365	2	20	27
9	367	0	22	25
10	366	1	21	26

Some common conclusions are available across the ten bootstrap samples.

The agreement between the two methods (Millipore and the analyst-specific cut-point) is high. Across the ten samples, agreement is seen in a minimum of 385 of 414 (93%) readings. Further, the disagreement is almost always a situation of a positive declaration made by the Millipore method and negative declaration made by the analyst-specific cut-point; that is, the Millipore methodology is more conservative, as it encourages further testing more often than does the analyst-specific cut-point developed above. Use of the new cut-point would have resulted in approximately 20 fewer tier 1 positive declarations.

The second table shows the joint positive/negative declarations for the Millipore and pooled cut-points.

Table 5: Millipore and pooled pre-treatment positive and negative declaration comparison

	Millipore declaration / bootstrap analyst-specific declaration			
Sample number	Negative / Negative	Negative / Positive	Positive / Negative	Positive / Positive
1	367	0	22	25
2	367	0	27	20
3	367	0	27	20
4	367	0	22	25
5	363	4	18	29
6	367	0	27	20
7	367	0	22	25
8	367	0	28	19
9	367	0	22	25
10	364	3	21	26

Similar conclusions can be made based on the pooled cut-point examination.

The level of agreement is high; a minimum of 386 of 414 (93%) of the samples show agreement. Two of the ten bootstrap samples yielded any "negative/positive" OD values. As with the analyst-specific cut-points, the Millipore method is more conservative, as it more likely to make a declaration of "positive" than is the analyst-specific cut-point based on the pre-treatment subjects.

The pre-treatment cut-points derived in the bootstrap samples can be applied to the post-treatment tier 1 OD values, just as they were applied to the pre-treatment data. As before, we present the outcomes for the cut-points from each of the samples.

Table 6: Millipore and analyst-specific post-treatment positive and negative declaration comparison

	Millipore declaration / bootstrap analyst-specific declaration			
Sample number	Negative / Negative	Negative / Positive	Positive / Negative	Positive / Positive
1	1172	10	161	208
2	1180	2	182	187
3	1176	6	135	234
4	1170	12	164	205
5	1170	12	129	240
6	1166	16	130	239
7	1177	5	131	238
8	1174	8	189	180
9	1180	2	146	223
10	1174	8	117	252

Table 7: Millipore and pooled post-treatment positive and negative declaration comparison

	Millipore declaration / bootstrap analyst-specific declaration			
Sample number	Negative / Negative	Negative / Positive	Positive / Negative	Positive / Positive
1	1175	7	143	226
2	1180	2	166	203
3	1180	2	166	203
4	1175	7	143	226
5	1171	11	116	253
6	1180	2	166	203
7	1175	7	143	226
8	1180	2	166	203
9	1175	7	143	226
10	1171	11	130	239

Across the ten bootstrap samples, the analyst-specific and pooled cut-points declared positive 159 times where the Millipore method declared negative. These 159 discordant results come from 21 subjects. The complete visit-by-visit OD values for these 21 subjects with suspect values are shown below.

All OD values are listed for each of the subjects below, along with the corresponding Millipore cut-point. Under the heading "Bootstrap sample outcome", the findings from the 10 bootstrap samples are given, with "A" showing that the analyst-specific cut-point declared Positive and a "P" showing that the pooled cut-point declared Positive. Of interest are those visits where the Millipore method declared Negative yet one or both of the pre-treatment, patient-based cut-points for at least one of the bootstrap samples did not.

Inspection of the subjects with bootstrap-declared positive OD values that the Millipore method did not declare as positive reveals that the suspect values are not particularly suspect when viewed in contrast to the other values within these particular subjects. For example, the suspect value for subject [redacted], the value at Visit 3, is 0.2801. The Millipore cut-point is 0.2889. The sequence of OD values are 0.16, 0.28, 0.53, 0.42, and 0.29, so the value of 0.28 at Visit 3 is consistent with the data seen for that subject as a whole.

Similar situations can be seen for all the other subjects with suspect OD values.

In general, the Millipore cut-points based on normal human serum produce positive declarations that are highly conservative, at least compared to those from pre-treated subjects. This conservative procedure leans toward caution, producing positive tier 1 declarations that can be followed up by further testing.

Table 8: Subjects with suspect declarations

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	082009MW01	0.1619	0.1340	Pos										
Visit 3	072309MLW02	0.2801	0.2889	Neg	AP		A	P	AP		AP	A	P	P
Visit 4	072309MLW02	0.5258	0.2889	Pos	AP		AP	AP	AP		AP	AP	AP	AP
Visit 6	072309MLW02	0.4193	0.2889	Pos	AP		AP	AP	AP		AP	AP	AP	AP
Visit 8	081909HH01	0.2929	0.1598	Pos	P			P	P		P		P	AP

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	071409MLW01	0.1467	0.2590	Neg										
Visit 3	071409MLW01	0.1636	0.2590	Neg										
Visit 4	071409MLW01	0.2379	0.2590	Neg	A				A			A		
Visit 6	071409MLW01	0.2171	0.2590	Neg										
Visit 8	071409MLW01	0.2280	0.2590	Neg	A				A			A		

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	071409MW01	0.1726	0.2382	Neg										
Visit 3	071409MW01	0.4783	0.2382	Pos				AP		AP				
Visit 4	071409MW01	0.6668	0.2382	Pos				AP		AP				
Visit 6	071409MW01	0.2448	0.2382	Pos				A		A				
Visit 8	071409MW01	0.2072	0.2382	Neg				A		A				

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	071409MW02	0.1902	0.3042	Neg						A				
Visit 3	082009MW02	0.0744	0.1387	Neg										
Visit 4	082009MW02	0.0621	0.1387	Neg										
Visit 6	071409MW02	0.1559	0.3042	Neg										
Visit 8	071409MW02	0.1626	0.3042	Neg										

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	071409MW02	0.1438	0.3042	Neg										
Visit 3	071409MW02	0.2022	0.3042	Neg				A		A				
Visit 4	071409MW02	0.4102	0.3042	Pos				AP		AP				
Visit 8	081909HH01	0.2748	0.1598	Pos										

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	032409MW02	0.1122	0.1693	Neg										
Visit 4	032409MW02	0.1289	0.1693	Neg										
Visit 6	062309MW01	0.2089	0.2254	Neg				A		A				
Visit 8	032409MW02	0.1333	0.1693	Neg										

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Visit 3	061209MW01	0.6813	0.1989	Pos				AP		AP				
Visit 4	061209MW01	0.3596	0.1989	Pos				AP		AP				
Visit 6	061209MW01	0.2514	0.1989	Pos				A		A				
Visit 8	061209MW01	0.1945	0.1989	Neg				A		A				

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	092308MW01	0.1673	0.2052	Neg										
Visit 3	091008MW02	0.2228	0.2745	Neg			A	A	A	A				
Visit 4	092308MW01	0.1662	0.2052	Neg										
Visit 6	091008MW02	0.2407	0.2745	Neg	A	A	A	A	A	A	A		A	A
Visit 8	091008MW02	0.2013	0.2745	Neg				A		A				

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	091008MW02	0.1615	0.2745	Neg										
Visit 3	091008MW02	0.1705	0.2745	Neg										
Visit 4	091008MW02	0.1575	0.2745	Neg										
Visit 6	091008MW02	0.1608	0.2745	Neg										
Visit 8	091008MW02	0.1829	0.2745	Neg						A				

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	091008MW02	0.1642	0.2745	Neg										
Visit 3	091008MW02	0.1715	0.2745	Neg										
Visit 4	091008MW02	0.2097	0.2745	Neg			A	A		A				
Visit 6	091008MW02	0.1632	0.2745	Neg										
Visit 8	091008MW02	0.1869	0.2745	Neg						A				

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	071709MW01	0.1521	0.2367	Neg										
Visit 3	071709MW01	0.1720	0.2367	Neg										
Visit 4	071709MW01	0.1309	0.2367	Neg										
Visit 6	071709MW01	0.2088	0.2367	Neg				A		A				
Visit 8	081909HH02	0.2937	0.1492	Pos				P						

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	061109MLW01	0.1523	0.1821	Neg										
Visit 3	061109MLW01	0.1710	0.1821	Neg										
Visit 4	061109MLW01	0.1182	0.1821	Neg										
Visit 6	062309MW01	0.2226	0.2254	Neg			A	A	A	A				

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	071709MLW01	0.1825	0.2333	Neg										
Visit 3	071709MLW01	0.2355	0.2333	Pos	A				A			A		
Visit 4	071709MLW01	0.2318	0.2333	Neg	A				A			A		
Visit 6	071709MLW01	0.2082	0.2333	Neg										
Visit 8	081909HH02	0.2969	0.1492	Pos	P				P					

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	031709HH02	0.0797	0.1849	Neg										
Visit 3	031709HH02	0.0867	0.1849	Neg										
Visit 4	032609MW02	0.2352	0.3471	Neg	A	A	A	A	A	A	A		A	A
Visit 6	032609MW02	0.1139	0.3471	Neg										
Visit 8	032609MW02	0.0942	0.3471	Neg										

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	032609MW01	0.1680	0.3739	Neg										
Visit 3	032609MW01	0.1704	0.3739	Neg										
Visit 4	032609MW01	0.1848	0.3739	Neg						A				
Visit 6	032609MW01	0.1784	0.3739	Neg										
Visit 8	032609MW01	0.1822	0.3739	Neg						A				

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	032609MW01	0.2206	0.3739	Neg			A	A		A				
Visit 3	032609MW01	0.1426	0.3739	Neg										
Visit 4	032609MW01	0.1410	0.3739	Neg										
Visit 6	032609MW01	0.1496	0.3739	Neg										
Visit 8	032609MW01	0.1525	0.3739	Neg										

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	072309HH01	0.2489	0.3001	Neg					P					
Visit 3	072309HH01	0.2377	0.3001	Neg										
Visit 4	072309HH01	0.2878	0.3001	Neg	P			P	P		P		P	AP
Visit 6	072309HH01	0.1827	0.3001	Neg										
Visit 8	072309HH01	0.2922	0.3001	Neg	P			P	P		P		P	AP

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	072309HH02	0.2701	0.3301	Neg					P					AP
Visit 3	072309HH02	0.3023	0.3301	Neg	P	P	P	P	P	P	AP	P	P	AP
Visit 4	072309HH02	0.2981	0.3301	Neg	P			P	P		P		P	AP
Visit 6	072309HH02	0.2770	0.3301	Neg	P			P	P		P		P	AP
Visit 8	072309HH02	0.3062	0.3301	Neg	P	P	P	P	P	P	AP	P	P	AP

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	072309MLW01	0.2721	0.2962	Neg	A				AP			A		P
Visit 3	072309MLW01	0.2611	0.2962	Neg	A				AP			A		P
Visit 4	072309MLW01	0.2745	0.2962	Neg	A				AP			A		P
Visit 6	072309MLW01	0.2749	0.2962	Neg	A				AP			A		P
Visit 8	072309MLW01	0.2675	0.2962	Neg	A				AP			A		P

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	072309MLW02	0.2757	0.2889	Neg	A				AP			A		P
Visit 3	072309MLW02	0.3983	0.2889	Pos	AP				AP			AP		AP
Visit 4	072309MLW02	0.6976	0.2889	Pos	AP				AP			AP		AP
Visit 6	072309MLW02	0.6016	0.2889	Pos	AP				AP			AP		AP
Visit 8	082009MW02	0.2234	0.1387	Pos					A					
Follow Up	030410HH01	0.3022	0.1619	Pos	P				P			P		AP

Screening number: [redacted]

Visit	Plate	OD	Cut-point	Pos/neg	Bootstrap sample outcome 1	2	3	4	5	6	7	8	9	10
Pre Treatment	082009MW01	0.0949	0.1340	Neg										
Visit 3	072809MW02	0.1931	0.2086	Neg				A		A				
Visit 4	072809MW02	0.1746	0.2086	Neg										
Visit 6	072809MW02	0.1628	0.2086	Neg										
Visit 8	072809MW02	0.2192	0.2086	Pos				A		A				

Question 3

3) *For both the ELISA method for the screening of anti-rhPDGF-BB antibodies and the ligand receptor binding assay (RIA) used as the neutralization assay, you did not supply supporting raw data (i.e. OD values) from their respective validation studies. Please provide the supporting raw data obtained in your validation study of the ELISA and RIA methods.*

Response

The supporting raw data for the validation studies, including individual OD values as well as averages of triplicates of each sample (OD averages for the ELISA and CPM averages for the RIA), are found in the appendices of the validation reports. Copies of the reports referenced can be found in Exhibit 3. The screening ELISA was co-developed with Millipore, validated at Millipore including statistical analysis of the assay cut point, and further qualified at BMTI. Validation reports are the following:

- Millipore Validation Report 07-109
- BMTI Qualification Report RnD-0009-RDR

The RIA was developed and qualified at BMTI using radiolabeled rhPDGF-BB. The qualification report includes the raw data in the form of average CPM of individual samples for every part of the qualification study (report appendices). The qualification report is the following:

- BMTI Qualification Report RnD-0008-RDR

Question 4

4) *You have validated a RIA as an assay to detect neutralizing antibodies. Although this type of assay is acceptable as a binding assay, the agency recommends the development of a bioassay as a better approach to evaluate the ability of antibodies to directly interfere with drug activity in vivo. Please develop a bioassay for the evaluation of anti-drug neutralizing antibodies. Please provide information to demonstrate that the assay is validated and supporting raw data. Please note if your RIA is sufficiently sensitive it could be considered as a confirmatory assay for the screening assay.*

Response

BMTI discussed the caveats of cell-based assays due to stimulatory effects of serum with the Agency (Dr. Susan Kirschner and Dr. Kathy Lee) three years ago at a teleconference on November 1st, 2007, and got agreement on the approach employed (reference is made to email communications on Oct. 30, November 1, and December 18, 2007, in Exhibit 4). However, BMTI has worked diligently in parallel to develop cell-based assays to detect neutralizing antibodies (NAb) in human as well as rat serum (in support of non-clinical studies). These assays are based

on inhibition of PDGF β-receptor phosphorylation at Tyrosine 751 using fibroblast cell lines. The human NAb assay is based on showing inhibition of receptor phosphorylation of human neonatal dermal fibroblast cells whereas the rat NAb assay is based on a rat lung fibroblast cell line. The human assay is in final development and planned to be validated by mid December 2010.

As discussed with the Agency at a teleconference October 15, 2010 including Dr. Susan Kirschner, BMTI is providing a summary assay development report RnD-102110-01R in Exhibit 4 including development data for review.

The sensitivity of cell based assay seems to be approximately 1000 ng/ml of the goat neutralizing antibody used as a positive control. In contrast, the current RIA to detect NAb is based on a sensitivity of 250 ng/ml of the goat Nab positive control with approx 75 % neutralization (RIA NAb Validation Report).

The rat NAb assay was developed as a commitment under the IDE on Augment and the assay is being qualified at this time. A summary development report for the rat Nab assay RnD-102110-02R and the assay qualification protocol RnD-062110-1R are included in Exhibit 4.

Question 5

5) *You supplied anti-drug-antibody screening of patient serum samples as part of the clinical studies conducted in Canada (BMTI-2005-03-CAN) and in North America (BMTI-2006-01) in immunogenicity reports 3.4 and 3.6. However, you did not provide the raw data to support your clinical conclusions. Please provide supporting raw data from individuals assessed as part of the clinical studies.*

Response

In response to the PMA 100 day letter regarding the immunogenicity data and testing program, BMTI performed a 100% verification of the raw data, the recorded read-outs and the reported results. This resulted in an amended immunogenicity report RnD-102810-1R as well as a report assessing the changes to the immunogenicity report and the potential effect on the results. The assessment of changes report is RnD-110710-1R. Both reports are included in Exhibit 5.

The raw data from the two clinical studies conducted in Canada (BMTI-2005-03-CAN) and in North America (BMTI-2006-01) are presented in Exhibit 5. Each patient serum sample at each visit is screened in Tier 1 and followed in Tier 2-4 if positive.

The spreadsheets contain individual patient raw data (OD values) for the screening ELISA and the corresponding assay floating cut points for Tier 1. The raw OD data for Tier 2 testing of the Tier 1 putative positives are presented along with the % inhibition for each sample to confirm specific ADA positives by immunodepletion. In cases where the OD value of a Tier 2 sample is below the floating cut point, no inhibition is calculated.

Furthermore, Tier 3 data demonstrating the antibody titer of the Tier 2 positives at individual visits are shown. And finally, Tier 4 data on Tier 2 positives showing no detection of neutralizing antibodies are included.

Included in the spreadsheet on the BMTI-2006-01 serum sample testing are graphic representations on % positives at Tier 1 and Tier 2 per treatment group as well as % positives per patient visit. The graphs show that the immunological response of the Augment group is highest at 8.8% at visits 4 and 6, decreasing to 4.4% at visit 8 and 0.7% (two subjects) at the first follow up visit.

Clinical

Question 6

6) *FDA has concerns about the increased number of cancer events seen in patients who received rhPDGF-BB; 1.8% (5/272) of adverse events in Augment patients categorized as Neoplasms and 1.4% (2/142) in autograft control patients. There is concern because there are reports of rhPDGF being associated with breast, endometrial, renal cell, and prostate cancer. Although the association between these cancers and rhPDGF is not clear, in order to better understand this association, further information should be collected and studied. In March, 2008, the FDA issued an Early Communication concerning a possible link between multiple uses of Regranex (rhPDGF-BB) and an increase in mortality from pre-existing cancers. In the current trial, there were 5 "neoplasms" reported in 5 investigational patients and 2 "neoplasms" in 2 control patients.*

Specifically there were 5 cases of "Neoplasms benign, malignant, and unspecified" noted in the summary of all adverse events by SOC and PT in the investigational group. Two were excluded from the investigational group for further analyses as a serious adverse event, but both control cases were included. To better understand how these two and other patients were evaluated and excluded, and in order to help determine whether a safety concern exists with the use of your device, please provide more details about how cases were determined as serious versus benign or undetermined.

a) *Please provide more detailed information on the clinical presentation of all 7 of the patients diagnosed with neoplasms during this study. Information should include how patients were screened for pre-existing cancer; the cancer risk factors for each patient; and pathological reports with histopathology. Specifically, please provide complete demographic data (e.g., age at onset, gender, race, ethnicity); the time to the onset of symptoms and the time to diagnosis in relation to the procedure; the location, specific diagnosis and histology of the tumor; any concomitant medications or medical or congenital conditions at the time of surgery; any family history of cancer (relative, age, and type of diagnosis); complete pathology reports if available; and the final study outcomes for each patient.*

Response

In response to FDA's request, BMTI is providing all available information on all neoplasms associated with the study, as well as rationale for why BMTI considers the total number of cancer events for this study to be 5 (3 Augment and 2 Autograft).

Prior to enrollment in the BMTI-2006-01 study, subjects were screened according to protocol exclusion criteria number four of the protocol (version 4.1 dated 05 April 2007). Per the exclusion criterion, subjects were excluded if they currently had

untreated malignant neoplasm(s) at the surgical site, or were currently undergoing radio- or chemo-therapy.

Enclosed in Appendix 6a is more detailed information on the clinical presentation of all seven of the patients diagnosed with neoplasms during this study as requested in significant deficiency 6a. As noted, five of these patients' diagnoses (patient screening numbers [redacted]) were reported by the corresponding principal investigators as serious adverse events (SAEs) and the enclosed details are intended to accompany the SAE narratives that were submitted as a part of PMA P100006 in May 2010.

Because the additional two patients' diagnoses were benign (screening numbers [redacted] and [redacted]), the events did not meet the criteria for serious adverse events. The enclosed detailed information has been obtained from the responsible principal investigators to provide a more complete picture of these two events.

These two subjects each experienced an event for which the coded term was neoplasm, but were not cancers or serious adverse events.

- Subject [redacted]: Colon polyps as an ongoing event in a subject with prior polyp history. The attending physician only recommended a follow-up colonoscopy on a regular basis.
- Subject [redacted]: Plantar fibroma (fibromatosis – benign soft tissue) in a subject without prior history. This issue was resolved through the use of an orthotic.

For each patient, BMTI has captured the requested information on a "Neoplasm Events" form, which is followed by case report information, and neoplasm event surgical and pathology reports (if available). This information is included in Exhibit 6. However, based on the non-cancerous nature of the two neoplasms, BMTI continues to believe that the data only support considering the original five cancer-related SAE's when calculating and reporting cancer incidence in the trial. As discussed in item 6c, BMTI intends to conduct a long term follow-up (Post Approval Study) to obtain additional long term safety data.

In conclusion, there were no trends noted in occurrence or recurrence of cancers. There were 5 SAEs related to cancer reported as summarized below:

Table 9: Incidence of Cancer

Treatment Group	Number of cancers	Incidence
Augment Bone Graft (n=272)	3	1.1%
Autograft (n=142)	2	1.4%

b) *FDA is aware of observations of epidemiologic studies wherein the use of the Regranex product, which contains the same rhPDGF-BB protein as your product, has been correlated with an apparent increase in cancer mortality in patients treated with the product. FDA's Center for Drug Evaluation and Research (CDER) issued an Early Communication (EC) about this in order to inform physicians and patients of the potential safety concern. Please provide any updated cancer data associated with the use of Regranex in the treatment of diabetic ulcers and rhPDGF-BB use under PMA #P040013 for periodontal bone defects. This information should include reports of MDRs and adverse events reported to the manufacture and any post-marketing surveillance or studies. Because the cancer risk associated with rhPDGF-BB is unclear in this population, any updated data may be helpful in further clarifying the cancer risks to any patient exposed to rhPDGF-BB. Additionally, please provide information on your worldwide experience with rhPDGF-BB, especially with respect to any noted increase in cancer incidence.*

Response

As requested, BMTI is providing available information and data regarding cancer incidence for other approved products containing rhPDGF-BB. BMTI is committed to collecting, analyzing, and reporting safety data that pertain to the Augment product, and as noted in 6c, we intend to support a long term follow-up PAS to assess, among other considerations, incidence of cancer and mortality due to cancer.

BMTI is aware of the epidemiologic study FDA references for the Regranex product. While BMTI understands and appreciates the agency's concerns resulting from this study, including the Early Communication and eventual Black Box warning for Regranex, BMTI does not believe these data directly relate to the Augment product.

It is important to recognize that the administration of Regranex and Augment are very different as Augment is a single-use application as a device, whereas Regranex is applied many times over a period of months as a drug.

The following table compares rhPDGF-BB exposure for Augment and Regranex.

Table 10: Comparison of rhPDGF-BB in Augment versus Regranex

Product	Augment™ Bone Graft	Regranex®	Ratio Regranex/Augment
Administration frequency	One time	Repeated over 13-20 weeks	
Typical clinical dose of rhPDGF-BB	1.8 mg	4.5 - 6.9 mg	2.5 - 3.8
Maximum clinical dose	2.7 mg	98 mg	36

In addition, the cited Regranex study had many design flaws, including:

1. Inadequate ability to determine the location and sizes of the diabetic foot ulcers being treated. This led to uncertainties with determining if the control group in this retrospective, insurance data base study actually matched the treatment group;
2. The actual use of Regranex could not be determined in the study as only the number of prescriptions filled was available;
3. There was not always a clear understanding of the actual cause of a patient's death. If no death certificate was available, it was assumed the patient did not die of cancer. Given the low number of cancer deaths in the study, this is a major flaw;
4. There was not an ability to measure cancer type or severity of cancer at the time of treatment; and,
5. There were no differences found in the incidence in cancer between the Regranex and the control group.

If rhPDGF-BB was found to increase the risk of cancer mortality by accelerating cancer growth, then an increase in the incidence of detectable cancers would be expected. Therefore, BMTI does not believe Regranex or the data from the cited reference should be applied to the Augment product.

However, BMTI acknowledges that FDA did incorporate a Black Box warning into the Regranex label and that Regranex does contain rhPDGF-BB. Therefore, it is understandable that FDA would consider these data relevant. As BMTI is very concerned with patient safety, BMTI has considered these data but still believe that the data from preclinical and clinical studies with the Augment product are more pertinent to the safety of Augment.

BMTI further believes that FDA's own Black Box warning on Regranex supports this presentation, as FDA states that there is only a potential concern when three or more tubes of Regranex are used over an extended time.

rhPDGF Dosing and Exposure Comparison between Regranex and Augment:
Due to slow healing of cutaneous ulcers, characteristically up to between 112 and 140 repeat administrations have been employed over 16-20 weeks. Typical ulcer sizes averaged approximately 5 cm^2 (up to a maximum of 100 cm^2), with treatment to 16-20 weeks duration (Smiell et al, 1998).

One study assessing the toxicology of rhPDGF-BB has been performed, whereby doses of up to 3.0 mg/kg, which is at least 50 times the maximum possible systemic exposure of subjects in the proposed study, were administered intravenously in mice with no significant acute toxicity (Knight et al, 1998). In a second study in mice, administration of single IV doses of up to 100 mg/kg, or greater than 1800 times the maximum possible exposure of subjects in the proposed study, resulted in dose-related symptoms which they disappeared within 4 hours of dosing. No other clinical signs of toxicity were observed. Finally, subcutaneous administration of up to 3 mg/kg of rhPDGF-BB in monkeys also produced no signs of toxicity.

Multiple dose toxicity studies of becaplermin (rhPDGF-BB) administered IV, SC, or topical in mice, rabbits, and monkeys were also reported in the above referenced publication. The no observed adverse effect level (NOAEL) for becaplermin in mice was 0.3 mg/kg/day for 14 days. One administration of this dose is greater than 1.5 times, and the cumulative dose is over 78 times, the maximum theoretical exposure of subjects in this study.

In summary, the risk of toxicity to rhPDGF-BB at implantation sites of Augment is transient, based on

- Rapid release of rhPDGF-BB from β-TCP
- Rapid disappearance of rhPDGF-BB from the Augment implantation site

Risk of toxicity to rhPDGF-BB in Augment is considered very low, as compared to Regranex® based on:

- Efficacy and lack of safety concerns from a randomized controlled trial in 180 subjects with periodontal bone defects using rhPDGF-BB concentrations of 0.3 mg/ml and 1.0 mg/ml, in which the lower concentration was observed to be most efficacious;
- Low intrinsic toxicity of the protein, as demonstrated by lack of any clinically relevant adverse response to rhPDGF-BB in numerous studies of Regranex®;
- Single-dose administration of Augment, in contrast to multiple-administration, booster exposures with Regranex®;
- Similar concentrations of rhPDGF-BB in Augment and Regranex®, but substantially less aggregate exposure from Augment.
- Safety of the device as demonstrated in multiple clinical trials where no device related adverse events were reported.

Commercial Use:
Although GEM21S (P040013) has been sold to Luitpold Pharmaceuticals, Inc., BMTI does have access to data under that application. BMTI has reviewed all the available information and after over 100,000 units have been implanted, BMTI was only able to locate one potential cancer-related event. In MDR #20090420 (attached in Exhibit 6), Luitpold reported on a patient in whom a squamous cell carcinoma was discovered approximately two months after a mineralized freeze dried bone graft saturated with the PDGF component of GEM 21S was used to fill a tooth extraction site. Luitpold maintains, and BMTI agrees, that a one-time single exposure to the PDGF in GEM 21S could not promote a squamous cell carcinoma in a mere two months and that it is much more likely that the patient had the carcinoma prior to the tooth extraction.

Finally, the only commercial use of Augment has been in Canada where the product was approved in November of 2009. Approximately 50 kits have been sold to date. There have been no reports of any kind of adverse events (including cancers) submitted to the company.

In summary, BMTI does not believe that any data exist that indicate a potential cancer risk associated with Augment. However, BMTI remains dedicated to surveillance of patient safety and is proposing a post-approval study to collect longer-term safety data on the product. This proposal is discussed in item 6c and presented in detail in item 25 below.

c) *Because of the potential health risk to patients, the potential for a long delay in receiving a diagnosis of cancer, and the association of increased cancer risk in Regranex's use in diabetic ulcers, even if you provide the information requested above, it still may not be adequate to explain the increased neoplastic events seen in the investigational patients. Therefore, FDA will potentially request a long term follow-up and post market study, should this device be approved. Please provide your post-market study design plan specifically to help answer this longer term safety question dealing with cancer. You should consider establishing a patient registry or prolonged post-market study to monitor for cancers in patients exposed to rhPDGF-BB. Please submit a post approval study to address these issues.*

Response

As requested, BMTI has proposed a long term follow-up post –approval study (PAS). The response to item 25 includes a proposed design for a long-term follow-up study as requested.

As discussed above in the response to 6a, there was no increase in the rate of malignancy in active versus control subjects (1.1% incidence in Augment Bone Graft subjects versus 1.4% incidence in autograft subjects).

Question 7

7) *You have provided additional analyses of your data in support of your primary endpoint in a modified intent-to-treat population. Your primary endpoint considers fusion for a full complement of joints as greater than 50% osseous bridging as defined by CT and was used to determine the success of your study. You have based this performance criterion on a literature review of 2 studies, as well as anecdotal reports, of patients who have undergone talar fusions with outcomes assessed by CT. You conclude that these studies indicate that this is a sensitive predictor of clinical success. FDA believes that in addition to the radiographic endpoint, the primary endpoint should be a composite of maintenance or improvement in both pain and overall function, in the absence of device-related adverse events or subsequent surgical intervention and retreatment at the index level. Please address the following concerns regarding your primary and secondary criteria:*

   a) *FDA believes that the primary effectiveness endpoint that assesses fusion should be a composite of not only radiographic measures, but clinical improvements in both pain and functional status. In FDA's April, 2009 IDE G050118 letter to you, these concerns were outlined. Without a clinically meaningful composite endpoint, the effectiveness of your device for the intended population cannot be determined. Please include and summarize the data obtained from VAS on weight bearing, SF-12, FFI, and AOFAS questionnaires, which you collected as secondary endpoints, analyzed as composite primary effectiveness endpoints and reanalyze your data for study success.*

Response

The primary endpoint analyzed was the endpoint established via the original approved IDE, namely: Fusion of the full complement of joints equal to or greater than 50% osseous bridging as assessed by the independent radiologist at 24 weeks post-operatively.

As requested by FDA, BMTI is including a new composite endpoint to include clinical, functional, and safety components. This new Subject Performance composite suggested by FDA is a post-hoc construct developed in order to address the parameters outlined above. This endpoint is constructed with the following required for success at the patient level:

Clinical

- Improvement from baseline of at least 20mm in the subject's weight bearing pain score measured via a 100mm visual analogue scale (VAS).
- Absence of any secondary procedures for the subject

Functional

- Improvement in subject function as indicated by a 10 point or greater reduction in score for the subject-reported Foot Pain and Disability Index (also referred to a the Foot Function Index or FFI); (Budiman-Mak, 1991)
- Documented absence of significant graft harvest site pain (i.e. pain less than 20mm as recorded by subject on a 100mm VAS scale)

Safety

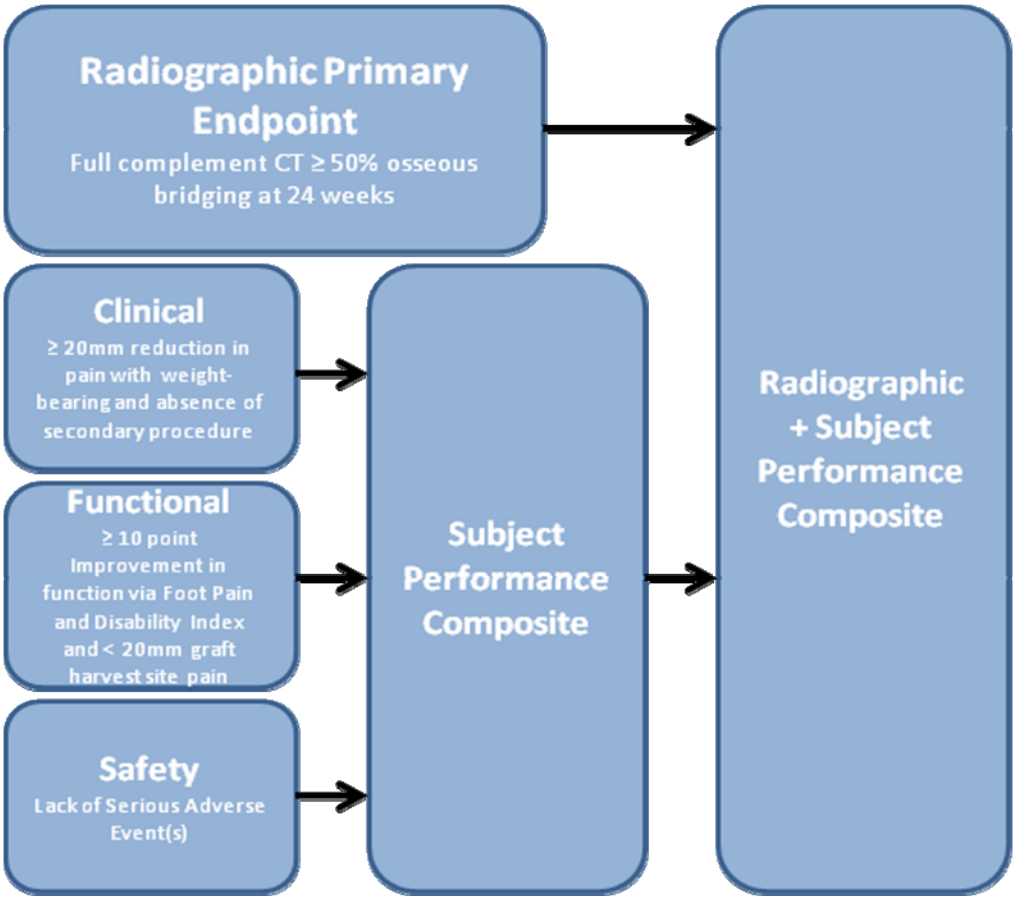
- Absence of serious adverse event(s) for the subject

The FFI score was selected as the functional component of the analysis as it is a single, validated instrument which addresses subject pain, disability, and activity limitation, as they relate to foot pathology (Budiman-Mak, 1991). The FFI was developed to measure the impact of such pathology on function in terms of pain, difficulty, and activity restriction. This instrument is considered to be more precise and sensitive to change than other previous instruments. Based on the above, it is noted that the FFI is itself a composite success parameter for foot function and disability at the patient level.

Inclusion of all the component measures listed in 7a above does not serve to produce a clinically meaningful endpoint as these measures overlap with other measures such as the SF-12 scale or AOFAS score, and thus are not independent evaluations. Inclusion of a larger number of measurements, by definition, will depress fusion rates. This reduction in rates may obscure a clinically relevant evaluation. However, as requested, BMTI has presented the data from analysis under the above noted parameters.

The Subject Performance composite was also analyzed in combination with the original primary endpoint of fusion via CT scan. Figure 1 demonstrates the hierarchy of the various components of the composite endpoint.

Figure 1: Composite Endpoints



Results of these requested analyses are included in Table 11 and Table 12 below:

Table 11: Subject Performance Composite

	All Patients (mITT)	Augment Bone Graft	Autologous Bone Graft	Rate Difference	Non-inferiority p-value (95% upper bound)	Lower Confidence Limit
Week 9	96 (24.2%)	69 (26.5%)	27 (19.7%)	6.8%	0.000	-0.3%
Week 12	127 (32.0%)	88 (33.8%)	39 (28.5%)	5.4%	0.001	-2.6%
Week 16	165 (41.6%)	113 (43.5%)	52 (38.0%)	5.5%	0.001	-3.0%
Week 24	**195 (49.1%)**	**130 (50.0%)**	**65 (47.4%)**	**2.6%**	**0.009**	**-6.1%**
Week 36	201 (50.6%)	131 (50.4%)	70 (51.1%)	-0.7%	0.039	-9.4%
Week 52	194 (48.9%)	126 (48.5%)	68 (49.6%)	-1.2%	0.047	-9.9%

Results of the Subject Performance composite endpoint continue to provide support for non-inferiority of Augment versus autograft at all timepoints.

Table 12 Subject Performance Composite Endpoint plus CT ≥ 50%

	All Patients (mITT)	Augment Bone Graft	Autologous Bone Graft	Rate Difference	Non-inferiority p-value (95% upper bound)	Lower Confidence Limit
Week 24	133 (33.5%)	90 (34.6%)	43 (31.4%)	3.2%	0.004	-4.9%

The combination of the Subject Performance composite with the Primary Endpoint at 24 weeks also supports non-inferiority of Augment versus autograft at 24 weeks (p=0.004). As discussed above, this measure, while statistically significant for non-inferiority, may suffer from limitations in utility due to the overall depressed rates incurred by the number of measures included in the endpoint calculation.

In summary, while BMTI believes the original primary endpoint of percent of study subjects achieving ≥50% osseous bridging by independent analysis of CT scans is an appropriate primary endpoint for hindfoot and ankle arthrodesis, it is reasonable to assess a composite endpoint incorporating clinical, functional, and safety outcomes. The specificity, sensitivity, and durability of this endpoint has not been validated for the study outcome, therefore the overall value of this endpoint in determining success of the index fusion procedure may be limited.

b) *You have provided a definition of radiographic fusion which is not adequate to fully define the characteristic of foot and ankle fusion. The FDA does not believe that there is sufficient information regarding the Augment system to assess its use based solely on an objective performance criterion (OPC). Moreover, we believe that the OPC that you have derived from the literature is based on several assumptions that have not been established or universally accepted. The FDA believes that the OPC is set for a device 'type' after a significantly large set of data is available to characterize the device.*

Currently, the use of Augment in foot and ankle fusions is a novel device use with no clinical data characterizing it. You are assuming that the effectiveness in fusion success is equivalent for the device and autograft use and that the patient populations and assessments are similar. However this is not the case. Thus, the OPC that you have proposed will not yield data that is adequate

valid scientific evidence per 21 CFR 860.7. Please reanalyze your primary endpoint for the experimental and control groups to include radiographic assessments of fusion by both CT and standard plain radiographic protocols at 24 weeks and 52 weeks in your analyses.

Response

As requested by FDA, analyses have been presented for both CT fusion and fusion by plain radiographs (see BMTI-2006-01 52-week Clinical Study Report included in Exhibit 6).

While BMTI acknowledges that fusion as assessed by CT is not a universally accepted criterion for the determination of fusion, evaluation of fusion via CT is the evolving standard for objective evaluation of fusion as supported both by recent literature and by the results of the subject study. Of all the radiologic measures studied in this clinical trial, evaluation via CT produces the highest balance of sensitivity and specificity for the prediction of clinical union (see also question e.). It is also more data-rich and less technique-sensitive than plain radiographs, as a CT scan represents a three dimensional image with multiple slices to which the independent assessor refers to analyze the entire fusion construct. In contrast, plain film radiographs represent a two dimensional image which, given the anatomy of the foot and ankle, makes independent analysis of hindfoot/ankle fusion/arthrodesis more technically challenging and less reproducible, as compared to fracture healing of a long bone or spine fusion.

While the primary endpoint for this study is the most rigorous analysis performed in clinical trials to date for assessment of fusion, the study also included multiple secondary endpoints, including clinical, functional, radiographic, and safety endpoints. We believe that each of these endpoints can independently be considered adequate objective performance criterion for a foot and ankle arthrodesis trial. Augment Bone Graft demonstrated non-inferiority across all of the above noted endpoint groups, without the need for an additional harvest site.

c) *The incidence of all surgical intervention/retreatments at the index level should be collected as part of a composite primary safety endpoint. You have defined secondary surgical procedures as "therapeutic failures". "Therapeutic failures" were determined as to whether or not a secondary procedure or other therapeutic intervention (such as a bone stimulator) was required due to delayed or non-union. This definition narrowly pre-defines which secondary procedures will be considered as success/failure criteria to determine the safety of your device and does not adequately address safety concerns in addition to interventions for delayed or non-unions. You have not defined or analyzed additional surgeries in terms of device removal and reoperation for other indications. Your definition and inclusion of only one component of secondary surgeries differs from the secondary surgical procedure definitions as outlined in the "Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications". Specifically, a revision is a procedure that adjusts or in any way modifies or removes part of the*

original implant configuration, with or without replacement of a component. A revision may also include adjusting the position of the original configuration. A removal is a procedure where the entire original system configuration is removed with or without replacement. A reoperation is any surgical procedure at the involved level(s) that does not include removal, modification, or addition of any components to the system. A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted (e.g., supplemental placement of a plate/screw system). The reporting of subsequent treatments and interventions is performed in the same manner as the reporting of deaths.

Please provide detailed narrative information on each secondary surgical intervention performed during the study and revise your categorizations to be consistent with those as defined in the guidance document above. Please also revise your overall success/failure analyses considering all secondary interventions and/or reoperations involving the treated level as "failures".

Response

As requested by FDA, BMTI has revised the accounting and definition for secondary procedures in line with the criteria posed by the FDA. Please see Table 13: Categorization of Secondary Procedures below.

Table 13: Categorization of Secondary Procedures

Type	Screening Visit 1	Surgery Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Revisions										
Removals								I =2	I = 1 C = 1	
Supplemental Fixations										
Reoperations							C = 1**	I = 1**	I = 2	
Other interventions (hardware removals)					I = 2		I = 2 C = 4**	I = 5** C = 1	I = 2 C = 2	
Total					**2**		**6**	**8**	**8**	

I = investigational group; C = Control group
*Grey shading indicates no secondary procedures occurred.
**Same subject multiple procedures with different [redacted]) classifications

Per FDA's recommendation, BMTI has identified the following surgeries categorized as 'removals' as being failures based upon protocol definitions and the rationale provided by the investigator on the eCRF:

- [redacted] (Augment)– as a result of non-union/delayed union the investigator performed a hardware/device removal surgery and used iliac crest bone graft.
- [redacted] (Augment)– as a result of non-union/delayed union the investigator performed a hardware/device removal surgery and used autologous bone graft.
- [redacted] (Autologous) – as a result of non-union/delayed union the investigator performed a hardware/device removal surgery and used autologous bone graft.
- [redacted] (Augment) – as a result of non-union/delayed union the investigator performed a hardware/device removal surgery and used autologous bone graft as the substitute.

As requested by FDA, additional patient level detailed information for secondary procedures (see Exhibit 7) is provided for your review.

Please note that many of the secondary procedures are, in reality, associated with other surgical hardware or issues unrelated to the investigational product. Per request, despite these limitations, secondary procedures have been treated as failures for the purposes of the revised composite endpoint as described under 7a above and are herein reported per "*Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications*".

d) *You have analyzed your primary endpoint in a modified intent to treat (mITT) population. Your original IDE statistical plan states that the primary analysis will be performed using the ITT dataset, with a Per Protocol (PP) data set as confirmatory. You have not provided an adequate justification for using mITT instead of ITT. Modified intent-to-treat analysis allows a subjective approach in entry criteria, which could be biased. Because patients have already been randomized to receive the device, their exclusion and withdrawal for not receiving treatment according to the protocol jeopardizes the baseline comparability of study groups established by randomization. Patients could be withdrawn from analyses for the occurrence of perioperative and postoperative adverse events that lead to their not receiving treatment according to protocol or their exclusion as "an intraoperative screen failure", which may or may not be device related after further analysis. The FDA requires a full accounting of all randomized and non-randomized participants in a trial. Subjects randomized to the device who have been selected according to the defined Inclusion/Exclusion criteria and have undergone an attempt at treatment should be analyzed as an intent-to-treat dataset. Please provide a reanalysis of the intent to treat dataset. Furthermore, the study has a fairly high number of Major Protocol Deviations (1,457 for 456 patients). In addition to your reanalysis of the ITT dataset, please provide a breakdown of protocol violations according to treatment group.*

Response

FDA is correct in that the protocol did state that an ITT population was planned for analysis. FDA pointed out that the population as defined by BMTI was not a true ITT (May 18, 2007 letter from FDA to G050118). In that letter, FDA stated that the population in the IDE as defined by BMTI could be considered a modified intent to treat and presented in the PMA. The population provided as the mITT is consistent with the intent of the approved protocol. This population only excludes (as seen in Figure 2 and Figure 3, plus supporting tables below) patients who were never treated or were intra-operative screen failures or who should have been withdrawn from the study by the physician. All patients excluded from the mITT were removed from the analysis in a blinded manner (i.e., BMTI did not know either their treatment assignment or any of their outcome measures). FDA's letter also requested that BMTI provide a "true ITT" and this is the definition of the ITT population as analyzed and presented in the PMA. As seen below, BMTI has conducted a study with excellent compliance and follow-up and the company continues to believe that the mITT is the most clinically valid dataset for analysis.

As requested by FDA, BMTI has provided a full accounting of all randomized and non-randomized subjects (e.g. screen failures) in this study as summarized in Figure 2: Subject Populations and further detailed in Figure 3: Description of Excluded Subjects. Please see tables and figures below. BMTI has illustrated this information per the guidance document (see patient accounting table). Please refer also to additional subject information included in the response to question 20.

Figure 2: Subject Populations

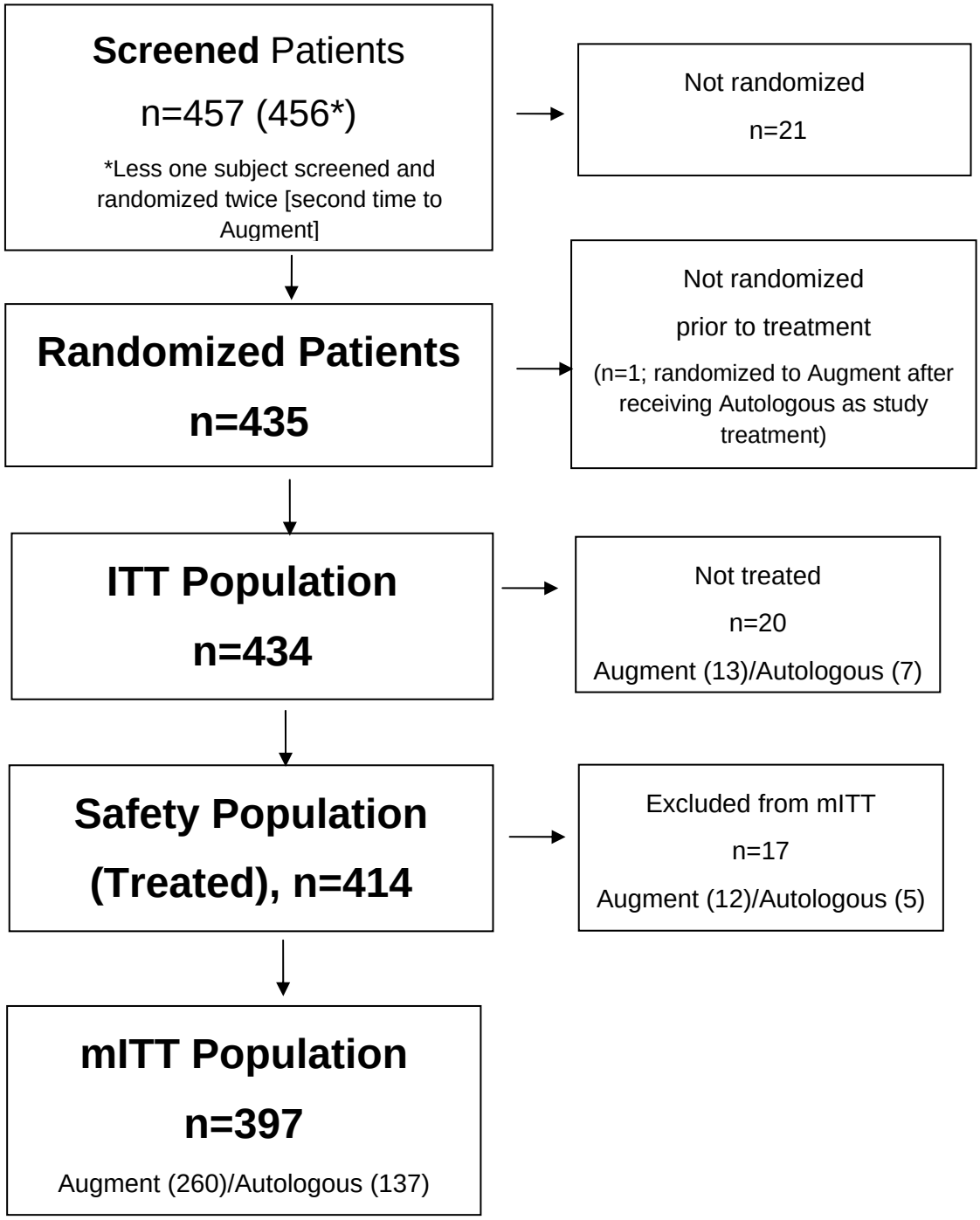


Figure 3: Description of Excluded Subjects

ITT Subjects not Treated (20)		
	Augment (13)	Autograft (7)
Subject Withdrew	[redacted]	
Failed exclusion for hardware or surgical procedure		
Subject not cleared for surgery		
Subject required both hindfoot and ankle surgery		
Subject presented with infection at surgery		
Exclusionary material (allograft) required for procedure		
Site closed prior to subject treatment		
Other surgical procedure required		

ITT Subjects Excluded from mITT (17)		
	Augment (12)	Autograft (5)
Deviation for exclusionary hardware (plate)	[redacted]	
Deviation for exclusionary surgical procedure (procedure or graft material)		
Deviation for exclusionary hardware and surgical procedure (Augment, autograft, plates and screws)		
Deviation for exclusionary surgical procedure (midfoot procedure)		
Deviation for exclusionary surgical procedure (both hindfoot and ankle surgery)		
Deviation for exclusionary medication		
Subject non-compliance (early weight bearing)		
Deviation for exclusionary material (too much graft volume)		

BMTI has prepared a list of all subjects excluded from the mITT dataset with the detail regarding the reasons for exclusion. All randomized patients were previously analyzed as part of the ITT population; therefore, no re-analysis has been conducted.

Of the 457 subjects screened (one subject entered twice into screening module of the CRF), there were a total of 435 patients randomized in the study. One (1) patient was randomized post-treatment and was excluded from analysis. The corresponding listing and details of the 21 subjects who were screened but never randomized can be found in below. Given their attrition prior to randomization, per BMTI guidance, clinical sites were not required to collect data on these subjects; therefore, no follow-up data are available for analysis. For the reasons noted within the table, these subjects are excluded from all study analyses.

Table 14: Subjects Screened But Never Randomized or Treated

Subject	Randomization date	Surgery date	Comment
[redacted]	N/A	N/A	SUBJECT REQUESTED TO BE WITHDRAWN FROM THE STUDY PRIOR TO RANDOMIZATION/SURGERY.
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	THE SUBJECT WAS DETERMINED NOT ELIGIBLE FOR THE STUDY
	N/A	N/A	THE SUBJECT WAS DETERMINED NOT ELIGIBLE FOR THE STUDY
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	PATIENT ENROLLMENT WAS CEASED PRIOR TO RANDOMIZATION
	N/A	N/A	Screen failure
	N/A	N/A	PI DISCRETION
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	DIABETIC NEUROPATHY IN FEET
	N/A	N/A	UNABLE TO OBTAIN PRE-APPROVAL FROM INSURANCE COMPANY PRIOR TO SURGERY
	N/A	N/A	UNABLE TO OBTAIN INSURANCE PREAPPROVAL PRIOR TO SURGERY
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified
	N/A	N/A	Screen failure - unspecified

The remaining 434 patients (excluding the single patient noted above who was randomized post-treatment and excluded from analysis) compose the ITT population.

There were 20 patients that were randomized but were screen failures intra-operatively or were otherwise not treated. There were a total of 414 patients randomized and treated in the study. These subjects are listed first on Table 15, and are noted to have "N/A" as the surgery date, as they did not have surgery under this study protocol. Another 17 patients, also included in Table 15, were further excluded from the mITT population (n=397; see Table 15). Prior to database lock, BMTI reviewed all surgical procedures for each subject in a blinded manner to determine evaluability for statistical analysis. The stringent review of subject's data for statistical analysis in the mITT analysis populations did not exclude the subject data from the safety analysis. Reasons for exclusion from the mITT population include:

- Surgery required use of excluded hardware (plate) (4);
- Surgery and graft placement were not done per protocol (2)
- Subject had 5 screws used across fusion site (1)
- Surgery incorporated excluded procedure (midfoot fusion) (4)
- Surgery incorporated excluded procedure (both ankle and hindfoot fusions) (3)
- Subject received excluded medication (1)
- Subject noncompliant with protocol (early weightbearing) (1)
- Surgery required use of excluded amount of graft (graft volume in excess of 9cc) (1)

The listing and details of subjects excluded from the mITT patient population are noted below.

Table 15: Summary of Subject Exclusion from mITT Population*

Subject	Treatment Assignment	Treated	Randomization Date	Surgery Date	Withdrawal Date	Reason for Exclusion
[redacted]	Control (Autograft)	No	26 Mar 2008	N/A	26 Mar 2008	Subject withdrew consent prior to surgery
[redacted]	Active (Augment)	No	11 Sep 2007	N/A	11 Sep 2007	Subject withdrew consent prior to surgery
[redacted]	Active (Augment)	No	21 Nov 2007	N/A	21 Nov 2007	Subject withdrew consent prior to surgery
[redacted]	Active (Augment)	No	23 Aug 2007	N/A	14 Aug 2007	Subject withdrew consent prior to surgery
[redacted]	Active	No	09 Dec 2008	N/A	24 Nov 2008	Subject withdrew consent prior

Subject	Treatment Assignment	Treated	Randomization Date	Surgery Date	Withdrawal Date	Reason for Exclusion
	(Augment)					to surgery
	Active (Augment)	No	13 Jan 2008	N/A	14 Jan 2008	Planned surgery required exclusionary hardware or procedure
	Active (Augment)	No	09 May 2008	N/A	08 May 2008	Planned surgery required exclusionary hardware or procedure
	Active (Augment)	No	14 Dec 2007	N/A	17 Dec 2007	Planned surgery required exclusionary hardware or procedure
	Control (Autograft)	No	06 May 2008	N/A	30 Apr 2008	Planned surgery required exclusionary hardware or procedure
	Active (Augment)	No	15 May 2008	N/A	16 Jan 2008	Planned surgery required exclusionary hardware or procedure
	Control (Autograft)	No	17 Apr 2008	N/A	22 Apr 2008	Planned surgery required exclusionary hardware or procedure
	Control (Autograft)	No	05 Sep 2008	N/A	08 Sep 2008	Planned surgery required exclusionary hardware or procedure
	Control (Autograft)	No	30 Sep 2008	N/A	25 Sep 2008	Subject not cleared for surgery
	Control (Autograft)	No	05 Dec 2008	N/A	01 Dec 2008	Subject not cleared for surgery
	Active (Augment)	No	06 Aug 2008	N/A	06 Aug 2008	Subject not cleared for surgery
	Control (Autograft)	No	07 May 2008	N/A	13 May 2008	Planned surgery required ankle and hindfoot fusion procedures
	Active (Augment)	No	15 Apr 2008	N/A	16 Apr 2008	Procedure aborted due to active infection
	Active (Augment)	No	17 Dec 2008	N/A	19 Dec 2008	Planned surgery required exclusionary material (allograft)
	Active (Augment)	No	06 Mar 2008	N/A	25 Feb 2008	Site closed prior to surgery
	Active (Augment)	No	15 Sep 2008	N/A	15 Sep 2008	Determined intraoperatively that a second procedure would be necessary.
	Control	Yes	14 Nov 2007	16 Nov 2007	04 Dec 2008	Surgery required use of

Subject	Treatment Assignment	Treated	Randomization Date	Surgery Date	Withdrawal Date	Reason for Exclusion
	(Autograft)					excluded hardware (plate)
[redacted]	Active (Augment)	Yes	19 Sep 2008	19 Sep 2008	16 Dec 2008	Surgery required use of excluded hardware (plate)
[redacted]	Control (Autograft)	Yes	20 Nov 2008	20 Nov 2008	16 Nov 2009	Surgery required use of excluded hardware (plate)
[redacted]	Active (Augment)	Yes	29 Oct 2008	31 Oct 2008	09 Nov 2009	Surgery required use of excluded hardware (plate)
[redacted]	Active (Augment)	Yes	13 Aug 2008	15 Aug 2008	11 Aug 2009	Surgery and graft placement were not done per protocol
[redacted]	Active (Augment)	Yes	15 Aug 2008	18 Aug 2008	12 Aug 2009	Surgery and graft placement were not done per protocol
[redacted]	Active (Augment)	Yes	05 Oct 2007	08 Oct 2007	02 Oct 2008	Subject had 5 screws used across fusion site.
[redacted]	Control (Autograft)	Yes	05 Jun 2008	06 Jun 2008	04 Jun 2009	Surgery included excluded procedure (midfoot fusion)
[redacted]	Active (Augment)	Yes	22 Feb 2008	25 Feb 2008	18 Feb 2009	Surgery included excluded procedure (midfoot fusion)
[redacted]	Active (Augment)	Yes	17 Nov 2008	18 Nov 2008	16 Nov 2009	Surgery included excluded procedure (midfoot fusion)
[redacted]	Active (Augment)	Yes	29 Oct 2008	31 Oct 08	20 Oct 2009	Surgery included excluded procedure (midfoot fusion)
[redacted]	Active (Augment)	Yes	14 Nov 2007	19 Nov 2007	11 Nov 2008	Surgery included excluded procedure (both ankle and hindfoot fusions)
[redacted]	Control (Autograft)	Yes	22 Jan 2008	28 Jan 2008	05 Jan 2009	Surgery included excluded procedure (both ankle and hindfoot fusions)
[redacted]	Active (Augment)	Yes	28 Oct 2008	29 Oct 2008	15 Oct 2009	Surgery included excluded procedure (both ankle and hindfoot fusions)
[redacted]	Active (Augment)	Yes	01 Nov 2007	01 Nov 2007	29 Oct 2008	Subject received excluded medication
[redacted]	Active (Augment)	Yes	01 Jun 2008	02 Jun 2008	28 May 2009	Subject noncompliant with protocol (early weightbearing)
[redacted]	Control (Autograft)	Yes	10 Dec 2007	12 Dec 2007	11 Dec 2008	Surgery required use of excluded amount of graft (graft volume in excess of 9cc)

*Corresponds to Figure 3, Description of Excluded Subjects

Finally, there were 24 patients (5.8% of treated patients) that discontinued early following randomization. The most common reasons given as "subject or investigator request" (8 patients), "revision surgery required" (7 patients), and "lost to follow-up" (5 patients). For details regarding early discontinuations please refer to the response to Question 17.

Subject attrition prior to and during the study is equally distributed across both treatment groups. This equal distribution, in combination with blinded process used to determine the mITT population further supports the validity of this population.

Protocol Deviations:
As requested by FDA, BMTI has provided the deviation dataset with respect to treatment group. Please see Exhibit 7.

At the 24 week data point there were 1566 protocol deviations entered by the Investigator, 1457 were actually deviations and 109 were recorded as "not a protocol deviation by the investigator". A detailed accounting by treatment group and protocol category for both 24 week and 52 weeks has been provided for your review.

All deviations or exceptions were assessed and documented in accordance to GCPs. The CRO and study sponsor concluded that the deviations and exceptions did not affect the study outcome or the conclusions drawn from the study. On average, each subject experienced 4-5 deviations during the course of the study. Given the number of study visits and procedures, including blood draws, x-rays, CT scans, and patient questionnaires, BMTI believes this number to be within the expected range and generally believe subjects and sites achieved a high level of compliance.

e) *The radiographic fusion rates are considered low at 24 months in the investigational cohort. Based on clinical experience and literature, ankle fusion, for example is generally a successful procedure with outcomes that are better than 80% at 2 years. In analyzing the benefit and risk of the use of this treatment in the population studied, please provide a discussion (with references) that justifies the radiographic outcomes suggesting a rate of no greater than 62% at 24 weeks as safe and effective. We recommend that you review the peer-review literature for ankle and hind foot fusions from the last 5 years to assist you with this discussion of the fusion rate for the ankle and of similar bones in the foot to help evaluate the fusion rates reported in your*

clinical trial, including both the experimental and control group. In addition, please discuss in detail how your device is as effective as the standard treatment for ankle or foot fusion, given that a substantially higher number of patients had infection/infestation adverse events in the investigational group as compared to the control group.

Response

As requested by FDA, BMTI has reviewed the literature for ankle and hindfoot fusions and seeks to clarify the rationale and significance of the CT fusion rates observed in this study for both the active and control groups. BMTI respectfully notes that the comparison of interest in randomized, controlled trials is the direct comparison between the treatment and control groups. As such the non-inferiority test, not the overall rate, is the critical outcome and primary endpoint of the study.

Plain film radiographic assessments, clinical/functional assessments, and quality-of-life questionnaires are standard for assessing healing/union in patients who have undergone a hindfoot or ankle fusion procedure. Most clinical trials assessing the outcomes of treatments targeted at fusion or fracture repair have a combination of radiologic endpoints, clinical endpoints, and outcomes assessments. Such studies have typically used radiographs as the imaging modality of choice, which remains a widely accepted standard for evaluation of fracture healing/union.

Standard radiographs, however, may not be ideal for evaluation of fusion and healing. The ability to determine union on radiographs has been recently questioned. The subject IDE study has been acknowledged as a landmark study in the field of orthopedic foot and ankle surgery, as it is the first RCT in this field of study to assess fusion of the foot and ankle using serial CT scans for assessment of bony fusion. As requested, the Sponsor will refer to recent literature for a discussion of the emerging role and significance of CT scans to assess fusion in hindfoot and ankle surgery.

Prior to initiation of the IDE study, Coughlin and co-authors reported that CT scanning appears to be the most reliable and sensitive method to determine fusion (Coughlin et al, 2006). The study demonstrated that the mean observed fusion rate for subtalar fusions ranged from 41% at 6 weeks to 61% at 12 weeks, and to 86% at six months on radiographs; however the fusion rates as determined by independent assessment of CT scans for the same time intervals were 23%, 48%, and 64% fused. The authors concluded that CT scans are more reliable than standard radiographs and provide a more rigorous and reproducible assessment of fusion.

More recently, Dorsey and co-authors reported results of tibiotalar and subtalar arthrodesis using CT scans (Dorsey et al, 2009). The authors studied correlation between clinical evaluation of joint stability and CT evaluation of joint fusion. The authors reported that in twelve clinically unstable joints assessed, the fusion ratios ranged from 0-32.8%, whereas 30 clinically stable joints had fusion of at least 33.2%. The authors found that, when using the 33% threshold for defining a stable fusion, the sensitivity, specificity, and accuracy were all 100%. The authors also concluded

that CT scans were more reliable than x-rays. Anecdotal reports also suggest that perhaps a lower threshold of fusion than the at least 50% osseous bridging used in the Augment Bone Graft trial should be required to establish a stable fusion.

The above cited publications are included in Exhibit 7:

- Coughlin MJ, Grimes JS, Traughber PD, Jones CP. Comparison of radiographs and CT scans in the prospective evaluation of the fusion of hindfoot arthrodesis. Foot and Ankle Int 2006 Oct; 27(10): 780-87.
- Dorsey M, Liu P, Roberts C, Kile T. Correlation of arthrodesis stability with degree of joint fusion on MDCT. American Journal of Radiology. 192: 496-499, Feb. 2009.

In the Augment pivotal trial at six months post-surgery, a statistically significant CT fusion rate was demonstrated for non-inferiority in favor of Augment versus autograft for the full complement and all joints analyses ($p=0.038$ and $p<0.001$, respectively) indicating that the fusion rates (61.2% for Augment and 62.0% for autograft) are equivalent among the two groups, as analyzed by the most rigorous methodology (CT scan). CT scanning is the most rigorous methodology for evaluation of fusion/arthrodesis; and while use of CT scanning is not considered to be the standard of care for assessment of union, recent studies cited above (Dorsey et al, 2009; Coughlin et al, 2006) and regulatory proceedings have highlighted the importance of CT scans in assessing fusion in a reliable and reproducible way. In addition, a reliability analysis was performed to examine intra-rater consistency. This analysis demonstrated a strong relationship between the initial assessment and subsequent assessments of the same scan ($\kappa=0.70$).

It is important to note that while independent review of CT scans is a rigorous methodology by which to assess fusion for randomized controlled trials, there was a significant percentage of patients considered to achieve union who did not achieve 50% osseous bridging. The below discussion will address the correlation between clinical and radiologic fusion (based upon CT scans).

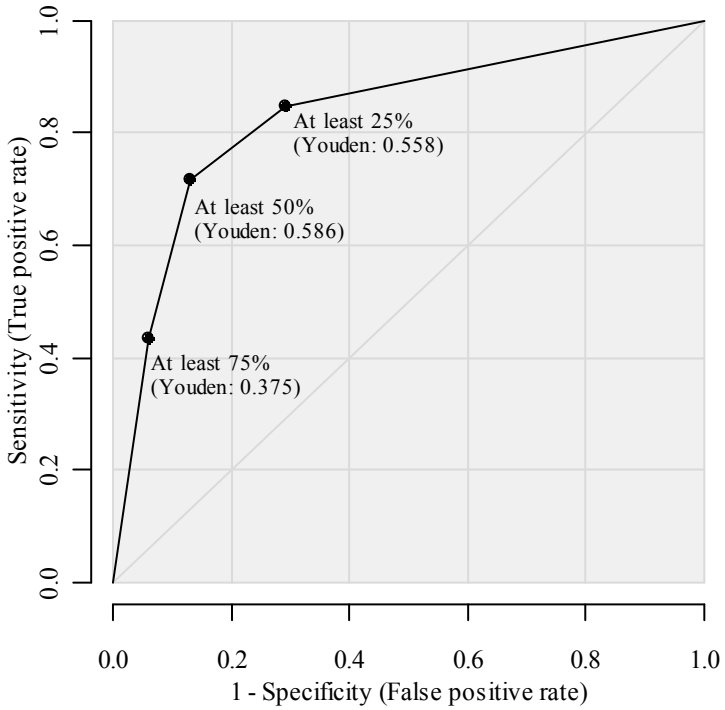
Relationship between CT and Clinical Union

Most clinical trials assessing the outcomes of treatments targeted at fusion or fracture repair have a combination of radiologic endpoints, clinical endpoints, and outcomes assessments. Such studies have historically used radiographs as the imaging modality of choice, as this is the widely accepted standard for evaluation of fracture healing/union. Standard radiographs, however, may not be ideal for evaluation of fusion and healing.

Based on the 24 week full complement of joints data, CT fusion defined as “at least 50% osseous bridging” is a better predictor of clinical union than CT fusion defined as either “at least 25%” or “at least 75%”. A criterion based on a 25% cutoff generates twice as many false positives, while a criterion based on a 75% cutoff generates significant false negatives. The 50% criterion provides the best balance between false positives and false negatives, as evidenced by the greatest sum of

sensitivity (true positive rate) and specificity (true negative rate). This sum of sensitivity and specificity, minus one, is referred to as the Youden index or Youden statistic.

Figure 4: CT Scan Specificity and Sensitivity



The "at least 50%" criterion for declaring CT fusion is the better predictor versus the other two possible cutoff points, 25% and 75%, in that it finds the best compromise between false positives and false negatives. Of the 69 patients who were not clinically healed, only nine were falsely declared successes by this CT fusion criterion, demonstrating that this criterion is certainly conservative, in the sense that a declaration of CT fusion failure might end up being a be a clinical success but a declaration of CT fusion success is nearly certain to be a clinical success for the patient. While it is not as conservative in this sense as the 75% criterion, the 75% criterion suffers from an untenable false negative rate of well over 50%, rendering the 75% criterion ineffective and unacceptable.

A more optimal criterion between 25% and 50% osseous bridging might exist but the data from this study (a four-point ordinal scale) are not capable of determining what that cutoff might be.

Thus, the threshold set at "at least 50%" osseous bridging can be used to reliably assess clinical healing and, as such, provides a valuable objective radiographic measure for determining success in foot and ankle arthrodesis; however, as stated above, there are many patients who achieved clinical success, who did not reach the 50% osseous bridging threshold. Given that the majority of literature reports fusion

based on clinical outcomes, BMTI disagrees that the CT fusion rates in this trial do not demonstrate safety and effectiveness for both groups. The fact that the clinical outcomes in this trial are comparable to reported literature and that 50% osseous bridging threshold on CT at 24 weeks is a strong predictor of clinical outcome is a fundamental conclusion that should be drawn from these data.

Infections and Infestations:
It is noted that the FDA has requested clarification regarding the safety and effectiveness of Augment based upon the increased incidence of infections and infestations. BMTI is clarifying the different types of infections and incidence rates for Augment and autograft.

The incidence of complications coded as infections was reported as 26 events for 24 patients with 4.8% reported for Augment Bone Graft (13 patients) compared to 7.7% for autologous bone graft (11 patients). The surgical wound infection rate was also lower for Augment (7.3% versus 9.5%). As rhPDGF-BB is a wound healing agent, the lower incidence of unexpected surgical complications coded as infection is not unexpected. Serious infection and infestations were reported in the categories of osteomyelitis with 0.4% Augment Bone Graft compared to 1.4% for autologous bone graft. Information regarding subjects with adverse events coded to Infection or Infestation is included in Exhibit 7.

Nine (9) surgical wound infections met the criteria for serious adverse events (e.g. required hospitalization; life threatening). Of these 9 serious surgical wound infections, four (4) were in the Augment Bone Graft treatment group and five (5) were in the autologous bone graft treatment group. Serious post operative wound infection and wound infection staphylococcal preferred terms were noted in zero (0.0%) Augment Bone Graft and one (0.7%) autologous bone graft patients. There was at least one (1) serious wound infection at the bone graft harvest site in an autologous bone graft patient. The adverse events SOC coded as “Infections and Infestations”, includes any potential infection, such as respiratory or urinary tract infection, which are important events to be analyzed; however, it is seemingly unlikely that these events have any relationship the fusion site. Furthermore, these adverse events appear to be similar in terms of the overall incidence reported in the study (22.4% of Augment Bone Graft patients, and 19.7% of autologous bone graft patients). BMTI has provided by subject all adverse events coded to infections and infestations using the lower level term. In addition to the event data, BMTI also included the outcome and treatment group by subject (see Infection and Infestation by treatment group table).

Question 8

8) *Your safety analyses includes 7 subgroups defined as pre-treatment signs and symptoms; treatment emergent adverse events (TEAE); complications; serious complications; infections related TEAEs; and serious TEAEs. All adverse events should be a part of the composite primary endpoint that determines device safety. Currently these safety endpoints are not used in the overall determination of your study's success. FDA is concerned that you have not used a*

conservative approach to capture all adverse events and to determine the severity and implant relatedness of these events. Please address the following concerns:

a) You have defined adverse events as only those which are "treatment emergent". You have further defined "Complications" (a subset of treatment emergent adverse events) to include those associated with the surgical procedure, but do not consider "routine post operative events" as adverse events. FDA requires that all adverse events be recorded and monitored for a final determination of device/procedure-relatedness and severity. Therefore we do not agree with the exclusion of specified events, such as' non-treatment emergent or "routine post-operative events" as you have listed, to determine study-related safety. It is not possible to determine relatedness until all adverse events have been captured and the data analyzed accordingly. The preferred data presentation formats are explained in "Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications". http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072263.htm. Please present all of the adverse events as part of the safety analysis as indicated, without exclusion.

Response

As requested by FDA, BMTI is providing the preferred data presentation formats as explained in the "Guidance for Industry and FDA Staff Clinical Data Presentation for Orthopedic Device Applications". See Exhibit 8.

BMTI has addressed the issue of safety endpoints with the inclusion of safety in the post-hoc Subject Performance composite success endpoint, and with additional references to adverse events reported by incidence in question. Conversely, BMTI has captured all adverse events that occurred after randomization of the subject through study completion. Although BMTI provided classification of adverse events into separate categories of treatment emergent and non-treatment emergent in the PMA response, we have reclassified all adverse events as instructed in the guideline.

The initial display of the adverse events stratified into these distinct categories was not to propose to the Agency that non-treatment emergent adverse events or routine post-operative adverse events were not included or assessed for relatedness and severity during the study. Indeed all adverse events after randomization were reported by the subjects to the investigator and were captured on the appropriate eCRF, monitored for any adverse events from visit to visit, and the data analyzed accordingly. BMTI is providing the preferred data presentation formats as explained in the "Guidance for Industry and FDA Staff Clinical Data Presentation for Orthopedic Device Applications". See Exhibit 8.

Clarification:
Treatment emergent events are all adverse events that occurred after the subject has been treated. This would include but not be limited to post-operative adverse events of swelling, pain, etc. as specified in the protocol (pg. 13) as follows: "all

post-operative complications will be recorded on the appropriate CRF." Additionally, BMTI prompted the primary investigators to provide data collection of clinical symptoms which are expected during recovery and rehabilitation - warmth of fusion site, evidence of infection, swelling of fusion site, tenderness at fusion site, neurovascular and healing status, as well as range of motion – were identified and recorded on the physical exam CRF. Furthermore, investigators recorded whether there were clinically significant examination findings indicative of a complication or adverse event. Non-treatment emergent adverse events were also collected on all 414 subjects (safety population) whether randomized or excluded as not having been treated according to protocol.

The number of adverse events originally presented in the 52-week Safety Report has not changed from what BMTI originally reported.

b) *Based on our review of the submitted adverse event narratives, FDA does not believe that you used an appropriate conservative approach to categorize adverse events in terms of device relatedness and severity. We are concerned that you did not appropriately capture all of the study adverse events that should be considered failures. The PMA states that there was only 1 patient who had an investigational device-related adverse event (nausea and diarrhea); however, in the narrative Table 9 patient number* [redacted] *was categorized under Preferred Term as "Device Related Infection", but under the category Investigator Causality was listed as "Not related". Out of 285 investigational and 149 control patients you identified thirteen patients (8 Augment; 5 Controls) as "therapeutic failures" who were noted as receiving either a bone stimulator or revision surgery for delayed or non-union. It is unclear if any other type of adverse events were considered to be study failures. There were other subjects who, in FDA's opinion, should be included in the analysis as therapeutic failures: an Augment subject with infection at the fusion site; an Augment subject who required a second surgery for revision; and a Control subject who received too much graft material. Your protocol references Data Quality Assurance Monitoring to oversee the progress and accumulation of clinical data and evaluate the results of the study on a periodic basis, but it is not clear if an independent Data Safety Monitoring Board (DSMB) played a role in determining which adverse events were considered study failures. If so, please clarify if the DSMB made these determinations in a blinded or un-blinded manner.*

   i) *Please provide information regarding how adverse events were investigated to determine their seriousness and relationship to the device or procedure. In addition, please provide information on the role of any monitoring board for*
   safety in each trial and provide minutes from their meetings documenting what they reviewed their conclusions, and their recommendations. Specifically, please clarify what role (if any) an independent DSMB played in classifying adverse events. If you have not previously supplied

the charter and other information associated with the DSMB make up and meeting schedule in your
IDE, please submit this information as suggested in our guidance, "Guidance
for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees"
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCMI2 657 8.pdf

Response

Safety was assessed by the frequency and severity of adverse events/serious adverse events reported by the investigator on the designated CRF. The relationship of each adverse event to treatment rendered (test or control) as judged by the investigator was recorded on the Adverse Event Report Form.

Serious Adverse Events
Events were classified as serious if they met any of the following criteria (in accordance with 21 CFR 812.3(s)) and the recommendations of International Conference on Harmonization [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45]):

- Any death.
- Any life-threatening event, i.e., an event that places the subject, in the view of the investigator at immediate risk of death from the event as it occurred (does not include an event that, had it occurred in a more severe form, might have caused death).
- Any event that requires or prolongs in-patient hospitalization.
- Any event that results in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a subject who participated in this study following the study procedure.
- Other medically important events that in the opinion of the investigator may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.
- Any serious problem associated with the device that relates to the rights, safety or welfare of study subjects.

The Principal Investigator was to notify the Sponsor or its Designee within 24 hours.

Following receipt and independent review by the company's designated independent medical monitor (Averion) reviewed the information submitted to confirm or query the initial assessment by the investigator, in accordance with the Safety Management Plan.

Specific cases:

Subject [redacted] underwent a left ankle incision and drainage due to osteomyelitis found intra-operatively after being randomized to Augment. Per protocol (p.13), "if the surgeon determines intra-operatively that the bone defect does not meet enrollment criteria or the fusion site cannot be adequately reduced and stabilized the subject will not be randomized into the study." The subject arthrodesis/implantation of Augment was discontinued and the subject was discontinued from the study. The subject was admitted from antibiotics treatment after the hardware was removed. For this reason, the PMA accurately reports the 1 patient who had an investigational device-related adverse event (nausea and diarrhea) as subject [redacted] did not receive the Augment investigational device due to the presence of infection (purulent discharge) noted intra-operatively from a previously implanted hardware. The coded term for this event was device related infection associated to the hardware infection (culture positive for staphylococcus aureus) not investigational device related infection.

The 52-week Safety report identified subjects who were withdrawn from the study due to an adverse event or due to death as follows with complete narratives of each event provided in the 52-week Clinical Study Report contained in Exhibit 6:

1. SAE case [redacted]) – see information noted above in question 8b.

2. SAE case [redacted] – death due to pulmonary embolism.

3. SAE case [redacted]) – bilateral MRSA of the knees w/ bilateral total knee replacements.

As referenced by the FDA, the following subjects' status was determined prospectively prior to database lock as follows:

1. Subject [redacted]: An Augment subject with infection at the fusion site was randomized but not treated with Augment. The subject was removed from the study as an intra-operative failure and consequently not included in the mITT population. The subject is considered a failure, although not specifically categorized as a therapeutic failure as our definition of this term is noted as non-union, delayed union, bone stimulator, or revision surgery

2. All subjects who received a second surgery for revision of the study related ankle/hindfoot were considered therapeutic failures.

3. Subject [redacted] A Control subject who received too much graft material –received 12cc of Autograft at the fusion site per physician decision. Per protocol, exclusion criteria #2 states that "the fusion site requires plate fixation, more than three (3) screws across the fusion site to achieve rigid fixation, or more than 3 kits, or 9cc of graft material. The subject was excluded from the study as a result of too much graft

material and consequently not included in the mITT population. The subject is considered a failure, although not specifically categorized as a therapeutic failure as our definition of this term is noted as non-union, delayed union, bone stimulator or revision surgery.

Data Monitoring Committee:
As requested by FDA, BMTI is including all meeting minutes for both open and closed sessions with a summary of the data that was reviewed at each meeting (See Exhibit 8). Also included, are the DMC membership roles, DMC Charter, and the signatory document providing the DMC determination for this study. It is noted that the DMC was not involved in ongoing review of clinical or safety data. Serious Adverse Events were monitored by the independent Medical Monitor (Averion) during the study, which independently reviewed SAEs and other pertinent safety data during the course of the study.

ii) Please repeat your overall success analyses using a more conservative approach to determine which adverse events warrant classification as study failures. Specifically, please address the significant number of adverse events whose relationship to the device or procedure is classified as undetermined.

Response

As requested by FDA, BMTI has categorized SAEs and secondary procedures as study failures under the post-hoc Subject Performance composite endpoint. BMTI has also classified secondary therapeutic interventions as a result of non-union or delayed union as therapeutic failures. No other adverse events were classified as failures.

Clarification:
Per protocol (p. 29) "the relationship of each adverse event to treatment rendered (test or control) were to be judged by the investigator and to be recorded on the adverse event form." Listing 16 includes adverse events recorded by the investigator with data presented by subject, treatment group, relationship to control, relationship to study device, action taken, outcome, seriousness, AE name, SOC term, preferred term, onset and resolution/unresolved dates, and severity. Importantly, the primary investigator's Adverse Event (listing 16) does not record any subjects with relationship to the device or procedure as undetermined; as the only options available to the primary investigator for both data collection points for relationship to the device or procedure were "none, possible, unlikely, probable/definite" per the CRF.

BMTI believes FDA is referencing information from Listing 48 (Overall Complications) with your assessment of "significant number of adverse events whose relationship

to the device or procedure" directly relate to the independent medical monitor assessment of the AE.

In an effort to provide another level of safety review, BMTI requested the medical monitor for the study to further classify adverse events coded as device complications into one of four complication categories, as either: surgical, hardware, indeterminate, or device (i.e. investigational product). These classifications were determined by the medical monitor without knowledge of the subject's medical information. These subsequent levels of safety review by an independent medical monitor were in addition to the investigators assessment of the patient's adverse event specified in the protocol and statistical analysis plan. As previously discussed in the response to 8a above, BMTI is resubmitting the Adverse Event data as specified in the "Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications".

c) *The narrative taken from page 25 of the updated Safety Report states that the proportion of patients having serious adverse events were similar for the investigational and control groups at 11.0% (30/272 subjects, 32 events) and 16.9% (24/142 subjects, 25 events) respectively. This appears to contradict the information on Table 1 (page 12), which indicates that there were 10.3% investigation serious adverse events and 14.8% serious control events. Please explain this apparent discrepancy.*

Response

Serious complications were a combination of investigator rating of seriousness and the independent medical monitor's review of the subject's adverse event. In keeping with the regulatory definition of serious adverse events, BMTI has provided to the agency accurate accounting of the serious adverse events for this study as noted in this item. However, the assessment of the apparent discrepancy is accurate as serious complications are a subset of serious adverse events.

As requested by FDA, BMTI is resubmitting the adverse event data to be consistent with the guideline for the industry, without the additional subclassification by the independent medical monitor. See Exhibit 8.

d) *The PMA describes an overall rate of adverse events related to infections in both groups greater than 2%. For all treatment emergent adverse events by the major SOC category, there are a high number of infections and infestations in both groups, but higher in the investigational group by over 2 percentage points (22.4 vs. 19.7%). Because these patients are being treated with surgical fusions, this is of clinical concern. However, when these are divided into separate subgroup analyses, it is noted that the Control group has a higher rate of "Complications" associated with surgical procedure coded as infections, 4.8% for Augment (13 patients) compared to 7.7% for Controls (11 patients). It is not clear how "Infections and Infestations" are greater in the investigational group when all adverse events are considered*

and greater in the Control group when only "Complications" are considered. Moreover, there are 10 subcategories of Infections and Infestations listed as "Complications". It is not clear how distinctions are made between each category. For example, please clarify how the distinction between an infection, a post-procedural infection, and a post-operative infection was made, and why each warranted separate sub categorizations. Please provide detailed narrative information on each infection/infestation noted in SOC categorization during the study. For each patient who experienced ml infection/infestation adverse event, please specify whether that patient was considered a success or a failure in terms of the primary study endpoint.

Response

BMTI believes the overall definition of adverse events that were coded to infections and infestations are consistent with the FDA's definition as stated in the guideline titled, "Safety Reporting Requirements for INDs and BA/BE Studies". Therefore, the overall rate of adverse events coded to infections appears to be greater than 2% per group without taking into account the subcategories within the system organ class (SOC). The SOC of infections and infestations are divided into several subcategories (preferred term) with the adverse event seemingly associated with the surgical procedure or having no relationship to the study fusion or graft harvest site.

Given an overall rate of 20% and the sample sizes in the current trial, the standard error of the difference in two proportions is approximately four percentage points, essentially double the observed difference under consideration. It is difficult to call such a difference noteworthy.

As requested by FDA, BMTI has taken all the infections and infestations for this study and specified whether subjects were considered a success or failure in terms of the primary endpoint as outlined in the protocol and statistical plan. A clear distinction is evident between study related infections and infestations when filtering on the subcategories of the SOC. It is clear that a majority of the adverse events reported and further coded within this SOC were not events considered to be related to the investigational product. By excluding the adverse events that were non-study related infections and infestations there were only 35 events (0.7%) which are applicable for purposes of reporting of study related infections.

As requested by FDA, BMTI is resubmitting the Adverse Event data as specified in the "Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications". As stated previously, the adverse events with classifications of complications were determined by the medical monitor without knowledge of the subject's medical information. In addition, this subsequent level of safety review has no bearing on the investigators assessment of the patient's adverse event.
Clarification: There are distinctions between subcategories coded in the SOC infections and infestations. To clarify the distinctions of how adverse events for infection, post-procedural, and post-operative infections were coded BMTI provides each sub-category with descriptive narrative below. Please reference the Table titled, "Infection and

Infestations by treatment group" in Exhibit 7 for complete details by population, treatment group, 24-week primary end point assessment, adverse event term, and preferred term.

Infection - Adverse event term provided by the investigator did not specify the type of infection, so the adverse event was coded to the general subcategory of infection. There were a total of 8 events/8 subjects which fall in this subcategory. The investigational group reported 7 subjects [redacted] with the Control group reporting 1 subject [redacted].

Post procedural infections - One adverse event was coded as a post-procedural infection in the Investigational group [redacted]). The adverse event term was recorded by the investigator and originally coded by the medical monitor as the event met the criteria for Serious Adverse Event (see GEM[redacted] – Device breakage, post operative wound infection). In summary, the subject received treatment on the left Ankle joint on 05DEC2008 with three soft tissue osteotomy procedures - Tibia, Fibula, and hindfoot – as well as a tendon lengthening procedure of the left Achilles. Post surgery the subject was hospitalized with an admission date of 05DEC2008 and discharge date of 10DEC2008. The subject continued subsequent follow up visits with physical examination without incident through Visit 7 (31MAR2009). Preceding the Visit 8 (19MAY2009) follow up the subject post-operatively experienced poor healing of the distal tibia-fibula area accompanied with pain near the osteotomy site. On 13APR2009, the subject underwent a vision of the left tibial osteotomy with operative findings that revealed a plate fracture and a completely unhealed osteotomy. Wound culture performed on 04MAY2009 revealed the presence of MRSA and the subject was started on Bactrim and antibiotics. The investigator determined that the wound infection and failed osteotomy were not related to study device.

Post operative infections – These infections are derived from surgical procedures with classifications as incisional, organ, or other organs and spaces being manipulated during an operation. Importantly, incisional infections are further divided into superficial (skin and subcutaneous tissue) and deep (deep soft tissue-muscle and fascia). Adverse events recorded by the investigator included surgical or incision within the verbatim term and were subsequently coded to post-operative infections. There were 9 events/9 subjects with adverse events coded to post-operative infection. The investigational group had 4 subjects with adverse events coded as post –operative infections and the Control with 5 subjects.

e) *The incidence of serious "complications" coded as vascular disorders was reported as 13 events for 12 patients or by treatment group of29% Augment versus 2.8% for Controls (DVT: 2.2% Augment versus 2.1% Control; Pulmonary Embolus: 0.7% Augment versus 0.7% Control; and Thrombosis: 0.4% Augment versus 0% Control). The categories of "DVT" and "Thrombosis" were higher for the investigational group. When these same terms (DVT and Pulmonary Embolus) are categorized as serious TEAEs the incidence of events is quite different (DVT: 1.5% Augment versus 2.1% Controls and Pulmonary Embolus: 1.1% Augment versus 0.7% Controls).*

Please clarify how the distinction is made between categorization of vascular events as a Complication compared to a serious TEAE. You will also need to provide detailed narrative information on each vascular event noted in the SOC categorization during the study. For each patient who experienced a vascular adverse event, please specify whether that patient was considered a success or a failure in terms of the primary study endpoint. For example, please provide c1arification as to why investigational patient No 44-07 HVH who died 14 days postoperatively from a pulmonary embolus, was not indicated as a device and/or procedure-related event.

Response

As stated previously, the adverse events with classifications of complications were determined by the medical monitor without knowledge of the subject's medical information. In addition, this subsequent level of safety review has no bearing on the investigator's assessment of the patient's adverse event, and as requested by FDA, BMTI has removed this level of review. BMTI is resubmitting all of the Adverse Event data as specified in the "Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications". To clarify the distinction, the TEAEs coded to the SOC Vascular disorders were recorded on the adverse event CRF by the investigator. BMTI has further taken each patient who experienced a vascular adverse event and specified if the patient was considered a success or failure in terms of the primary study endpoint. Please review the table titled, "Vascular Disorders by Treatment Group" in Exhibit 8 for detailed information.

Subject [redacted](SAE case: [redacted] died fourteen days post-operatively from a pulmonary embolism. The investigator indicated that the subject was not at risk for VTE prior to or following the study procedure. The subsequent autopsy report revealed the cause of death as "bilateral acute pulmonary thromboemboli". However, in the investigator's opinion, the event "bilateral acute pulmonary thromboemboli" was severe, resulted in death, but was not related to the medical device. Please see SAE report and narrative as included in Exhibit 6.

f) Anti-rhPDGF-BB binding antibodies were detected in 46 out of the 423 patients tested. In the Augment treatment group 13.1% (37/282) developed non-neutralizing binding antibodies, while 3.5% (5/141) in the autologous bone graft group were positive. It is unclear if you have adequately categorized adverse event outcomes as they relate to antibody monitoring. Please address the following:

i) Please clarify why it is stated that 46 subjects out of 423 tested had binding antibodies, but further information is provided on only 42 subjects (37 Augment and 5 autologous bone graft). Please provide additional follow up on the remaining patients with binding antibodies.

Response

As described in detail in the next response (8.f.ii), the immunogenicity report has been amended and an assessment of the changes has been documented. Both reports are included in Appendix 5. All subjects with a confirmed ADA positive response at any visit have been followed throughout the study. Antibody results for these patients as well as all patients are shown in the study results in Appendix 5.

It is stated in the amended immunogenicity report that 47 subjects out of 414 tested had binding antibodies at one or more visits during the study. However, 4 subjects of the 47 showed pre-existing binding antibodies and no detectable levels of antibodies at any visit after surgery. Therefore, only 43 subjects (38 Augment and 5 autologous bone graft) were included in the incidence calculation.

ii) You state that the increase in anti-rhPDGF-BB-specific binding antibodies in Augment patients is highest at 9.6% at visit 6 and decreases to 4.5% at visit 8; and that antibody titers for patients with multiple positive samples were lower in visit 8. Please provide actual titer values for a progressive display and comparison for all patients.

Response

In response to the PMA 100 day letter regarding the immunogenicity data and testing program, BMTI performed a 100% verification of the raw data, the recorded read-outs and the reported results. This resulted in an amended immunogenicity report RnD-102810-1R (Appendix 5) as well as a report assessing the changes to the immunogenicity report and the potential effect on the data. The assessment of changes report is RnD-110710-1R (Appendix 5).

In particular, the amended report describes the updates of antibody titer values for the 47 patients exhibiting positive antibody response in Tier 2 confirmatory assays (Table 1 of study report). Upon review of the titer values reported, it was recognized that some titers were reported one dilution too high, i.e. reporting the titer below the cut point instead of the value above the cut point. In the same table, four transcription errors were also noted. The table was further updated with the inclusion of the follow up testing of patients with positive antibody titers at visit 8 (week 24). Only two patients were still antibody positive at the first follow up sample but were tested negative after the second sample.

The amended immunogenicity report also excludes 9 patients out of the previously described 423 patients who were screened and randomized into the BMTI-2006-01 study, but were not treated under the study protocol, and therefore, were never exposed to any investigational treatment. These patients had pre-screening blood draws that were submitted for antibody baseline level testing. All 9 subjects tested anti-drug antibody (ADA) negative. After excluding these 9 subjects the report includes 414 subjects, which corresponds to the safety populated defined in the clinical study report.

The amendment also includes a 47th patient where all visit samples were tested antibody positive in Tier 1 but only tested positive in the confirmatory Tier 2 assay for the sample at the last visit (visit 8). This patient was randomized to Augment™ Bone Graft (Augment) and was inadvertently not listed in the titer table. Including this patient in the antibody response incidence changes the incidence rate from 13.1% to 13.9% (38/274) for the Augment group whereas the Autograft control group is at 3.6% (5/140).

Three patient samples were recovered late and all tested ADA negative. All samples received are included in the amended immunogenicity report.

The 47th patient was added to the table on the testing of antibody positives for neutralization activity. It should be emphasized that all of the 47 ADA positive patients showed binding, but non-neutralizing antibodies. The 47th patient has been requested a follow-up serum sample, and the IRB will be notified of this additional blood draw.
The raw data in the form of ELISA and RIA results for all patient serum samples tested in Tier 1 through Tier 4 are provided in Appendix 5.

Actual titer values for all 47 subjects showing positive binding antibodies are presented in Table 1 of the amended immunogenicity report. In addition, the titer values for these subjects as well as the titer values of the follow up patient samples with positive antibody response are shown in table 1 below.

Please note that there were no implications to the study decisions for Tier 4, i.e. all Tier 2 positives were tested in Tier 4 for neutralizing activity.

Table 16: ELISA Tier 3 titration results from confirmed positive BMTI-2006-01 serum samples analyzed for the presence of anti-rhPDGF-BB antibody

	Pretreatment	Visit 3	Visit 4	Visit 6	Visit 8	Follow #1	Follow #2
			1 : 800				
		1 : 50	1 : 50	1 : 50	1 : 50		
			1 : 800				
			1 : 100	1 : 50			
				1 : 50			
				1 : 800			
			1: 400	1 : 200			
			1 : 400	1 : 100			
					1 : 400	1 : 200	
			1 : 100				
			1: 200				
				1 : 50			
					1 : 100	New draw	
				1 : 50			
			1 : 100	1 : 100			
					1 : 400		
			1 : 200	1 : 100			
				1 : 800	1 : 200		
					1 : 800	1 : 50	
			1 : 100	1 : 100			
			1 : 50	1 : 50			
			1 : 400	1 : 100			
				1 : 50			
		1 : 50			1 : 50		
	1 : 100						
		1 : 100	1 : 800	1 : 200	1 : 200		

	Pretreatment	Visit 3	Visit 4	Visit 6	Visit 8	Follow #1	Follow #2
[redacted]			1 : 100	1 : 100			
			1 : 200	1 : 100			
		1 : 100					
			1 : 200	1 : 200			
	1 : 100		[redacted]				
			1 : 400		[redacted]		
	1 : 200						
			1 : 50				
			1 : 100	1 : 100			
	1 : 100				1 : 100		
		1 : 800	1 : 800	1 : 400	1: 100		
					1 : 50		
		1 : 800	1 : 800	1: 800			
			1 : 400	1 : 800			
			1 : 200	1 : 100			
				1 : 800	1 : 400		
		1 : 50		1 : 100	1 : 50		
	1 : 50						
			1 : 50	[redacted]			
					1 : 200		
		1 :100					

*patient changed site and ID to [redacted]

Sample tested negative in Tier 2 testing

Patients receiving Autograft

No sample submitted for testing

Sample not required

iii) It was noted on review that 50% (7/14) of patients who had positive antibodies at the end of the 6 month study were negative at preceding visits. Please provide times at which samples tested positive and times at which samples tested negative for all patients. Please perform additional antibody testing past 24 weeks (Visit 8) on all patients to better understand the true nature of the long term antibody response.

Response

As requested by FDA, details on the antibody testing for all patients including times where samples tested positive and antibody titers are presented in the response to 8fv below with detailed information regarding subjects included in Exhibit 8.

Additional testing was performed for 14 patients who tested positive after the 24 week visit. The clinical protocol required blood draws for serum testing up to visit 8, but not further out unless the Visit 8 titer had not returned to baseline levels. Therefore, only the 14 patients were asked to consent to additional blood draws and antibody testing. The report RnD-102210-01R "Follow up immunogenicity testing of serum samples from Clinical Study BMTI-2006-01." in Exhibit 5 describes the follow up antibody testing and shows antibody levels in all 14 patients returning to baseline level. In looking at the antibody data from the 7 patients with a perceived late antibody response it shows that all except one had a positive response in Tier 1 testing at some point however did not consistently meet the Tier 2 % inhibition criteria for rhPDGF-BB specificity. Other factors in the patient history may explain the late positive response, but the fact remains that 12 of the 14 patients tested antibody negative in the 1st follow up serum sample and the last two patients tested antibody negative in the second follow up sample. None of the sample in these patients showed neutralizing activity. As explained above, subject [redacted]) did not return for additional serum draw(s) subsequent to Week 24 despite having a positive antibody titer at Week 24. The subject has been requested to return for serum acquisition and testing. Results of antibody testing will be provided upon completion.

iv) At the 6 months follow up, 13 patients (11 Augment and 2 Controls) still had a titer of binding antibodies and were asked to submit at least 2 additional serum samples 3 months apart. You state that of 14 subjects with elevated antibodies at six months, 13 have since returned to baseline. Please provide detailed information (i.e., any adverse events and titer studies) on the remaining patient whose antibody response has not returned to normal.

Response

Fourteen patients showing positive binding antibodies at visit 8 were asked to submit additional samples for antibody testing. Twelve of these had returned to baseline

whereas two patients still showed a positive antibody titer (1:50 and 1:200, respectively) and were followed for another serum sample. At this second follow up both patients' antibody level had returned to baseline.

Detailed information on these two patients is provided along with results for all positive-titer subjects in the response to 8fv below.

v) For all patients who had a positive antibody response, please provide a narrative which describes all adverse events that occurred in each of these patients.

Response

As requested, BMTI has provided more information regarding subjects with positive antibody tests. Table 17 displays the rates of adverse events by SOC between subjects who tested positive for serum antibodies and subjects who did not. Subject profiles for each subject with a positive serum antibody test are included in Exhibit 8.

Table 17: Adverse Event Rates by SOC in Antibody Positive vs. Antibody Negative Subjects

System Organ Class	Subjects # (%)	
	Serum Positive for antibodies to rh-PDGF-BB	Serum Negative for antibodies to rh-PDGF-BB
Blood and lymphatic system disorders	--	2 (0.5%)
Cardiac disorders	2 (4.3%)	7 (1.9%)
Congenital, familial and genetic disorders	1 (2.1%)	1 (0.3%)
Ear and labyrinth disorders	--	3 (0.8%)
Endocrine disorders	--	1 (0.3%)
Eye disorders	--	5 (1.4%)
Gastrointestinal disorders	2 (4.3%)	49 (13.4%)
General disorders and administration site conditions	6 (12.8%)	50 (13.6%)
Hepatobiliary disorders	--	2 (0.5%)
Immune system disorders	3 (6.4%)	9 (2.5%)
Infections and infestations	11 (23.4%)	75 (20.4%)
Injury, poisoning and procedural complications	11 (23.4%)	96 (26.2%)
Investigations	1 (2.1%)	8 (2.2%)
Metabolism and nutrition disorders	--	8 (2.2%)
Musculoskeletal and connective tissue disorders	18 (38.3%)	144 (39.2%)
Neoplasms benign, malignant and unspecified	--	7 (1.9%)
Nervous system disorders	7 (14.9%)	50 (13.6%)
Psychiatric disorders	1 (2.1%)	14 (3.8%)
Renal and urinary disorders	3 (6.4%)	23 (6.3%)
Reproductive system and breast disorders	--	3 (0.8%)
Respiratory, thoracic and mediastinal disorders	3 (6.4%)	22 (6.0%)
Skin and subcutaneous tissue disorders	6 (12.8%)	54 (14.7%)
Surgical and medical procedures	--	15 (4.1%)
Vascular disorders	2 (4.3%)	24 (6.5%)

There are no observed trends or signals in the adverse event rates between subjects with positive antibody results and subjects with negative results.

Table 18 provides a summary of outcome and adverse events (verbatim term) reported for subjects exhibiting any positive antibody response. Subject profiles for each subject with a positive serum antibody test are included in Exhibit 8.

Table 18: Subject Positive Serum Antibody Titers and Adverse Events

	Primary Endpoint	Pre-treatment	Visit 3	Visit 4	Visit 6	Visit 8	Follow #1	Follow #2	ADVERSE EVENTS
	Failure			1 : 800					NA
	Success		1 : 50	1 : 50	1 : 50	1 : 50			INSOMNIA
	Success			1 : 800					ALLERGIC TO VANCOMYCIN (ITCHING) FLU NUMBNESS ON DORSUM OF FOOT RIGHT PLANTAR HEEL PAIN ACUTE BRONCHITIS
	Success			1 : 100	1 : 50				BRONCHIPSPASM RIGHT ANKLE SWELLING
	Failure				1 : 50				HICCUPS HIVES MUSCLE SPASMS INFECTION ON LEG/ANKLE
	Failure				1 : 800				COLD HARDWARE COMPLICATION
	Failure			1: 400	1 : 200				NA
	Failure			1 : 400	1 : 100				NA
	Success					1 : 400	1 : 200		NA
	Success			1 : 100					KNEE PAIN

	Primary Endpoint	Pre-treatment	Visit 3	Visit 4	Visit 6	Visit 8	Follow #1	Follow #2	ADVERSE EVENTS
	Success			1: 200					MIDFOOT PAIN
	Failure				1 : 50				PYELONEPHRITIS RASH FOREFOOT BULLOUS TINEA PEDIS GRANULOMA HEEL
	Success					1 : 100	New draw		RIGHT SINUS TARSI SYNOVITIS PAIN TOP OF RIGHT FOOT INSOMNIA
	Failure				1 : 50				DECREASED O2 SATURATION RASH ON FOOT
	Failure			1 : 100	1 : 100				DISCRETE, RED, FLAT RASH ON RIGHT LEG AND ANKLE RIGHT FOOT POSTERIOR TIBIAL TENDINOPATHY
	Success					1 : 400			BILATERAL DISCOLORATION OF THE NAILBED MUSCLE SPASMS UPPER RESPIRATORY INFECTION MIDFOOT ARTHRITIS TOE PAIN
	Success			1 : 200	1 : 100				EPIDERMOLYSIS
	Success				1 : 800	1 : 200			NA
	Success					1 : 800	1 : 50		TACHYCARDIA FEVER URINARY RETENTION
	Failure			1 : 100	1 : 100				CONTINUAL PAIN IN SUBTALAR AREA
	Failure			1 : 50	1 : 50				MUSCLE SPASMS IN BILATERAL LEGS HARDWARE IRRITATION NUMBNESS IN TOES HEEL PAIN
	Failure			1 : 400	1 : 100				NA
	Failure				1 : 50				LOW POTASSIUM SHROTNESS OF BREATH HEART FAILURE GI BLEED MYOCARDIAL INFRACTION PNEUMONIA BRONCHITIS ACID REFLUX
	Failure		1 : 50			1 : 50			INCREASED PAIN IN RT ANKLE DISLOCATION MIDDLE PHALANX OF SECOND DISTAL FINGER

Primary Endpoint	Pre-treatment	Visit 3	Visit 4	Visit 6	Visit 8	Follow #1	Follow #2	ADVERSE EVENTS
Failure	1 : 100							SCREW INSERTION INCISION ON HEEL SLIGHT DEHISENCE
Failure		1 : 100	1 : 800	1 : 200	1 : 200			NA
Failure			1 : 100	1 : 100				NA
Failure			1 : 200	1 : 100				NA
Failure		1 : 100						DEPRESSION
Success			1 : 200	1 : 200				BAKERS CYST FOOT EDEMA LYMPHEDEMA INFECTION IN ANKLE UNABLE TO URINATE FOLLOWING SURGERY
Success	1 : 100							NEURITIC TENDERNESS
Failure			1 : 400					MOTION AT ARTHRODESIS SITE SUPERFICIAL CELLULITIS WOUND DEHISCENCE
Success	1 : 200							INGROWN TOE NAIL WHOLE FOOT SWOLLEN
Success			1 : 50					DISLOCATED SHOULDER NUMBNESS IN FOOT WEEKNESS IN FOOT
Success			1 : 100	1 : 100				HEEL PAIN NUMBNESS SINUSITIS HARDWARE PAIN
Success	1 : 100				1 : 100			NA
Success		1 : 800	1 : 800	1 : 400	1: 100			DVT ALLERGIC REACTION TO VICODIN
Success					1 : 50			PLANTAR TOE ULCERATION EXACERBATION
Success		1 : 800	1 : 800	1: 800				BLISTERS
Failure			1 : 400	1 : 800				URINARY INCONTINENCE

	Primary Endpoint	Pre-treatment	Visit 3	Visit 4	Visit 6	Visit 8	Follow #1	Follow #2	ADVERSE EVENTS
	Failure			1 : 200	1 : 100				FINGER LACERATION TENDON PAIN FOOT PAIN
	Failure				1 : 800	1 : 400			INFECTION
	Failure		1 : 50		1 : 100	1 : 50			NA
	Success	1 : 50							NA
	Failure			1 : 50					NUMBNESS
	Success					1 : 200			TENDERNESS/SWELLING ANKLE PAIN KNEE PAIN
	Success		1 :100						KNEE PAIN SWELLING KNEE INFECTION AT INCISION SITE SKIN NECROSIS ANKLE

vi) You have stated that, because 5 controls tested positive for the anti-rhPDGF antibody, "there is a naturally occurring baseline rate of immune response to PDGF". Please provide both a reference to support this statement as well as the sensitivity and specificity of the assays used to determine an anti-rhPDGF antibody response.

Response

The statement on the natural occurring immune response to PDGF in autograft patients is based on the data from the pivotal clinical study (BMTI-2006-01). To BMTI's knowledge there have been no other studies reported in literature or elsewhere of baseline immune response in autograft or allograft patient populations similar to the clinical study population. Further, to our knowledge, the control patients who tested positive for anti-rhPDGF-BB antibodies did not have prior exposure to rhPDGF-BB (e.g., Regranex or GEM 21S).

vii) The numbers of overall and serious adverse events present in January, 2009have not changed significantly since your latest updated safety report (52 weeks). However, the investigational group had 4 times as many additional events when compared to the controls (100 for investigational,

24 for controls). Please provide detailed adverse event information for these 124 patients, including the major SOC categorization for each.

Response

BMTI has stratified the adverse events reported between the interim report and 52-week safety data as requested (see Exhibit 8).

Clarification:
The adverse events reported to the FDA for the primary endpoint analysis (i.e. week 24 data cut) comprised the data which had been reported by the investigator in the EDC system at the time of the database freeze. Frequently in clinical trials when data is submitted to the Agency in an interim report, additional information may be obtained by the investigators and a follow-up or final study data is again submitted to ensure all data is properly reported to the Agency. Subsequently, adverse events which were not entered prior to the freeze were entered once the data had been pulled, and the database re-opened for data entry to the investigators.
For clarity, there were 124 *adverse events* reported from the August 2009 data cut point (interim data) to December 2009 (52-week safety data) instead of 124 *patients*.

In addition, please refer to the Adverse Event timeline in Exhibit 8 for operative and systemic site events, as the majority of the 124 adverse events occurred during week 24 data cut of the study, but were not included in the 24 week data point analysis, as noted above.

Question 9

9) *It is not clear from your patient accounting descriptions what patients are being used as the primary dataset to determine the safety and efficacy of your device in the intent-to-treat population. Of the 25 investigational patients and 12 control patients who were excluded from the study, 17 investigational and 9 controls were excluded after randomization and have undergone the surgical procedure. These patients should have been categorized as therapeutic failures rather than being excluded from the study and part of the final analysis. Per the "Guidance for Industry and FDA Staff, Clinical Data Presentations for Orthopedic Device Applications," please clearly define the intent to treat and per protocol populations which include the effectiveness population and the safety cohort (all patients). In addition, please clearly distinguish the safety failures from effectiveness failures that would not remove the patients from the study prior to the endpoint. Some patient effectiveness results are determined failures only at the 24-week period (or study endpoint), but these would not affect the accounting table. Please update your accounting tables for the Augment trial to be consistent with that which is requested in the Guidance Document. Specifically, please include failures recorded according to the scheduled follow-up visit and update the "Expected" rows such that Expected = Theoretical- [Deaths + Failures].*

Response

BMTI has reclassified the patient accounting as instructed by the guideline. A brief explanation of the accounting is noted below:

The condition column provides information for theoretical follow -up, deaths, failures, expected and actual at each study visit. Category definitions are as follows:

- Theoretical follow-up: defined as the number of investigational and control treatments from screening through study completion (visit 10);
- Deaths: any SAEs reported as death;
- Failures: identified at every visit with intra-operative failures recorded at visit 2 (surgery);
- Expected: the number of patients who were anticipated completing each visit;
- Evaluated: per protocol and in the window time frame;
- Actual: patients that missed in numerical values and percentages.

Theoretical follow-up at screening is displayed as ITT (434) population which include subjects who met the criteria of randomization, and were analyzed according to treatment plan. This population includes screen failures (for list of these subjects refer to question 7d (Table 14: Subjects Screened But Never Randomized or Treated as well as subjects who were randomized but never treated in Table 15: Summary of Subject Exclusion from mITT Population.

Expected mITT (397) population are displayed by visit by treatment group to include subjects who were eligible, properly randomized, and received treatment according to protocol. Patients in this population had either Augment or autologous bone graft.

Patients that were excluded from the mITT population violated protocol to the extent that their outcome could not be contributed to the treatment received during the study. Importantly, subjects which were excluded from analysis within this population were not categorized as therapeutic failures as these patients did not receive the study specific treatment, but an exclusionary treatment prohibited by protocol (for a list of these subjects refer to Table 15).

BMTI identified failures within the patient accounting table as non-unions/delayed unions at the primary end point per protocol. Additionally, per the guideline BMTI provided a revised presentation of the data for secondary procedures with a total of 4 removals (Investigational group = 3, and Control group =1) which were included in the overall effectiveness failures.

As requested, BMTI patient accounting descriptions for safety (414) population includes all subjects treated with either Augment or autologous bone graft. The subjects not included in this population were screen failures, other subjects not randomized, and a subject treated with a different bone graft substitute (i.e. allograft) (for a list of these subjects refer to Table 15). The table of accounting is included in Exhibit 9.

Question 10

10) The radiographic information you provided is unclear or inconsistent:

a) When fusion is compared at each individual time point (Table 10) and for the most complete osseous bridging (75% to 100%) (Table 11), the Control group outperforms the Augment group in fusion success rates. Please provide a direct comparison statistical analysis with p-values for each of these parameters provided in tables 10 and 11.

Response

BMTI is providing the requested data and summaries below. See Table 19: Comparison of Analyses below. In addition, after examination of the ordinal osseous bridging outcomes, FDA requested a post-hoc comparison of CT fusion rates when CT fusion is defined as a stricter "at least 75% osseous bridging" on CT. BMTI provides these multiple summaries as well as discussion of statistical issues inherent to these post-hoc inquiries.

Based on the six-month data cut, BMTI provided CT fusion rates at time points where CTs were taken (weeks 9, 16, and 24) with CT fusion prospectively defined as at least 50% osseous bridging based on CTs, conditional on: (1) the existence of such a CT reading in that visit window and (2) the lack of a disqualifying revision surgery or application of a bone stimulator. The first condition is a consequence of BMTI requiring "documented evidence of success" in the case of binary endpoints; the second condition was part of the evaluability procedures that were examined prior to unblinding the data --- patients with such an aggressive intervention were automatically considered to be failures for binary endpoints that were evaluated after the intervention (i.e. "autofail").

Table 10 in the 52-week CSR, included in Exhibit 6, presented at each time point, along with the CT fusion rates, p-values for non-inferiority (based on a 10-percentage-point margin) and for superiority of Augment over autograft. Consistent with those p-values are corresponding lower confidence limits.

Table 19 below presents the CT fusion rates, p-values for non-inferiority and corresponding lower confidence limits, and p-values for superiority of autograft over Augment and corresponding upper confidence limits.

Table 19: Comparison of Analyses

Measure	Population	Visit	N	Augment	Autograft	Rate Difference	Non-inferiority p-value	Non-inferiority Lower Confidence Limit	p-value Superiority: Autograft over Augment	Superiority Upper Confidence Limit
50% Osseous Bridging via CT (all joints)	mITT	9 Weeks	597	105/394 (26.6%)	78/203 (38.4%)	-11.8%	0.67	-18.5%	0.00	-3.9%
50% Osseous Bridging via CT (all joints)	mITT	16 Weeks	597	215/394 (54.6%)	118/203 (58.1%)	-3.6%	0.07	-10.5%	0.41	4.9%
50% Osseous Bridging via CT (all joints)	mITT	24 Weeks	597	262/394 (66.5%)	127/203 (62.6%)	3.9%	0.00	-2.8%	0.34	12.1%
50% Osseous Bridging via CT (all joints)	mITT	36 Weeks	597	271/394 (68.8%)	150/203 (73.9%)	-5.1%	0.10	-11.3%	0.19	2.7%
50% Osseous Bridging via CT (all joints)	ITT	9 Weeks	628	111/416 (26.7%)	83/212 (39.2%)	-12.5%	0.73	-19.1%	0.00	-4.7%
50% Osseous Bridging via CT (all joints)	ITT	16 Weeks	628	225/416 (54.1%)	126/212 (59.4%)	-5.3%	0.13	-12.1%	0.20	2.9%
50% Osseous Bridging via CT (all joints)	ITT	24 Weeks	628	273/416 (65.6%)	137/212 (64.6%)	1.0%	0.00	-5.5%	0.80	9.0%
50% Osseous Bridging via CT (all joints)	ITT	36 Weeks	628	286/416 (68.8%)	158/212 (74.5%)	-5.8%	0.13	-11.8%	0.13	1.8%
75% Osseous Bridging via CT (all joints)	mITT	9 Weeks	597	21/394 (5.3%)	21/203 (10.3%)	-5.0%	0.02	-9.4%	0.02	-0.6%
75% Osseous Bridging via CT (all joints)	mITT	16 Weeks	597	99/394 (25.1%)	65/203 (32%)	-6.9%	0.21	-13.5%	0.07	0.6%
75% Osseous Bridging via CT (all joints)	mITT	24 Weeks	597	156/394 (39.6%)	90/203 (44.3%)	-4.7%	0.11	-11.8%	0.26	3.6%
75% Osseous Bridging via CT (all joints)	mITT	36 Weeks	597	202/394 (51.3%)	114/203 (56.2%)	-4.9%	0.12	-11.9%	0.26	3.6%
75% Osseous Bridging via CT (all joints)	ITT	9 Weeks	628	22/416 (5.3%)	21/212 (9.9%)	-4.6%	0.01	-8.8%	0.03	-0.4%
75% Osseous Bridging via CT (all joints)	ITT	16 Weeks	628	103/416 (24.8%)	70/212 (33%)	-8.3%	0.33	-14.7%	0.03	-0.9%
75% Osseous Bridging via CT (all joints)	ITT	24 Weeks	628	160/416 (38.5%)	97/212 (45.8%)	-7.3%	0.26	-14.1%	0.08	0.8%
75% Osseous Bridging via CT	ITT	36 Weeks	628	213/416 (51.2%)	119/212 (56.1%)	-4.9%	0.11	-11.8%	0.24	3.3%

Measure	Population	Visit	N	Augment	Autograft	Rate Difference	Non-inferiority p-value	Non-inferiority Lower Confidence Limit	p-value Superiority: Autograft over Augment	Superiority Upper Confidence Limit
(all joints)										
50% Osseous Bridging via CT (full complement)	mITT	9 Weeks	397	64/260 (24.6%)	51/137 (37.2%)	-12.6%	0.70	-20.8%	0.01	-3.2%
50% Osseous Bridging via CT (full complement)	mITT	16 Weeks	397	127/260 (48.8%)	76/137 (55.5%)	-6.6%	0.26	-15.2%	0.21	3.7%
50% Osseous Bridging via CT (full complement)	mITT	24 Weeks	397	159/260 (61.2%)	85/137 (62%)	-0.9%	0.04	-9.2%	0.86	9.3%
50% Osseous Bridging via CT (full complement)	mITT	36 Weeks	397	165/260 (63.5%)	95/137 (69.3%)	-5.9%	0.20	-13.8%	0.24	4.0%
50% Osseous Bridging via CT (full complement)	ITT	9 Weeks	434	66/285 (23.2%)	54/149 (36.2%)	-13.1%	0.75	-20.8%	0.00	-4.1%
50% Osseous Bridging via CT (full complement)	ITT	16 Weeks	434	131/285 (46%)	81/149 (54.4%)	-8.4%	0.38	-16.6%	0.10	1.5%
50% Osseous Bridging via CT (full complement)	ITT	24 Weeks	434	165/285 (57.9%)	90/149 (60.4%)	-2.5%	0.07	-10.5%	0.61	7.3%
50% Osseous Bridging via CT (full complement)	ITT	36 Weeks	434	173/285 (60.7%)	99/149 (66.4%)	-5.7%	0.19	-13.5%	0.24	3.9%
75% Osseous Bridging via CT (full complement)	mITT	9 Weeks	397	13/260 (5%)	14/137 (10.2%)	-5.2%	0.05	-10.6%	0.05	0.0%
75% Osseous Bridging via CT (full complement)	mITT	16 Weeks	397	54/260 (20.8%)	42/137 (30.7%)	-9.9%	0.49	-17.7%	0.03	-1.0%
75% Osseous Bridging via CT (full complement)	mITT	24 Weeks	397	87/260 (33.5%)	59/137 (43.1%)	-9.6%	0.47	-18.1%	0.06	0.4%
75% Osseous Bridging via CT (full complement)	mITT	36 Weeks	397	112/260 (43.1%)	73/137 (53.3%)	-10.2%	0.52	-18.8%	0.05	0.1%
75% Osseous Bridging via CT (full complement)	ITT	9 Weeks	434	14/285 (4.9%)	14/149 (9.4%)	-4.5%	0.02	-9.5%	0.07	0.4%
75% Osseous Bridging via CT (full complement)	ITT	16 Weeks	434	55/285 (19.3%)	45/149 (30.2%)	-10.9%	0.58	-18.4%	0.01	-2.5%
75% Osseous Bridging via CT (full complement)	ITT	24 Weeks	434	89/285 (31.2%)	62/149 (41.6%)	-10.4%	0.53	-18.4%	0.03	-0.9%
75% Osseous Bridging via CT (full complement)	ITT	36 Weeks	434	117/285 (41.1%)	75/149 (50.3%)	-9.3%	0.44	-17.5%	0.06	0.6%
50% Osseous Bridging via CT (ankle)	mITT	9 Weeks	152	33/100 (33%)	24/52 (46.2%)	-13.2%	0.65	-26.8%	0.11	3.0%

Measure	Population	Visit	N	Augment	Autograft	Rate Difference	Non-inferiority p-value	Non-inferiority Lower Confidence Limit	p-value Superiority: Autograft over Augment	Superiority Upper Confidence Limit
50% Osseous Bridging via CT (ankle)	mITT	16 Weeks	152	54/100 (54%)	33/52 (63.5%)	-9.5%	0.47	-22.7%	0.26	7.2%
50% Osseous Bridging via CT (ankle)	mITT	24 Weeks	152	68/100 (68%)	39/52 (75%)	-7.0%	0.35	-18.9%	0.37	8.7%
50% Osseous Bridging via CT (ankle)	mITT	36 Weeks	152	70/100 (70%)	40/52 (76.9%)	-6.9%	0.34	-18.6%	0.37	8.5%
50% Osseous Bridging via CT (subtalar)	mITT	9 Weeks	214	34/140 (24.3%)	33/74 (44.6%)	-20.3%	0.93	-31.5%	0.00	-7.1%
50% Osseous Bridging via CT (subtalar)	mITT	16 Weeks	214	78/140 (55.7%)	47/74 (63.5%)	-7.8%	0.38	-19.0%	0.27	6.1%
50% Osseous Bridging via CT (subtalar)	mITT	24 Weeks	214	94/140 (67.1%)	46/74 (62.2%)	5.0%	0.01	-6.1%	0.47	18.6%
50% Osseous Bridging via CT (subtalar)	mITT	36 Weeks	214	95/140 (67.9%)	56/74 (75.7%)	-7.8%	0.37	-17.9%	0.23	5.2%
50% Osseous Bridging via CT (calcaneocuboid)	mITT	9 Weeks	95	14/64 (21.9%)	10/31 (32.3%)	-10.4%	0.52	-27.2%	0.27	7.7%
50% Osseous Bridging via CT (calcaneocuboid)	mITT	16 Weeks	95	34/64 (53.1%)	14/31 (45.2%)	8.0%	0.05	-10.0%	0.47	28.3%
50% Osseous Bridging via CT (calcaneocuboid)	mITT	24 Weeks	95	43/64 (67.2%)	15/31 (48.4%)	18.8%	0.00	1.1%	0.08	38.7%
50% Osseous Bridging via CT (calcaneocuboid)	mITT	36 Weeks	95	47/64 (73.4%)	21/31 (67.7%)	5.7%	0.06	-10.0%	0.56	26.0%
50% Osseous Bridging via CT (talonavicular)	mITT	9 Weeks	136	24/90 (26.7%)	11/46 (23.9%)	2.8%	0.05	-10.9%	0.73	17.2%
50% Osseous Bridging via CT (talonavicular)	mITT	16 Weeks	136	49/90 (54.4%)	24/46 (52.2%)	2.3%	0.09	-12.4%	0.80	19.7%
50% Osseous Bridging via CT (talonavicular)	mITT	24 Weeks	136	57/90 (63.3%)	27/46 (58.7%)	4.6%	0.05	-9.6%	0.60	22.0%
50% Osseous Bridging via CT (talonavicular)	mITT	36 Weeks	136	59/90 (65.6%)	33/46 (71.7%)	-6.2%	0.32	-19.2%	0.47	10.8%
50% Osseous Bridging via CT (ankle)	ITT	9 Weeks	158	34/103 (33%)	25/55 (45.5%)	-12.4%	0.62	-25.7%	0.12	3.3%
50% Osseous Bridging via CT (ankle)	ITT	16 Weeks	158	55/103 (53.4%)	36/55 (65.5%)	-12.1%	0.60	-24.8%	0.14	4.2%
50% Osseous Bridging via CT (ankle)	ITT	24 Weeks	158	69/103 (67%)	42/55 (76.4%)	-9.4%	0.47	-20.9%	0.22	5.9%

Measure	Population	Visit	N	Augment	Autograft	Rate Difference	Non-inferiority p-value	Non-inferiority Lower Confidence Limit	p-value Superiority: Autograft over Augment	Superiority Upper Confidence Limit
50% Osseous Bridging via CT (ankle)	ITT	36 Weeks	158	72/103 (69.9%)	43/55 (78.2%)	-8.3%	0.41	-19.5%	0.27	6.6%
50% Osseous Bridging via CT (subtalar)	ITT	9 Weeks	225	37/148 (25%)	35/77 (45.5%)	-20.5%	0.94	-31.4%	0.00	-7.4%
50% Osseous Bridging via CT (subtalar)	ITT	16 Weeks	225	82/148 (55.4%)	49/77 (63.6%)	-8.2%	0.40	-19.2%	0.23	5.4%
50% Osseous Bridging via CT (subtalar)	ITT	24 Weeks	225	99/148 (66.9%)	49/77 (63.6%)	3.3%	0.02	-7.5%	0.63	16.6%
50% Osseous Bridging via CT (subtalar)	ITT	36 Weeks	225	101/148 (68.2%)	59/77 (76.6%)	-8.4%	0.40	-18.1%	0.19	4.3%
50% Osseous Bridging via CT (calcaneocuboid)	ITT	9 Weeks	100	15/68 (22.1%)	11/32 (34.4%)	-12.3%	0.59	-28.8%	0.19	5.7%
50% Osseous Bridging via CT (calcaneocuboid)	ITT	16 Weeks	100	36/68 (52.9%)	16/32 (50%)	2.9%	0.11	-14.4%	0.78	23.3%
50% Osseous Bridging via CT (calcaneocuboid)	ITT	24 Weeks	100	45/68 (66.2%)	17/32 (53.1%)	13.1%	0.01	-4.0%	0.21	33.0%
50% Osseous Bridging via CT (calcaneocuboid)	ITT	36 Weeks	100	50/68 (73.5%)	22/32 (68.8%)	4.8%	0.07	-10.5%	0.62	24.6%
50% Osseous Bridging via CT (talonavicular)	ITT	9 Weeks	145	25/97 (25.8%)	12/48 (25%)	0.8%	0.08	-12.5%	0.92	14.9%
50% Osseous Bridging via CT (talonavicular)	ITT	16 Weeks	145	52/97 (53.6%)	25/48 (52.1%)	1.5%	0.10	-12.8%	0.86	18.5%
50% Osseous Bridging via CT (talonavicular)	ITT	24 Weeks	145	60/97 (61.9%)	29/48 (60.4%)	1.4%	0.09	-12.3%	0.87	18.4%
50% Osseous Bridging via CT (talonavicular)	ITT	36 Weeks	145	63/97 (64.9%)	34/48 (70.8%)	-5.9%	0.31	-18.7%	0.48	10.7%
75% Osseous Bridging via CT (ankle)	mITT	9 Weeks	152	6/100 (6%)	5/52 (9.6%)	-3.6%	0.09	-13.0%	0.41	4.9%
75% Osseous Bridging via CT (ankle)	mITT	16 Weeks	152	27/100 (27%)	20/52 (38.5%)	-11.5%	0.57	-24.9%	0.15	3.9%
75% Osseous Bridging via CT (ankle)	mITT	24 Weeks	152	38/100 (38%)	29/52 (55.8%)	-17.8%	0.82	-31.2%	0.04	-1.1%
75% Osseous Bridging via CT (ankle)	mITT	36 Weeks	152	46/100 (46%)	32/52 (61.5%)	-15.5%	0.75	-28.8%	0.07	1.2%
75% Osseous Bridging via CT (subtalar)	mITT	9 Weeks	214	8/140 (5.7%)	9/74 (12.2%)	-6.4%	0.20	-14.5%	0.10	1.1%

Measure	Population	Visit	N	Augment	Autograft	Rate Difference	Non-inferiority p-value	Non-inferiority Lower Confidence Limit	p-value Superiority: Autograft over Augment	Superiority Upper Confidence Limit
75% Osseous Bridging via CT (subtalar)	mITT	16 Weeks	214	34/140 (24.3%)	30/74 (40.5%)	-16.3%	0.82	-27.4%	0.01	-3.3%
75% Osseous Bridging via CT (subtalar)	mITT	24 Weeks	214	58/140 (41.4%)	37/74 (50%)	-8.6%	0.42	-20.2%	0.23	5.3%
75% Osseous Bridging via CT (subtalar)	mITT	36 Weeks	214	74/140 (52.9%)	44/74 (59.5%)	-6.6%	0.32	-18.0%	0.36	7.4%
75% Osseous Bridging via CT (calcaneocuboid)	mITT	9 Weeks	95	3/64 (4.7%)	4/31 (12.9%)	-8.2%	0.39	-21.7%	0.15	2.9%
75% Osseous Bridging via CT (calcaneocuboid)	mITT	16 Weeks	95	14/64 (21.9%)	7/31 (22.6%)	-0.7%	0.15	-16.9%	0.94	15.8%
75% Osseous Bridging via CT (calcaneocuboid)	mITT	24 Weeks	95	23/64 (35.9%)	10/31 (32.3%)	3.7%	0.09	-13.9%	0.72	22.5%
75% Osseous Bridging via CT (calcaneocuboid)	mITT	36 Weeks	95	33/64 (51.6%)	17/31 (54.8%)	-3.3%	0.27	-20.7%	0.76	17.8%
75% Osseous Bridging via CT (talonavicular)	mITT	9 Weeks	136	4/90 (4.4%)	3/46 (6.5%)	-2.1%	0.03	-11.2%	0.60	5.7%
75% Osseous Bridging via CT (talonavicular)	mITT	16 Weeks	136	24/90 (26.7%)	8/46 (17.4%)	9.3%	0.00	-3.7%	0.23	22.6%
75% Osseous Bridging via CT (talonavicular)	mITT	24 Weeks	136	37/90 (41.1%)	14/46 (30.4%)	10.7%	0.01	-3.9%	0.22	26.4%
75% Osseous Bridging via CT (talonavicular)	mITT	36 Weeks	136	49/90 (54.4%)	21/46 (45.7%)	8.8%	0.02	-6.1%	0.33	25.9%
75% Osseous Bridging via CT (ankle)	ITT	9 Weeks	158	6/103 (5.8%)	5/55 (9.1%)	-3.3%	0.07	-12.2%	0.44	4.9%
75% Osseous Bridging via CT (ankle)	ITT	16 Weeks	158	27/103 (26.2%)	22/55 (40%)	-13.8%	0.68	-26.8%	0.07	1.3%
75% Osseous Bridging via CT (ankle)	ITT	24 Weeks	158	39/103 (37.9%)	31/55 (56.4%)	-18.5%	0.85	-31.6%	0.03	-2.2%
75% Osseous Bridging via CT (ankle)	ITT	36 Weeks	158	47/103 (45.6%)	35/55 (63.6%)	-18.0%	0.84	-30.8%	0.03	-1.7%
75% Osseous Bridging via CT (subtalar)	ITT	9 Weeks	225	9/148 (6.1%)	9/77 (11.7%)	-5.6%	0.15	-13.5%	0.14	1.8%
75% Osseous Bridging via CT (subtalar)	ITT	16 Weeks	225	37/148 (25%)	30/77 (39%)	-14.0%	0.73	-24.9%	0.03	-1.3%
75% Osseous Bridging via CT (subtalar)	ITT	24 Weeks	225	60/148 (40.5%)	38/77 (49.4%)	-8.8%	0.43	-20.2%	0.21	4.8%

Measure	Population	Visit	N	Augment	Autograft	Rate Difference	Non-inferiority p-value	Non-inferiority Lower Confidence Limit	p-value Superiority: Autograft over Augment	Superiority Upper Confidence Limit
75% Osseous Bridging via CT (subtalar)	ITT	36 Weeks	225	78/148 (52.7%)	44/77 (57.1%)	-4.4%	0.21	-15.7%	0.53	9.3%
75% Osseous Bridging via CT (calcaneocuboid)	ITT	9 Weeks	100	3/68 (4.4%)	4/32 (12.5%)	-8.1%	0.38	-21.2%	0.14	2.5%
75% Osseous Bridging via CT (calcaneocuboid)	ITT	16 Weeks	100	15/68 (22.1%)	8/32 (25%)	-2.9%	0.22	-19.1%	0.74	13.6%
75% Osseous Bridging via CT (calcaneocuboid)	ITT	24 Weeks	100	24/68 (35.3%)	12/32 (37.5%)	-2.2%	0.23	-19.5%	0.83	16.9%
75% Osseous Bridging via CT (calcaneocuboid)	ITT	36 Weeks	100	36/68 (52.9%)	18/32 (56.3%)	-3.3%	0.27	-20.3%	0.76	17.4%
75% Osseous Bridging via CT (talonavicular)	ITT	9 Weeks	145	4/97 (4.1%)	3/48 (6.3%)	-2.1%	0.03	-10.9%	0.57	5.2%
75% Osseous Bridging via CT (talonavicular)	ITT	16 Weeks	145	24/97 (24.7%)	10/48 (20.8%)	3.9%	0.03	-9.0%	0.60	17.3%
75% Osseous Bridging via CT (talonavicular)	ITT	24 Weeks	145	37/97 (38.1%)	16/48 (33.3%)	4.8%	0.04	-9.4%	0.57	20.4%
75% Osseous Bridging via CT (talonavicular)	ITT	36 Weeks	145	52/97 (53.6%)	22/48 (45.8%)	7.8%	0.02	-6.7%	0.38	24.4%

Index joint summaries are not provided due to agreement that this parameter is not clinically valid.

Salient statistical issues

Computations

P-values, and the corresponding confidence intervals, are computed under asymptotic theory, using an estimate of the standard error based on the individual rate estimates rather than on a pooled, overall rate. BMTI also computed exact confidence intervals and p-values (via StatXact) but do not present them here as they are generally consistent with the results shown. For example, for the primary endpoint of the trial, CT fusion based on a cutoff of 50% osseous bridging in the mITT population at Week 24, the rates were 61.2% for Augment (137/260) and 62.0% for autograft (85/159), yielding a rate difference of -0.9%, a lower 95% confidence limit of -9.3%, and a non-inferiority p-value of 0.038. StatXact reports an exact lower 95% confidence limit of -9.279% and a corresponding p-value of 0.03693. Certainly those differences are not worthy of more discussion, although the exact values can be provided if needed. Naturally, for endpoints where the rates are closer to 0% or 100%, the disparity between the methodologies will be greater.

Independence

Computations are based on the assumption of independent observations. Therefore, computations of the p-values and confidence limits for the 'all joints' investigations can be considered statistically inappropriate, as the multiple observations within a subject with more than one joint under consideration are correlated. The statistical reviewer noted this issue in question 18 of this letter. While one can compute the summaries as they are presented in the table, inference based on these numbers is difficult, as assuming independence likely overstates the precision in the estimate (underestimates the standard error) and may produce an estimate that is a biased estimate of the overall success rate in each treatment group.

Proper formal inference of the all joints data requires a statistical model that accounts for the correlation within a patient and then appropriately adjusts the standard error of the estimated quantity. Such a model is presented in the response to question 18, where non-inferiority of Augment is demonstrated under the all-joints analysis at 24 weeks.

Multiplicity

Six joint specifications times four time points times two populations times two criteria for success yields 96 comparisons, although the 96 investigations are clearly not independent. Formal Type I error control is probably necessary if one seeks a controlled investigation of these endpoints; however, exactly how to carry out that adjustment is not obvious due to the correlation between the endpoints.

Consequently, caution must be exercised in drawing inference from the data here, as the correlation between the endpoints, the post-hoc nature of the tests, and the multiplicity issue likely inflates the perceived importance of any collection of results.

b) *Please provide detailed information for all patients who specifically had a radiographic adverse event (non-union, periosteal reaction, etc), and how this was used to determine overall success. For example, there were patients who were noted descriptively as having possible radiographic evidence of infection. Please provide further narratives on follow up and tests that were performed in these patients to confirm or deny the suspected diagnosis. Please include these patients in the overall analyses of infections as adverse events, and be considered as a "failure" for the primary endpoint.*

Response

The presence of abnormal bone formation radiographically is a nonspecific observation that may or may not have clinical implications. More specifically, radiographic evidence of periosteal reaction and soft tissue swelling can be part of a normal post-operative course following arthrodesis. However, when corroborated by clinical findings (e.g. edema, warmth, etc) indication of potential events may be seen in the context of infection and/or loosening. Per protocol, all adverse events were recorded based upon clinical and radiographic examination by the investigator. As requested by FDA, a listing is provided below detailing both the radiographic observation and the reported adverse events for the subject as assessed by the investigator. Based on clinical observation by the principal investigators as described in the adverse event reporting, no trend or signal appears present. Subjects were not considered failures for the primary endpoint based on these supplementary radiographic parameter data.

Table 20: Radiographic Observations with Treatment and Adverse Events

Subject	Treatment	Visit #	Type	Verbatim Comment	Reported Adverse Events
[redacted]	Autologous Bone Graft	1	Other	Old TT hardware. Only lateral view available but acceptable for pre-op assessment	NONE
	Autologous Bone Graft	8	Evidence of infection	None	RASH RIGHT ANKLE SWELLING RIGHT ANKLE KIDNEY STONES CONSTIPATION ERYTHEMA RIGHT ANKLE LEFT SHOULDER PAIN
		9	Evidence of infection	Suspicious for infection	
	Augment Bone Graft	10	Heterotopic bone formation	2mm focus of H.O. coalescence of particles	LEFT HIP BURSITIS VENOUS STASIS ULCERS - RIGHT FOOT – RECURRENCE LUMBAR SPINE PAIN

Subject	Treatment	Visit #	Type	Verbatim Comment	Reported Adverse Events
[redacted]	Augment Bone Graft	1	Evidence of non-union	Calcaneal fracture (non-union) ST joint OK	NAUSEA DIABETIC ULCER-RIGHT HEEL DIZZINESS HYPERGLYCEMIA HYPERGLYCEMIA GASTRITIS OSTEOMYELITIS OF RIGHT FOOT PNEUMONIA HIGH FEVER DM ULCER WITH CELLULITIS, MRSA RIGHT LEG PAIN ARTHRITIS OF RIGHT KNEE CATARACTS OF RIGHT EYE DIABETIC ULCER OF RIGHT HEEL CELLULITIS OF RIGHT FOOT
	Augment Bone Graft	9	Heterotopic bone formation	5mm focus of heterotopic ossification	SKIN IRRITATION
		10	Heterotopic bone formation	5mm focus of heterotopic ossification	
	Augment Bone Graft	4	Heterotopic bone formation (ST joint)	None	EAR INFECTION SKIN IRRITATION
		5	Heterotopic bone formation (ST and CC joints)	None	
		6	Heterotopic bone formation (ST and CC joints)	None	
		7	Heterotopic bone formation (ST and CC joints)	Small focus of heterotopic ossification	
		8	Heterotopic bone formation (ST and CC joints)	None	
		9	Heterotopic bone formation (CC joint)	5mm focus of heterotopic ossification	
		9	Hetertopic bone formation (ST joint)	Decrease in size of heterotopic ossification	
		10	Heterotopic bone formation (ST and CC joints)	No change in heterotopic focus	
	Autologous Bone Graft	1	Other	Superior subluxation of navicular by 1cm. Old trauma.	MILD ERYTHEMA AT INCISION SITE

Subject	Treatment	Visit #	Type	Verbatim Comment	Reported Adverse Events
[redacted]	Augment Bone Graft	1	Other (CC joint)	Sizable bone cyst in calcaneus 2.7 cm	ADJACENT JOINT ARTHRITIS AT NAVICULOCUNEIFROM JOINT SYSTEMIC RASH ON TORSO, FEET AND FACE INCREASED PAIN-LEFT DUE TO BROKEN HARDWARE
		6	Heterotopic bone formation (ST joint)	None	
		7	Heterotopic bone formation (ST joint)	None	
		8	Heterotopic bone formation (ST joint)	None	
		9	Heterotopic bone formation (ST joint)	Stable 6mm focus of H.O.	
	Augment Bone Graft	10	Abnormal subperiosteal bone resorption at or around the fusion site	None	TRACHEAL INFECTION LT INGUINAL HERNIA
	Augment Bone Graft	7	Abnormal subperiosteal bone resorption at or around the fusion site	Suspicious for infection	BLOOD IN RT EYE REDNESS IN LOWER LEFT LEG/FT/ANKLE LT CALF PAIN EDEMA IN LOWER LEFT LEG/FT/ANKLE BLEED LT EYE
		8	Abnormal subperiosteal bone resorption at or around the fusion site AND Evidence of infection	None	
		9	Abnormal subperiosteal bone resorption at or around the fusion site AND Evidence of infection AND Evidence of non-union	Infection progressing	
		10	Abnormal subperiosteal bone resorption at or around the fusion site AND Evidence of infection AND Evidence of non-union	Infection	
	Autologous Bone Graft	1	Other	OA. Large subchondral cyst tibial plafond 18mm width	POSTERMEDIAL NONDISPLACED PARTIAL MALLEOLAR FRACTURE MILD DEPRESSION BRONCHITIS

Subject	Treatment	Visit #	Type	Verbatim Comment	Reported Adverse Events
[redacted]	Autologous Bone Graft	6	Other	Abnormal periosteal reaction posterior tibia	LARGE AMOUNT OF FLUID AROUND ANKLE NOTED INTRA-OP REDNESS AND EDEMA POST OP INCREASED PAIN LT ANKLE DECREASED SENSATION IN SUPERFICIAL PERONEAL NERVE DISTURB
		8	Other	Periosteal reaction loosening versus infection	
		9	Other	Stable periosteal reaction	
		10	Other	Stable benign periosteal reaction	
	Augment Bone Graft	8	Other	Positive soft tissue swelling. Effusion. Periosteal reaction.	NONE
		9	Other	Positive soft tissue swelling. Positive effusion. Periosteal reaction.	
		10	Other	Stable soft tissue swelling and periosteal reaction.	
	Augment Bone Graft	9	Abnormal subperiosteal bone resorption at or around the fusion site	None	CHEST PAIN
		10	Abnormal subperiosteal bone resorption at or around the fusion site	Tough case radiographically to decide union status	
	Autologous Bone Graft	9	Abnormal subperiosteal bone resorption at or around the fusion site	None	COMPLETE HEART BLOCK PERSISTANT PAIN LT ANKLE
	Augment Bone Graft	4	Other	Abnormal periosteal reaction posterior tibia	NONE
		5	Other	Abnormal periosteal reaction	
		6	Abnormal subperiosteal bone resorption at or around the fusion site AND Other	Abnormal periosteal reaction. Increase soft tissue swelling	

Subject	Treatment	Visit #	Type	Verbatim Comment	Reported Adverse Events
[redacted]		7	Abnormal subperiosteal bone resorption at or around the fusion site AND Other	Persistent soft tissue swelling and periosteal reaction	
		8	Other	Abnormal tibial periosteal reaction. Persistent soft tissue swelling. Suspicious for infection.	
		9	Abnormal subperiosteal bone resorption at or around the fusion site	None	
	Augment Bone Graft	8	Heterotopic bone formation	Small focus of heterotopic ossification	CELLULITUS TENDON PAIN - WALKING DIFFICULT AND PAINFUL ANKLE MALALIGNMENT
		9	Heterotopic bone formation	Stable focus of heterotopic ossification	
		10	Heterotopic bone formation	Stable small focus of heterotopic ossification posterior to OS perineum	
	Autologous Bone Graft	6	Heterotopic bone formation	None	INCREASED SWELLING LEFT LOWER EXTREMITY
		7	Heterotopic bone formation	None	
		10	Heterotopic bone formation	Mild anterior heterotopic ossification	
	Augment Bone Graft	8	Heterotopic bone formation	5mm focus of heterotopic ossification	INFILTRATING LOBULAR CARCINOMA BLOOD CLOT JOINT PAIN (WRIST AND OTHER JOINTS) DUE TO RHEUMATOID ART
		9	Heterotopic bone formation	5mm focus of heterotopic ossification	
	Autologous Bone Graft	6	Heterotopic bone formation	None	None
		7	Heterotopic bone formation	Anterior focus of H.O.	
		9	Heterotopic bone formation	Anterior focus of H.O.	

Subject	Treatment	Visit #	Type	Verbatim Comment	Reported Adverse Events
[redacted]		10	Heterotopic bone formation	Stable heterotopic ossification	
	Augment Bone Graft	4	Other	Periosteal reaction	PAIN AND SWELLING IN OPERATIVE FOOT
		5	Other	Periosteal reaction	
		7	Other	Periosteal reaction	
		8	Other	Periosteal reaction	
		9	Abnormal subperiosteal bone resorption at or around the fusion site AND Other	Smooth periosteal reaction and sclerosis	
	Augment Bone Graft	3	Other	Periosteal reaction	NUMBNESS & TINGLING IN TOP OF RIGHT FOOT
		4	Other	Periosteal reaction	
		5	Other	Periosteal reaction AND tibial periosteal reaction	
		6	Other	Periosteal reaction	
		7	Other	Periosteal reaction	
		8	Other	Periosteal reaction	
		9	Other	Mild periosteal reaction	
		10	Other	Periosteal reaction now new bone	
	Augment Bone Graft	9	Heterotopic bone formation	Tiny amount on lateral (heterotopic bone)	BACK PAIN
		10	Heterotopic bone formation	Stable tiny H.O. on lateral	
	Autologous Bone Graft	7	Heterotopic bone formation	Small focus 5mm of heterotopic ossification	ASTHMA EXACERBATION GOUT IN LEFT WRIST
		8	Heterotopic bone formation	Stable small focus of heterotopic ossification	
		9	Heterotopic bone formation	Stable small focus adjacent to joint	
		10	Heterotopic bone	Stable small focus of	

Subject	Treatment	Visit #	Type	Verbatim Comment	Reported Adverse Events
[redacted]			formation	heterotopic ossification	
	Augment Bone Graft	7	Heterotopic bone formation	Small 3mm focus of heterotopic ossification	LEFT ANKLE SWELLING
		8	Heterotopic bone formation	Small stable 3mm focus of heterotopic ossification	
		9	Heterotopic bone formation	Stable 3mm focus of heterotopic ossification	
		10	Heterotopic bone formation	Slightly less distinct focus of H.O. posterior to ST joint	
	Augment Bone Graft	8	Other	Periosteal reaction	DIZZINESS CHEST PAIN DYSPNEA PAIN ANKLE LEFT SWELLING ANKLE LEFT
		9	Other	Periosteal reaction	
		10	Other	Periosteal reaction	
	Augment Bone Graft	9	Other	Periosteal reaction smooth	PAIN IN RIGHT BUTTOCK/SACRUM (SCIATIC) SHOOTING PAIN IN RT ANKLE SWELLING ANKLE RIGHT
		10	Other	Smooth incorporating periosteal new bone	

As can be inferred from the above noted information, some radiographic assessments may translate into clinical adverse events, such as subject [redacted] who was noted by the independent radiologist as having "periosteal reaction" and for whom the adverse event "numbness and tingling in top of right foot". In such a case, the adverse event was reported and coded based upon the clinical symptoms. Likewise, subject [redacted] was observed as having radiographic evidence of infection and clinical adverse event was reported as "swelling right ankle", which is perhaps a correlated clinical event to the radiographic observation.

Conversely, subjects [redacted] and [redacted] both had observations of "heterotopic bone formation", but no clinical adverse events reported.

In conclusion, the investigator who has access to all data and information regarding each subject is in the best position to evaluate the significance of radiographic and clinical observations, and was responsible for reporting and recording such events as per the study protocol. BMTI believes these events were reported and data were coded and managed conservatively to allow appropriate interpretation regarding safety of Augment and autograft.

c) *It is unclear from the adverse event narratives and the radiographic information if any of the patients demonstrated evidence of excessive bone formation. Excessive bone formation has been a clinical concern with other growth factors, and it is unclear if that has or would be the case with the current radiographic evaluations. Therefore, please provide radiographic information and/or operative data on the presence or absence of excessive bone formation (Heterotopic Ossification or Myositis Ossificans) in the investigational group.*

Response

The presence of heterotopic bone formation was identified in eleven (11) patients (8 Augment and 3 autograft). As per the independent radiologist, in all cases the heterotopic ossification measured less than 6 mm and was based on a confluence of two adjacent punctuate bone graft particles that failed to completely resorb. These foci were stable on serial radiographs. There were no cases in which there was progression of heterotopic ossification. There were no cases of myositis ossificans.

Question 11

11) *There were some differences noted between the two treatment groups with regards to age of injury/deformity requiring surgery. The mean age of injury/deformity at baseline for subjects in the control group (315 weeks) was higher than the mean age of subjects in the investigational group (261 weeks). This increase in time from baseline injury to time of surgery in the control group may favor the investigational group, who would present as less technically demanding cases. Please provide a sensitivity analysis for a comparison of outcomes using this demographic variable.*

Response

As mentioned by FDA, mean ages of injuries are presented as 261 weeks and 315 weeks for Augment and autograft, respectively. Distributional summaries of the ages of injury/deformity are presented below with these ages expressed in weeks and also in years.

Table 21: Distribution of Age of Injury / Deformity

	Age of Injury						
Population	Treatment Group	N	Mean (weeks)	Mean (years)	Std. Dev. (years)	Median (years)	10th Percentile (years)
ITT	Augment	177	261	5.0	8.8	1.9	0.25
	Autograft	93	315	6.0	8.7	2.6	0.34
mITT	Augment	164	242	4.6	7.8	1.8	0.25
	Autograft	85	322	6.2	8.9	2.8	0.34

Table 22: Distribution of Subject Age

		Age of Subject		
Population	Treatment Group	N	Mean (years)	Median (years)
ITT	Augment	281	56.2	58.6
	Autograft	148	57.5	59.7
mITT	Augment	260	55.8	57.9
	Autograft	137	57.3	58.3

The mean ages of injuries/disease states in years are 5.0 and 6.0 for the Augment and autograft, respectively, with corresponding standard deviations of 8.7 and 8.8 years. With the ages being restricted to positive values, these standard deviations represent a substantial skew in the data. Further, as the disease state is generally a degenerative progression of arthritis, and the index surgical procedure is a reconstruction consisting of debridement, fixation, and bone grafting, these differences are not clinically significant.

The corresponding median ages of injuries are 1.8 and 2.5 years, a difference of less than one year, while 90 percent of the Augment injury ages exceed 0.25 years, while 90 percent of the autograft injuries exceed 0.34 years.

The summaries for the MITT patients follow the same general pattern as those for the ITT population, as shown in the table. Note that the differences in patient age is slightly less than two years via the mean and less than one year via the median, values consistent with the differences in age of injury.

Note that 249 injury ages are known. These 249 injury ages are split 164:85=1.929:1, consistent with the overall 260:137=1.898:1 split of the patients in the MITT population.

Based on the age-of-injury quartiles defined from the ITT population, BMTI partitioned the mITT patients and examined the primary endpoint (CT fusion based on at least 50% osseous bridging at week 24) for these subgroups. BMTI also examined the CT fusion rate for the subgroup of patients without injury age data. These results are presented below.

Table 23: Age of Injury / Deformity Quartile Fusion Rates

Age of Injury Category		CT Fusion Rates at 24 weeks			
	Total	Augment		Autograft	
	N	x/n	%	x/n	%
Unknown	148	56/96	58	28/52	54
1st Quartile	62	30/46	65	8/16	50
2nd Quartile	61	26/42	62	11/19	58
3rd Quartile	63	25/41	61	18/22	82
4th Quartile	63	22/35	63	20/28	71

At least two points are worth noting, when examining the stratified CT fusion data.

First, a Breslow-Day test for homogeneity of the odds ratio for fusion is insignificant at p=0.2968. While failing to reject this test is not an explicit statement of support for a null hypothesis of homogeneity, this test result shows that the data, as they vary somewhat across the five strata, are not more variable across these strata than would be expected via chance.

Second, any variation that does exist across the strata is driven not by large variation in the Augment group but rather by variation in the autograft group. The five Augment success rates are 58%, 65%, 62%, 61%, and 63%, with the greatest difference between groups being 7 percentage points. Correspondingly, the autograft success rates are 53%, 50%, 58%, 82%, and 71%, a range of 32 percentage points. These splits, along with others observed, speak consistently to the reduced variability of outcome available with Augment when compared to autograft.

One may be tempted to conclude that only older patients can produce old injuries and might wish to attribute patient age the rates seen above. Splitting ages into quartiles results in the following rates.

Table 24: Age of Subject Quartile Fusion Rates

Age of Subject Category	CT Fusion Rates at 24 weeks				
	Total	Augment		Autograft	
	N	x/n	%	x/n	%
1st Quartile	103	41/71	58	22/32	69
2nd Quartile	101	38/64	59	27/37	73
3rd Quartile	91	44/64	69	17/27	63
4th Quartile	102	36/61	59	19/41	46

These splits based on age also fail to reject the null hypothesis of odds ratio homogeneity of Breslow and Day's test (p=0.1860). Again, variation within the autograft group exceeds that seen within Augment. The Augment rates are 58%, 59%, 69%, and 59%, for a range of 10 percentage points, while autograft rates bounce from 69%, to 73%, 63%, and 46%, a range of 27 percentage points.

BMTI further split the patients jointly based on medians for injury age and patient age, yielding 6 strata; see below:

Table 25: Age of Subject plus Age of Injury / Deformity Fusion Rates

Subject Age plus Age of Injury Category	CT Fusion Rates at 24 weeks				
	Total	Augment		Autograft	
	N	x/n	%	x/n	%
Young subject / Unknown age of injury	61	21/45	47	10/16	63
Young Subject / Recent injury	68	30/49	61	11/19	58
Young Subject / Older injury	75	28/41	68	28/34	82
Older subject / Unknown age of injury	87	35/51	69	18/36	50
Older Subject / Recent injury	55	26/39	67	8/16	50
Older Subject / Older injury	51	19/35	54	10/16	63

Again, the Breslow-Day test fails (p=0.1648), while the variation in the Augment group (30 percentage points) is lower, albeit only slightly, than the variation in the autograft group (32 percentage points).

While the median age of injury / deformity differs between groups, the standard deviations are large and no pattern in support of a treatment difference based on the injury / deformity characteristics emerges from the analyses.

Question 12

12) *You have provided 5 different secondary endpoints. Several of these outcomes are potentially not clinically meaningful. The success of your device is difficult to assess utilizing these secondary outcome measures analyzed independently or with less stringent outcome criteria. Because these outcomes were not defined apriori as part of the power of the study they cannot be used to base a determination of safety and effectiveness of your device, however they may be used to support a determination for or against safety and effectiveness as determined by the primary endpoint of your study. Whether fusion is defined by 25% or 50% osseous bridging determines the clinical composite success, by the subgroups "composite outcome" versus "clinical success". To help us to better understand this data, please provide tables that clearly highlight (for each time-point) the number of patients who had improved "clinical healing", "composite success", "clinical success", and quality of life success, as stratified by the amount of improvement. These should clearly highlight the number of those with clinically significant improvements, those that worsened, and those who did not improve in regard to pain scores, radiographic scores, and scores for each quality of life assessment. In addition, please clarify how the radiographic*

endpoint utilizing only 25% osseous bridging as defined by CT is an appropriate measure of a successful fusion; why only serious AEs related to the device are considered; and how "clinical healing" based on pain at the graft site only in Controls (does not assess pain at the fusion site in either group), with no functionally related assessments, is clinically relevant.

Response

As requested by FDA, BMTI has supplied tables describing subject change in endpoints across study visits in the tables noted below.

Clarification:
While these endpoints were not defined as part of the formal power calculation, they were prospectively defined in the Statistical Analysis Plan.

As requested, please see the following definitions of the noted secondary endpoints, and the requested data for improvement or worsening for each of the parameters. The margins used for demarcation of improvement or decline are the margins used in calculation of the non-inferiority p-values.

CLINICAL UNION (CLINICAL HEALING STATUS)

Among the physical examination assessments performed at each visit was a determination of "healing status", a check-box with five possible outcomes: union, evidence of progressive healing, delayed union, non-union, and uninterpretable. A patient achieved "clinical union" at a particular visit if the investigator selected "union" for the clinical healing status at that particular visit.

Patient-level clinical union prior to 24 weeks was a clinical determination based on physical examination and available data and this determination was made at the patient level, not the joint level. At weeks 24, 36, and 52 joint-level clinical union was also assessed. These per-joint assessments were subjected to the same full complement and index joint summarization algorithms as used by the CT scans and radiographs.

As a binary endpoint, clinical union, like CT fusion, is also subject of the "documented evidence" and autofail determinations.

The significance of clinical healing is underscored as a global assessment of patient progress as observed by the surgeon, as would be assessed in standard patient evaluation by a surgeon. This assessment is generally based upon physical examination, pain, and function and considering the timepoint at which the assessment is made.

Table 26: Clinical Healing Change by Visit (patient level)

	Change from Prior Visit											
	Augment						Autograft					
	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52
Fail → Succeed		69	63	62	14	12		42	24	27	8	3
Succeed → Succeed		29	95	154	206	216		25	66	88	113	118
Fail → Fail		156	99	40	30	28		68	46	20	14	13
Succeed → Fail		6	3	4	10	4		2	1	2	2	3
Net Change in Success		63	60	58	4	8		40	23	25	6	0
Total Success at Visit	35	98	158	216	220	228	27	67	90	115	121	121
Total Failure at Visit	225	162	102	44	40	32	110	70	47	22	16	16

Table 26. Clinical Healing Change by Visit demonstrates progression of clinical healing over time relative to previous visit.

Table 27: Clinical Union Per Joint Change by Visit (full complement of joints)

	Change from Prior Visit					
	Augment			Autograft		
	Week 24	Week 36	Week 52	Week 24	Week 36	Week 52
Fail → Succeed		17	12		7	3
Succeed → Succeed		202	212		112	117
Fail → Fail		29	29		16	15
Succeed → Fail		12	7		2	2
Net Change in Success		5	5		5	1
Total Success at Visit	214	219	224	114	119	120
Total Failure at Visit	46	41	36	23	18	17

Table 27. Clinical Union per Joint Change by Visit demonstrates progression of clinical union over time relative to previous visit.

CLINICAL SUCCESS

Clinical success is defined as improved pain with weightbearing compared to baseline and no need for revision surgery. Thus, patients who withdrew from the study so as to undergo revision surgery were not considered clinical successes.

Pain with weight-bearing was measured on a visual-analog-scale. Thus, improved pain with weight-bearing compared to baseline was achieved at a particular visit if the patient's pain with

weight-bearing was lower at that visit than it was baseline. Given that the primary patient complaint resulting in hindfoot or ankle fusion is pain, it is reasonable to assess improved pain as a component of clinical success. For any patient who did not achieve improved pain with weightbearing, it can be assumed that they did not achieve clinically significant improvement in pain.

The need for revision surgery was determined from a check-box on the study completion assessment, filled out only if the patient did not complete the study according to the protocol. For a surgery that is known to have a 10-40% nonunion/revision rate, a notable endpoint is lack of need for revision surgery.

Based upon the above noted observations, this endpoint is a reasonable endpoint to quantify clinical success by addressing patient/surgeon parameters, including improved pain and lack of need for additional surgical intervention relative to the index procedure.

Table 28: Clinical Success Change by Visit

	Change from Prior Visit											
	Augment						Autograft					
	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52
Fail → Succeed		37	26	17	17	15		20	17	7	6	8
Succeed → Succeed		144	162	177	175	185		76	88	100	98	99
Fail → Fail		59	53	55	49	53		28	24	25	24	25
Succeed → Fail		20	19	11	19	7		13	8	5	9	5
Net Change in Success		17	7	6	-2	8		7	9	2	-3	3
Total Success at Visit	20	181	188	194	192	200	13	96	105	107	104	107
Total Failure at Visit	59	79	72	66	68	60	28	41	32	30	33	30

Table 28. Clinical Success Change by Visit demonstrates progression of clinical success over time relative to previous visit.

Table 29: Weight Bearing Pain Change by Visit

	Change from Prior Visit											
	Augment						Autograft					
	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52
Missing	53	31	15	14	19	20	26	12	4	5	8	5
Improvement		40	53	47	53	35		28	23	34	30	16
No Change		109	129	151	154	171		56	70	83	80	97
Decline		42	41	39	26	27		22	30	14	16	15
Net Change		-2	12	8	27	8		6	-7	20	14	1

Table 29. Weight bearing pain change by visit demonstrates change in weight-bearing pain over time relative to previous visit.

Table 30: Fusion Site Pain Change by Visit

	Change from Prior Visit											
	Augment						Autograft					
	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52
Missing	18	19	11	12	18	19	11	7	4	4	7	5
Improvement		31	38	41	43	33		15	22	32	20	14
No Change		156	159	165	166	181		76	81	86	95	103
Decline		38	38	36	27	21		30	25	14	13	12
Net Change		-7	0	5	16	12		-15	-3	18	7	2

Table 30. Fusion Site Pain Change by Visit demonstrates progression/improvement of fusion site pain over time relative to previous visit.

COMPOSITE SUCCESS

Composite success was a combination endpoint constructed from six other outcomes. Composite success was achieved for a patient at a time point if all of the following were simultaneously achieved:

- Surgical treatment complete per protocol, determined from a blinded review of the data.
- Union or evidence of progressive healing at a given timepoint. The source of this information was the per visit determination of "clinical healing status" where the potential outcomes were union, evidence of progressive healing, delayed union, non-union, or uninterpretable. .
- Assessment of at least 25% osseous bridging via CT scan for each of the full complement of joints.
    - Clinical Significance: This endpoint was developed using 25% osseous bridging as the fusion criteria for the composite. Dorsey and co-authors suggest that, as measured via CT, a lower percentage of osseous bridging may be sufficient to declare fusion. It is noted that previous fusion studies and FDA reviews have highlighted the importance of "presence of bridging bone" as being an important determinant for fusion, and previous sponsors have been criticized for using "presence of bone" as an endpoint. It is noted that ≥25% osseous bridging is consistent with presence of bridging bone, and is therefore clinically significant as a parameter for this multivariate endpoint. Thus, in the presence of the other indicators of clinical progress composing the composite endpoint, a lower threshold of osseous bridging was defined in the composite endpoint.

- No SAEs of possible relation to study treatment.
    - Clinical Significance: any serious adverse event considered to be related or possibly related to study treatment should effect the determination of composite success. Adverse events that are noted to be related or possibly related to the study treatment, or that cannot be ruled out, may or may not have a determination as to the success of the fusion, relative to the many potential complications associated with the procedure, regardless of bone graft utilization.
- Less than 20 mm of VAS pain assessment at bone graft harvest site at week 6 and after. Graft harvest site pain was one of three VAS measurements in the study. Each VAS was 100 mm long. At each visit on and after week 6, graft harvest site pain was measured via VAS. If this VAS was less than 20 mm, then this criterion was met at that visit.
    - Clinical significance: For surgeons and patients, a second surgical procedure and the potential morbidity associated with bone graft harvest must be considered as an important parameter for success. While this endpoint does not effect any other clinical assessments, such as clinical healing or clinical success, clinically significant (≥20mm on VAS) must be considered in the overall assessment of the success of the procedure.
- No need for therapeutic intervention or a secondary procedure due to delayed or non-union.
    - Clinical Significance: See Clinical Success.

Table 31: Composite Success Change by Visit

	Change from Prior Visit							
	Augment				Autograft			
	Week 9	Week 16	Week 24	Week 36	Week 9	Week 16	Week 24	Week 36
Fail → Succeed		62	25	14		34	17	14
Succeed → Succeed		113	159	172		54	78	92
Fail → Fail		75	60	62		40	32	28
Succeed → Fail		10	16	12		9	10	3
Net Change in Success		52	9	2		25	7	11
Total Success at Visit	123	175	184	186	63	88	95	106
Total Failure at Visit	137	85	76	74	74	49	42	31

Table 31. Composite Success Change by Visit demonstrates progression of composite success (as defined in original SAP) over time relative to previous visit.

Table 32: Osseous Bridging ≥ 50% via CT Change by Visit

	Change from Prior Visit							
	Augment				Autograft			
	Week 9	Week 16	Week 24	Week 36	Week 9	Week 16	Week 24	Week 36
Fail → Succeed		66	36	13		28	14	11
Succeed → Succeed		61	123	152		48	71	84
Fail → Fail		130	97	88		58	47	41
Succeed → Fail		3	4	7		3	5	1
Net Change in Success		63	32	6		25	9	10
Total Success at Visit	64	127	159	165	27	76	85	95
Total Failure at Visit	196	133	101	95	110	61	52	42

Table 32. Osseous Bridging ≥ 50% via CT Change by Visit demonstrates progression of osseous bridging over time relative to previous visit.

Table 33: Graft Harvest Site Pain Change by Visit

	Change from Prior Visit											
	Augment						Autograft					
	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52
Missing	N/A	N/A	N/A	N/A	N/A	N/A	13	9	7	6	9	7
Improvement		N/A	N/A	N/A	N/A	N/A		17	24	12	9	5
No Change		N/A	N/A	N/A	N/A	N/A		81	88	109	111	113
Decline		N/A	N/A	N/A	N/A	N/A		19	11	7	6	7
		N/A	N/A	N/A	N/A	N/A						
Net Change		N/A	N/A	N/A	N/A	N/A		-2	13	5	3	-2

Table 33. Graft Harvest Site Pain Change by Visit demonstrates progression/improvement of graft harvest site pain over time relative to previous visit. Patients in the Augment treatment group did not have a bone graft harvest site.

Table 34: SF-12 PCS Score Change by Visit

	Change from Prior Visit									
	Augment					Autograft				
	Week 12	Week 16	Week 24	Week 36	Week 52	Week 12	Week 16	Week 24	Week 36	Week 52
Missing	28	11	11	18	19	11	4	4	7	5
Improvement		47	61	44	26		24	33	28	12
No Change		145	160	165	184		84	86	90	105
Decline		39	22	28	25		16	13	10	12
Net Change		8	39	16	1		8	20	18	0

Table 34. SF-12 PCS Score Change by Visit demonstrates progression of SF-12 PCS score over time relative to previous visit.

Table 35: Foot Pain and Disability Index Score Change by Visit

	Change from Prior Visit											
	Augment						Autograft					
	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52
Missing	18	19	11	11	18	19	10	8	4	4	7	5
Improvement		63	62	52	28	19		41	33	28	10	11
No Change		135	148	178	196	207		74	83	99	113	111
Decline		21	25	13	13	9		6	11	5	5	7
Net Change		42	37	39	15	10		35	22	23	5	4

Table 35. Foot Pain and Disability Index Score Change by Visit demonstrates progression/improvement of foot pain and disability over time relative to previous visit. Note: Lower scores on FFI indicate improvement relative to higher scores.

Table 36: AOFAS Score Change by Visit

	Change from Prior Visit											
	Augment						Autograft					
	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52	Week 9	Week 12	Week 16	Week 24	Week 36	Week 52
Missing	22	20	9	12	18	19	10	7	3	4	6	5
Improvement		29	32	33	18	12		21	17	16	11	5
No Change		181	188	199	210	214		89	103	111	113	118
Decline		11	17	12	8	9		9	9	5	5	7
Net Change		18	15	21	10	3		12	8	11	6	-2

Table 36. AOFAS Score Change by Visit demonstrates progression of AOFAS score over time relative to previous visit. Note: Higher scores on AOFAS indicate improvement relative to lower scores.

Question 13

13) You have not provided information regarding the financial interests of the investigators as is required by 21 CFR part 54. Please provide the necessary information.

Response

Certification / disclosure of the financial interests of investigators was included in the clinical module submission. For reference, the documents (Forms 3454 and 3455 and supporting documentation) are re-attached herein as Exhibit 10.

Statistical

Question 14

14) *There is a discrepancy between the analysis datasets defined in the most recent statistical analysis plan (Vol 3, protocol v 4.1, p 44) and the analysis datasets listed in the clinical study report (Vol 2, P 51). FDA has several concerns with these differences. As the statistical significance of the trial's primary effectiveness endpoint is different depending on whether the mITT or ITT dataset is considered the primary analysis dataset, please submit additional details of the discussions with FDA leading to these changes. In addition, please clarify how many subjects were mis-randomized, as these subjects would be analyzed differently for the mIIT and ITT datasets.*

Response

Please refer to the response to question 7d for the requested information regarding the analysis datasets.

During the trial, there were two ITT subjects [redacted]) treated in the opposite treatment group. Subject [redacted] was randomized to Augment but received autograft. Subject [redacted] was randomized to autograft but received Augment.

Question 15

15) *In your exploration of the appropriateness of pooling data from different clinical centers, you conducted a Breslow-Day test of homogeneity for odds ratios for each of the three 24 week outcomes: CT fusion, radiographic fusion, and full complement clinical union. While the Breslow-Day test statistic is appropriate in this context, this does not appear to be consistent with the approach proposed in the final version of the statistical analysis plan (v 4.1), which stated that there would be an assessment of a treatment-by-center interaction term. Please submit a revised poolability assessment in line with the original proposal. In addition, as both the Breslow-Day test and a test of interaction lack power, please also submit a presentation of the number of subjects enrolled and treated at each center in each treatment arm, as well as the center-specific treatment estimates.*

Response

The three 24-week outcomes (CT fusion, radiographic fusion, and full complement clinical union) each presented a Breslow-Day test of homogeneity for odds ratio as shown below:

Table 37: Breslow-Day Test

Outcome	Breslow-Day test p-value
CT fusion (osseous bridging of at least 50%)	0.091
Radiographic fusion (at least 3 of 4 aspects fused)	0.558
Full complement clinical union (all attempted joints fused based on clinical determination)	0.577

The by-site success-rate subject accounting for these three outcomes that generates the summary data above are as follows, with site 00 representing the pooled site made up of subjects from sites with fewer than 10 subjects:

Table 38: Subject Success by Site

Site	CT fusion				Radiographic fusion				Full complement clinical union			
	Augment		Autograft		Augment		Autograft		Augment		Autograft	
	x/n	%	x/n	%	x/n	%	x/n	%	x/n	%	x/n	%
00	45/72	63	21/34	62	19/72	26	10/34	29	57/72	79	27/34	79
41	13/19	68	3/11	27	7/19	37	2/11	18	15/19	79	7/11	63
42	2/15	13	3/8	38	2/15	13	3/8	38	8/15	79	7/11	64
44	2/9	22	3/7	43	0/9	0	1/7	14	6/9	67	6/7	86
45	4/10	40	3/4	75	2/10	20	1/4	25	8/10	80	3/4	75
46	20/21	95	7/10	70	8/21	38	5/10	50	21/21	100	8/10	80
47	10/13	77	4/6	67	4/13	31	2/6	33	11/13	85	5/6	83
48	6/6	100	2/4	50	2/6	33	1/4	25	6/6	100	4/4	100
49	3/6	50	2/4	50	3/6	50	3/4	75	5/6	83	4/4	100
56	9/24	38	4/11	36	4/24	17	1/11	9	20/24	83	9/11	82
64	7/10	70	5/6	83	2/10	20	2/6	33	10/10	100	6/6	100
67	5/8	63	4/4	100	5/8	63	1/4	25	6/8	75	4/4	100
69	8/12	67	6/6	100	5/12	42	5/6	83	9/12	75	5/6	83
72	15/18	83	11/12	92	9/18	50	6/12	50	18/18	100	12/12	100
74	4/9	44	4/6	67	4/9	44	2/6	33	9/9	100	6/6	100
79	6/8	75	3/4	75	4/8	50	0/4	0	5/8	63	2/4	50
Total	159/260	61	85/137	62	80/260	31	45/137	33	214/260	82	114/137	83

Note that there are some site-treatment combinations (e.g., site 48, CT fusion for Augment, and site 79, radiographic fusion for autograft) for some measures with degenerate outcomes of 0% or 100%.

Simple modeling of the odds of success for each of the three types of fusion can be carried out using treatment, site, and treatment-by-site interaction in a logistic regression. Using the sites shown above, this model contains 1 degree of freedom for treatment group, 15 for site, and 15 for treatment-by-site interaction. It is this test for treatment-by-site interaction that measures consistency between treatments across the sites.

Employing SAS' logistic procedure to carry out this model on the CT fusion data results in two warnings in the SAS log ("There is possibly a quasi-complete separation of data points. The maximum likelihood estimate may not exist." and "The LOGISTIC procedure continues in spite of the above warning. Results shown are based on the last maximum likelihood iteration. Validity of the model fit is questionable.") and two similar warning in the formal SAS output. The same warnings are presented for the models for the other two endpoints.

At issue are the sites with 0% or 100% successes for a treatment; hence, the "quasi-complete separation of data points" mentioned in the log. BMTI will present two workarounds to this situation: pooling the affected sites into the pooled small-site group and pooling the affected sites into their own "affected site" group.

For purposes of simplicity and consistency, BMTI pools all the affected sites (44, 46, 48, 49, 64, 67, 69, 72, 74, and 79) across the three endpoints under consideration and presents the success rate table for the two further-pooling scenarios.

Scenario 1: Pooling affected sites with the small sites (site "00")

Table 39: Pooling of Affected Sites with Small Sites

Site	CT fusion				Radiographic fusion				Full complement clinical union			
	Augment		Autograft		Augment		Autograft		Augment		Autograft	
	x/n	%	x/n	%	x/n	%	x/n	%	x/n	%	x/n	%
00	121/179	68	68/97	70	61/179	34	36/97	37	152/179	85	84/97	87
41	13/19	68	3/11	27	7/19	37	2/11	18	15/19	79	7/11	63
42	2/15	13	3/8	38	2/15	13	3/8	38	8/15	79	7/11	64
45	4/10	40	3/4	75	2/10	20	1/4	25	8/10	80	3/4	75
47	10/13	77	4/6	67	4/13	31	2/6	33	11/13	85	5/6	83
56	9/24	38	4/11	36	4/24	17	1/11	9	20/24	83	9/11	82
Total	159/260	61	85/137	62	80/260	31	45/137	33	214/260	82	114/137	83

Scenario 2: Pooling affected sites as their own site (site "01")

Table 40: Pooling of Affected Sites as Single Site

Site	CT fusion				Radiographic fusion				Full complement clinical union			
	Augment		Autograft		Augment		Autograft		Augment		Autograft	
	x/n	%	x/n	%	x/n	%	x/n	%	x/n	%	x/n	%
00	45/72	63	21/34	62	19/72	26	10/34	29	57/72	79	27/34	79
01	76/107	71	47/63	75	42/107	39	26/63	41	95/107	89	57/63	90
41	13/19	68	3/11	27	7/19	37	2/11	18	15/19	79	7/11	63
42	2/15	13	3/8	38	2/15	13	3/8	38	8/15	79	7/11	64
45	4/10	40	3/4	75	2/10	20	1/4	25	8/10	80	3/4	75
47	10/13	77	4/6	67	4/13	31	2/6	33	11/13	85	5/6	83
56	9/24	38	4/11	36	4/24	17	1/11	9	20/24	83	9/11	82
Total	159/260	61	85/137	62	80/260	31	45/137	33	214/260	82	114/137	83

Breslow-Day P-values for the pooling scenarios

Table 41: Breslow-Day Results by Strategy

Outcome	Breslow-Day test p-value		
	Original pooling	Scenario 1	Scenario 2
CT fusion (osseous bridging of at least 50%)	0.091	0.139	0.209
Radiographic fusion (at least 3 of 4 aspects fused)	0.558	0.632	0.754
Full complement clinical union (all attempted joints fused based on clinical determination)	0.577	0.845	0.917

Both scenarios for pooling the affected sites produce Breslow-Day p-values that are consistent with the original pooling scheme although they are, for each outcome, less significant for heterogeneity of the odds ratio than the original p-values.

Running the logistic regression models on each of the two scenarios allows estimates of the odds ratio for treatment (odds of success on Augment divided by odds of success on autograft) within each site. P-values for the three effects (treatment, (pooled) site, and treatment-by-site interaction) in the model for the two pooling scenarios are shown in the next table.

Table 42 Type III Wald Chi-square p-values

	CT fusion		Radiographic fusion		Full complement clinical union	
	Scenario 1	Scenario 2	Scenario 1	Scenario 2	Scenario 1	Scenario 2
Treatment	.774	.768	.925	.895	.924	.973
Site	.001	.001	.215	.082	.163	.063
Treatment-by-site interaction	.172	.252	.659	.776	.852	.921

As with the Breslow-Day examination of the treatment-by-site effect, none of the p-values for treatment-by-site interaction is significant.

Site specific estimates of the odds ratio within each site for the two pooling scenarios are shown in the following table.

Table 43 Site specific estimates of the odds ratio within each site

	CT fusion				Radiographic fusion				Full complement clinical union			
	Scenario 1		Scenario 2		Scenario 1		Scenario 2		Scenario 1		Scenario 2	
Site	Est	CI	Est	CI	Est	CI	Est	CI	Est	CI	Est	CI
00	0.89	0.42,1.91	1.03	0.45,2.39	0.88	0.52,1.47	0.86	0.35,2.13	0.87	0.43,1.78	0.99	0.36,2.70
01			0.83	0.41,1.69			0.92	0.49,1.73			0.83	0.30,2.34
41	5.78	1.12,29.8	5.78	1.12,29.8	2.63	0.44,15.8	2.63	0.44,15.8	2.14	0.41,11.2	2.14	0.41,11.2
42	0.26	0.03,2.02	0.26	0.03,2.02	0.26	0.03,2.02	0.26	0.03,2.02	0.38	0.06,2.53	0.38	0.06,2.53
45	0.22	0.02,2.97	0.22	0.02,2.97	0.75	0.05,11.6	0.75	0.05,11.6	1.33	0.09,20.7	1.33	0.09,20.7
47	1.67	0.20,14.1	1.67	0.20,14.1	0.89	0.11,7.02	0.89	0.11,7.02	1.10	0.08,15.2	1.10	0.08,15.2
56	1.05	0.24,4.62	1.05	0.24,4.62	2.00	0.20,20.3	2.00	0.20,20.3	1.11	0.17,7.22	1.11	0.17,7.22

For each of the endpoints under consideration, at all sites or site groups, the confidence interval for the odds ratio for differences in treatment effect bounds the value of 1.000, providing support for homogeneity of the odds ratio across sites.

While the overall rates may be different across sites, poolability rests on the odds *ratios* for treatment within each site, not on the specific *rates* within each site. Poolability across sites is granted when the *odds ratio for treatment* is not dependent upon the particular level of investigative site.

Question 16

16) There appears to be a discrepancy in the clinical study report regarding the issue of blinding. On page 41 of the clinical study report, it says that treating subjects were blinded but control subjects would have become aware of the treatment received after surgery due to the additional surgical harvesting procedure. However, on page 36 it states that subjects were initially blinded to treatment allocation, but were un-masked prior to surgery. Please clarify whether subjects were blinded prior to receiving surgery; or if not, at what point they were un-blinded. This is a particularly relevant issue given that there were some pre-operative withdrawals. Therefore, please additionally clarify the treatment randomization and timing of the eight subjects classified as subject/investigator requests for early withdrawal.

Response

Clarification: Patients were not informed of their treatment assignments prior to the surgery. Treatment status would not be evident to study subjects until after the surgery, at which time the treatment administered (e.g. autograft or Augment) would become evident to patients. Following surgery, patients who received autograft were asked about the bone graft harvest site location.

The eight patients (5 Augment and 3 autologous bone graft) classified as subject/ investigator requests for early withdrawal are listed below. Please note that all of the below cases were withdrawn after treatment and are included in both the ITT and mITT populations. All were analyzed as failures for any evaluations missing subsequent to subject withdrawal.

Table 44: Summary of Subject/ Investigator Requests for Early Withdrawal

Patient #	Assignment	Date of Surgery	Date of withdrawal	Reason
[redacted]	Augment Bone Graft	26 Jul 2007	26 Sep 2007	Surgery required on both knees due to MRSA infection in subject with prior MRSA history
[redacted]	Autologous Bone Graft	26 Nov 2007	11 Dec 2007	Subject requested withdrawal due to number of study visits

[redacted]	Autologous Bone Graft	07 Apr 2008	16 Apr 2008	Subject requested withdrawal due to requirement for blood draws
[redacted]	Augment Bone Graft	03 Nov 2008	23 Feb 2009	Subject requested withdrawal, no reason given
[redacted]	Autologous Bone Graft	04 Feb 2008	16 Oct 2008	Subject requested withdrawal, no reason given
[redacted]	Augment Bone Graft	16 May 2008	10 Nov 2008	Subject requested withdrawal due to subject moving out of state
[redacted]	Augment Bone Graft	11 Dec 2008	29 Jun 2009	Subject withdrew consent, no reason given
[redacted]	Augment Bone Graft	13 Nov 2008	23 Jul 2009	Patient had surgery on adjacent joint, original surgery was a success and resulted in fusion

Question 17

17) In the presentation of the 24 subjects who did not complete the trial (Table 1.1 in file "Safety tables 05MAY2010" of A004), the information is not presented by treatment assignment. In addition, this data is based on the increased follow-up time, which was not submitted electronically. As a result, FDA is unable to replicate this table stratified by treatment assignment. Please submit a revised version of this table, stratified by treatment assignment.

Response

BMTI is providing the requested data and summaries below. See Table 45 for a summary of early withdrawals by treatment assignment and Table 46 for a list of treated subjects who were early withdrawals. Please note that all 24 subjects were included in both the ITT and mITT populations and were analyzed as failures for any evaluations missing subsequent to subject withdrawal.

Table 45: Subject Early Withdrawals by Treatment Assignment

Discontinuation Category	N	Augment	Autograft
Subject or Investigator request	8	5	3
Inability to return for follow-up	1	0	1
Non-compliance with protocol	2	2	0
Lost to follow-up	5	5	0
Death	1	1	0
Revision Surgery Required	7	6	1
TOTAL	24	19	5

Table 46: List of Treated Subject Early Withdrawals

Patient #	Assignment	Date of Surgery	Date of withdrawal	Reason
[redacted]	Augment Bone Graft	26 Jul 2007	26 Sep 2007	Subject or investigator requested discontinuation from the study
	Autologous Bone Graft	26 Nov 2007	11 Dec 2007	Subject or investigator requested discontinuation from the study
	Augment Bone Graft	14 Oct 2008	12 Mar 2009	Revision surgery required
	Augment Bone Graft	02 Dec 2008	09 Jun 2009	Subject lost to follow-up
	Augment Bone Graft	17 Jul 2007	27 Jul 2007	Subject expired during the study
	Augment Bone Graft	04 Oct 2007	03 Jul 2008	Subject non-compliant with protocol instructions
	Autologous Bone Graft	17 Dec 2007	13 Jun 2008	Subject unable to return for follow-up visits
	Augment Bone Graft	29 Feb 2008	21 Nov 2008	Subject lost to follow-up
	Augment Bone Graft	19 Sep 2008	16 Dec 2008	Subject non-compliant with protocol instructions
	Autologous Bone Graft	07 Apr 2008	16 Apr 2008	Subject or investigator requested discontinuation from the study
	Augment Bone Graft	03 Nov 2008	23 Feb 2009	Subject or investigator requested discontinuation from the study
	Autologous Bone Graft	04 Feb 2008	16 Oct 2008	Subject or investigator requested discontinuation from the study
	Augment Bone Graft	26 Dec 2007	08 Apr 2008	Revision surgery required
	Augment Bone Graft	09 Oct 2008	08 Jun 2009	Revision surgery required
	Autologous Bone Graft	21 Aug 2007	24 Jan 2008	Revision surgery required
	Augment Bone Graft	22 Jan 2008	07 Jul 2008	Revision surgery required
	Augment Bone Graft	16 May 2008	10 Nov 2008	Subject or investigator requested discontinuation from the study

Patient #	Assignment	Date of Surgery	Date of withdrawal	Reason
[redacted]	Augment Bone Graft	28 Apr 2008	12 Jun 2008	Subject lost to follow-up
	Augment Bone Graft	09 Oct 2008	17 Jun 2009	Revision surgery required
	Augment Bone Graft	08 Sep 2008	05 Mar 2009	Subject lost to follow-up
	Augment Bone Graft	06 Mar 2008	07 May 2008	Subject lost to follow-up
	Augment Bone Graft	11 Dec 2008	29 Jun 2009	Subject or investigator requested discontinuation from the study
	Augment Bone Graft	31 Dec 2008	03 Sep 2009	Revision surgery required
	Augment Bone Graft	13 Nov 2008	23 Jul 2009	Subject or investigator requested discontinuation from the study

Question 18

18) *You have conducted the primary analysis based on a full complement as well as an all-joints analysis. However, the all-joints analysis appears to treat all of the treated joints as independent. Please note that FDA believes such an analysis is statistically inappropriate, as the assumption of independence in correctly ignores the within-subject correlation induced by multiple joints being observed for a given subject. As a result, the standard error used in the hypothesis test is incorrect, as is the resulting-value. If you would like these all-joints analyses to be formally evaluated (e.g. if you plan to use them for marketing purposes), please submit a revised analysis which accounts for this within-subject correlation.*

Response

As requested by FDA, BMTI has provided below a revised analysis with modeling addressing within-subject correlation.

The all-joints CT fusion data at week 24 were examined taking into account the dependence present within observations taken within the same subject.

The 397 subjects in the MITT population represent 597 joints. Each of these joints was evaluated via CT scan, with a cutoff of 50% osseous bridging used to make a determination of fusion for each joint.

Four models were used to examine the joint-level CT fusion. A simple model only accounting for treatment group and correlation was fit as a naive first pass. A larger model employing effects for treatment, (pooled) investigative site, joint, risk factor status, age (age at least 65 vs. age less

than 65), gender, smoker category (never smoked, quit more than 5 years ago, quit less than 5 years ago, and current smoker), and interactions (treatment-by-site, treatment-by-joint, treatment-by-risk factor status, treatment-by-age, treatment-by-gender, treatment-by-smoker category, age-by-gender, and treatment-by-age-by-gender) was then fit in an attempt to examine effects known (or conjectured) to impact the chance of fusion. A smaller model was then created employing the significant effects ($p<0.10$) found in the larger model. Lastly, a model using prespecified predictors (treatment, site, age, gender, smoking, and interactions) was fit.

Models were fit using SAS' GENMOD procedure. The odds of fusion were estimated and contrasts based on GEE estimates were constructed to examine interesting effects. Results are presented as estimates of odds ratios and corresponding 90% confidence limits. Wald Type 3 GEE statistics, along with the estimated correlation matrix within a subject, are presented as well.

Non-inferiority may be investigated by examining the lower endpoint of the confidence interval. Under a null hypothesis that the fusion rates in the two treatment groups are 75% and 85%, the corresponding odds of fusion can be computed as (.75*.25)/(.85*.15) = 0.53. As such, a rational threshold for a determination of non-inferiority is in the neighborhood of 0.50; non-inferiority is supported by a lower confidence limit greater than 0.50.

Model 1

The first model employed only an intercept and a term for treatment group.

The estimated correlation matrix within a subject is shown below.

Table 47: Model 1 Correlation Matrix of Joint Within Subject

	Ankle	Subtalar	Calcaneocuboid	Talonavicular
Ankle	1.00	0.00	0.00	0.00
Subtalar	0.00	1.00	0.50	0.60
Calcaneocuboid	0.00	0.50	1.00	0.50
Talonavicular	0.00	0.66	0.50	1.00

Recall that a subject could have any combination of the three hindfoot joints (subtalar, calcaneocuboid, talonavicular) or the ankle joint fused. This results in the block-diagonal structure seen in the correlation matrix.

The estimate of the odds of fusion on Augment Bone Graft compared to autologous bone graft was 1.02 with 90% confidence limits of (0.72, 1.45), the corresponding chi-square p-value for a test of unequal odds is 0.92, showing that the treatments are not different.

The lower confidence limit is 0.72, providing support for non-inferiority.

Model 2

The second model employed effects for treatment, (pooled) investigative site, joint, risk factor status, age (age at least 65 vs age less than 65), gender, smoker category (never smoked, quit

more than 5 years ago, quit less than 5 years ago, and current smoker), and interactions (treatment-by-site, treatment-by-joint, treatment-by-risk factor status, treatment-by-age, treatment-by-gender, treatment-by-smoker category, age-by-gender, and treatment-by-age-by-gender).

Investigative sites were pooled as in the response to question 15, with the small sites together and those sites with extreme CT outcomes into a group of 'affected sites'.

The joint effect took one of four possible values, as there were four joints available for treatment, subject to the caveat, noted above, that only the ankle joint or only hindfoot joints existed within the same subject.

Risk factor status was dichotomized as either no risk factors or at least one risk factor, consistent with the randomization strata.

Smoker category produced an ordinal split of subjects, progressing from never smoked (level 0) to current smoker (level 3).

Appropriate interaction effects serve to investigate the poolability of the effects in the interaction.

The estimated correlation matrix within a subject is shown below.

Table 48: Model 2 Correlation Matrix of Joint Within Subject

	Ankle	Subtalar	Calcaneocuboid	Talonavicular
Ankle	1.00	0.00	0.00	0.00
Subtalar	0.00	1.00	0.27	0.46
Calcaneocuboid	0.00	0.27	1.00	0.33
Talonavicular	0.00	0.46	0.33	1.00

The correlation matrix for the joints shows smaller correlations than in the naive model 1.

The Wald Type 3 GEE analysis of variance table is shown below.

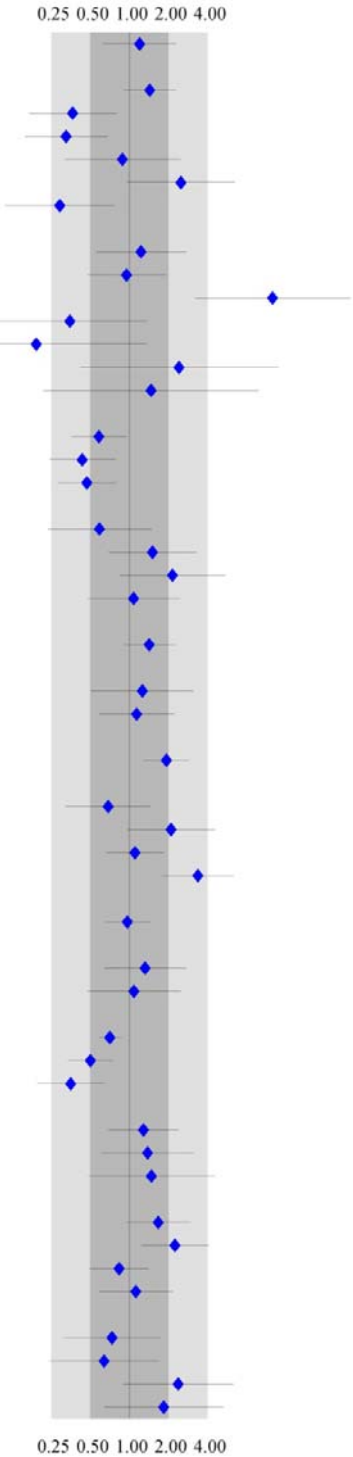
Table 49: Model 2 Wald Type 3 GEE Analysis of Variance

Source	Degrees of freedom	Chi-square	P
Treatment	1	0.21	0.65
Pooled site	6	25.71	0.00
Treatment-by-pooled site	6	14.08	0.03
Joint	3	6.85	0.08
Risk factors	1	1.61	0.20
Age	1	7.12	0.01
Gender	1	0.02	0.90
Smoker category	1	8.05	0.00
Treatment-by-joint	3	4.36	0.23
Treatment-by-risk factors	1	0.03	0.86
Treatment-by-age	1	5.06	0.02
Treatment-by-gender	1	0.15	0.70
Treatment-by-smoker category	1	0.08	0.77
Age-by-gender	1	0.35	0.55
Treatment-by-age-by-gender	1	0.01	0.91

Estimates of odds ratios and corresponding confidence intervals are shown in the following plot. Points of note can be harvested from the table and the plot.

Figure 5: Model 2 odds ratios and corresponding confidence intervals

Comparison	Odds ratio and 90% CI
Augment over autograft - overall	1.20 (0.63,2.30)
Offending sites over small sites	1.44 (0.90,2.29)
Site 41 over small sites	0.37 (0.17,0.79)
Site 42 over small sites	0.33 (0.16,0.68)
Site 45 over small sites	0.89 (0.32,2.47)
Site 47 over small sites	2.50 (0.97,6.48)
Site 56 over small sites	0.29 (0.11,0.77)
Augment over autograft - small sites	1.23 (0.56,2.72)
Augment over autograft - offending sites	0.95 (0.47,1.92)
Augment over autograft - Site 41	12.70 (3.21,50.27)
Augment over autograft - Site 42	0.35 (0.09,1.37)
Augment over autograft - Site 45	0.19 (0.03,1.34)
Augment over autograft - Site 47	2.42 (0.42,14.02)
Augment over autograft - Site 56	1.47 (0.22,9.87)
Subtalars over ankles	0.58 (0.36,0.95)
Calcaneocuboids over ankles	0.43 (0.24,0.78)
Talonaviculars over ankles	0.47 (0.28,0.79)
Augment over autograft - ankles	0.59 (0.24,1.48)
Augment over autograft - subtalars	1.51 (0.69,3.29)
Augment over autograft - calcaneocuboids	2.16 (0.84,5.51)
Augment over autograft - talonaviculars	1.08 (0.48,2.45)
No risk factors over risk factors	1.42 (0.90,2.25)
Augment over autograft - no risk factors	1.26 (0.51,3.12)
Augment over autograft - risk factors	1.14 (0.59,2.22)
Young (< 65 y.o.) over older (>= 65 y.o.)	1.94 (1.29,2.91)
Augment over autograft - young	0.69 (0.32,1.46)
Augment over autograft - older	2.09 (0.96,4.57)
Young over older - Augment	1.11 (0.67,1.84)
Young over older - autograft	3.38 (1.79,6.40)
Women over men	0.97 (0.64,1.47)
Augment over autograft - women	1.32 (0.64,2.73)
Augment over autograft - men	1.09 (0.48,2.47)
One level increase in smoking category	0.71 (0.58,0.86)
Two level increase in smoking category	0.50 (0.34,0.75)
Three level increase in smoking category	0.35 (0.19,0.65)
Augment over autograft - 1 smoke level inc.	1.29 (0.69,2.39)
Augment over autograft - 2 smoke level inc.	1.38 (0.61,3.13)
Augment over autograft - 3 smoke level inc.	1.48 (0.48,4.58)
Young women over older women	1.67 (0.95,2.94)
Young men over older men	2.25 (1.24,4.07)
Young women over young men	0.83 (0.50,1.40)
Older women over older men	1.12 (0.58,2.16)
Augment over autograft - young women	0.74 (0.31,1.73)
Augment over autograft - young men	0.64 (0.24,1.69)
Augment over autograft - older women	2.38 (0.90,6.34)
Augment over autograft - older men	1.84 (0.64,5.29)



While the overall main effect for treatment is not significant for a difference and could be used to conclude non-inferiority, interaction between treatment and other factors deserves closer inspection.

Sites 41, 42, and 56 show low overall fusion odds relative to the small sites; however, all three of these sites do not show significant interaction with treatment except site 41, which shows benefit with Augment. Thus, while different sites may have differences in odds of fusion, there is no appreciable worrisome interaction between treatments and site (even though the interaction test is significant), as BMTI cannot find sites where Augment performs significantly worse than autologous bone graft. The significant interaction shown in the table is driven by only one site with improved Augment odds.

All three hindfoot joints show lower fusion odds than ankles; yet, there is no interaction between treatment and joint. Thus, while the fusion odds of the joints may differ, the odds ratios for treatment within each of these groups are similar, granting an argument for poolability across joints, as poolability is a question of interaction between treatment and joint, not a question of fusion rate differences across joints.

Risk factors, in light of the other terms in the model, do not appear to appreciably impact the odds of fusion or the odds ratio between Augment and autograft within either risk factor group.

Age greatly impacts the odds of fusion, as the odds of fusion in those under 65 years old is nearly twice the odds in those 65 and older. Furthermore, this difference is impacted by treatment. While the odds for treatment for both young and old are not significantly different, the odds for young people compare to older people are significantly different for subjects treated with autograft, as evidenced by the odds of 3.38 (1.79,6.40). Thus, the interaction between treatment and age group is driven by the drastic difference in how young and old respond to treatment with autograft. This odds ratio of 3.38 is one of the largest found on the table.

Gender as a main effect, or simply interacted with treatment, demonstrates essentially no effect.

The odds of fusion when moving up one smoker category drop to 0.71, with current smokers having odds of 0.35 relative to non-smokers. Interaction between treatment and smoking (three levels of smoking category) is not significant.

Age and gender are not significantly interactive, and treatment does not interact with this combination.

In general, Augment Bone Graft and autologous bone graft appear to be essentially indistinguishable treatments, with the exception that older autologous bone graft patients are at a noticeable disadvantage. While some joints and sites have varying odds of fusion, these do not interact appreciably with treatment. Young subjects have greater odds of fusing, as do those who do not smoke.

Model 3

Using the terms in model 2 that were significant, we can generate a smaller model, one with fewer degrees of freedom. This model will include terms for treatment, site, treatment-by-site interaction, joint, age, smoker category, and treatment-by-age interaction.

The estimated correlation matrix and ANOVA table are shown below.

Table 50: Model 3 Correlation Matrix of Joint Within Subject

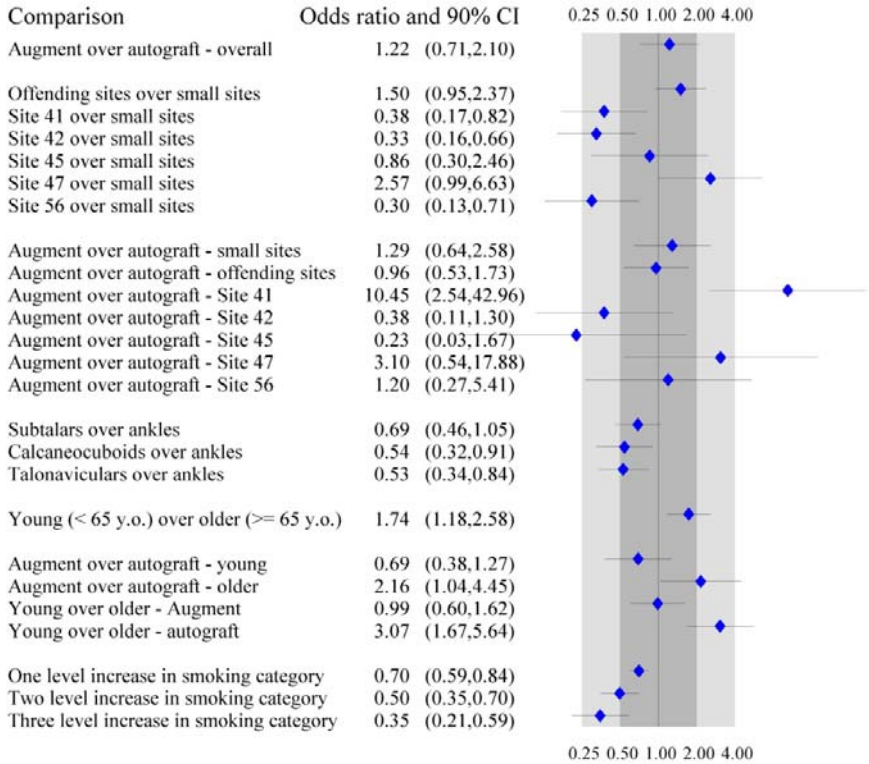
	Ankle	Subtalar	Calcaneocuboid	Talonavicular
Ankle	1.00	0.00	0.00	0.00
Subtalar	0.00	1.00	0.32	0.48
Calcaneocuboid	0.00	0.32	1.00	0.36
Talonavicular	0.00	0.48	0.36	1.00

Table 51: Model 3 Wald Type 3 GEE Analysis of Variance

Source	Degrees of freedom	Chi-square	P-value
Treatment	1	0.38	0.64
Pooled site	6	29.45	0.00
Treatment-by-pooled site	6	11.97	0.06
Joint	3	6.15	0.10
Age	1	5.39	0.02
Smoker category	1	11.15	0.00
Treatment-by-age	1	5.73	0.02

A plot of the effects shows results consistent with the fuller model.

Figure 6: Model 3 odds ratios and corresponding confidence intervals



Model 4

In an effort to avoid issues of overfitting and model selection bias, a small prespecified list of predictors was included in a fourth model. This model included terms for treatment, site, age, gender, smoking, and some interactions. This model contains 13 degrees of freedom and is shown below.

The correlation table is consistent with those found in the other models:

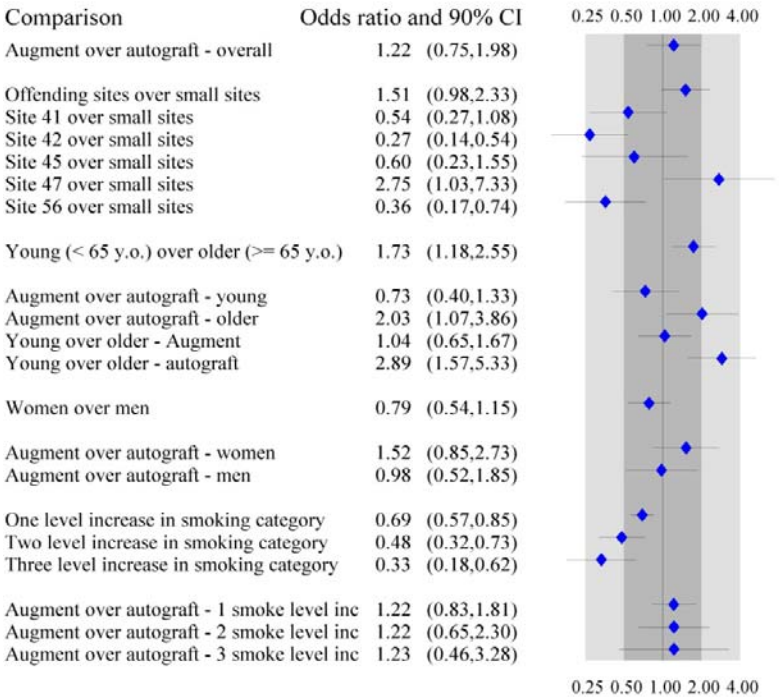
Table 52: Model 3 Correlation Matrix of Joint Within Subject

	Ankle	Subtalar	Calcaneocuboid	Talonavicular
Ankle	1.00	0.00	0.00	0.00
Subtalar	0.00	1.00	0.36	0.52
Calcaneocuboid	0.00	0.36	1.00	0.44
Talonavicular	0.00	0.52	0.44	1.00

Table 53: Model 3 Wald Type 3 GEE Analysis of Variance

Source	Degrees of freedom	Chi-square	P-value
Treatment	1	0.46	0.50
Pooled site	6	32.63	0.00
Age	1	5.50	0.02
Gender	1	1.10	0.29
Smoking category	1	8.58	0.00
Treatment-by-age	1	4.73	0.03
Treatment-by-gender	1	0.92	0.34
Treatment-by-smoking	1	0.00	0.99

Figure 7: Model 4 odds ratios and corresponding confidence intervals



Again, significantly lower odds of fusion are seen for sites 42 and 56, compared to the small sites.

Younger subjects have higher odds of fusion and that effect is interacted with treatment, with autograft producing a vast disparity between age groups while Augment shows similar odds for young subjects relative to older subjects. Smoking reduces the odds of most things health-related, in this case lowering the odds of fusion.

The results of these GEE models demonstrate the non-inferiority of Augment relative to autograft while taking into account relevant sources of variation between the subjects in the trial and accounting for the correlation within the possible multiple joints within a subject.

Question 19

19) You have not provided any analyses of the time-to-event data specified in the statistical analysis plan and protocol as clinical outcomes of interest. FDA believes that these analyses will help to provide a fuller picture of your product; therefore, please submit such analyses.

Response

Time to event analyses were not submitted with the 24 week clinical study report as not all subjects had completed evaluations to provide time-to –event data. As requested by FDA, these data are reported in the final clinical study report submitted with this response. Clinical Study Report BMTI-2006-01, Version 2.0 dated 17 November 2010 is included in Exhibit 6.)

Question 20

20) You have provided a breakdown of subjects excluded from the analysis by treatment group and exclusion cause (In Vol 2, p 65-66). However, it is unclear why some of these occurrences would require these subjects to have been excluded from the analysis. Specifically, the subject randomized to Augment who received an allograft would probably be better classified as a bone graft subject in an as-treated dataset or as an Augment failure in an intent-to-treat dataset. Similarly, in the absence of further justification for exclusion, the following subjects would be more appropriately included in the analysis as therapeutic failures: the Augment subject with infection at the fusion site, the Augment subject who required a second surgery, and the bone graft subject who received too much graft material. Please provide additional justification for why these subjects were excluded from the analysis.

Response

BMTI is providing information regarding subjects excluded from the mITT population as previously discussed. Specific instances of exclusion noted by FDA are discussed below:

- Subject [redacted] Subject surgery required allograft. The study does not define or anticipate use of allograft. While allograft is a logical bone graft material for hindfoot and ankle fusions, such application would confound any assessment of success or failure; therefore BMTI determined that it was inappropriate to include the subject in the analysis as part of the mITT population.
- Subject [redacted]: Presented at surgery with a previously unknown infection at the proposed fusion site was not a valid candidate for fusion surgery under any treatment assignment from a subject safety or efficacy standpoint due to the active infectious process. Lack of any treatment of the joint planned for fusion should exclude the subject from analysis as part of the mITT population.
- Subject [redacted] Required additional surgical procedures beyond those specified by the protocol cannot be evaluated effectively due to the confounding effect of exclusionary procedures, and cannot be compared accurately to the prospectively-defined patient population. The inability to distinguish the effect of the treatment from that of the exclusionary procedure(s) should exclude the subject from analysis as part of the mITT population.

- Subject [redacted] Required a volume of bone graft in excess of that specified by the protocol cannot be evaluated effectively due to the confounding effect of exclusionary graft volume, and cannot be compared accurately to the prospectively-defined patient population. The inability to distinguish the effect of the treatment from that of the volume of graft material should exclude the subject from analysis as part of the mITT population.

Please refer to Table 15 as presented previously for a complete summary of ITT subjects excluded from the mITT population.

Epidemiological Issues

Question 21

21) *You report the results of effectiveness mainly based on the analyses of data from an mITT population. The mITT was not defined in the FDA approved protocol. Since the patient grouping of the mITT population was not based on the original randomization, the 2 treatment groups in the mITT population might no longer be comparable. Please present and analyze the demographic and clinical characteristics at baseline for the 2 treatment groups of the mITT population.*

Response

As requested, BMTI has provided analysis of the baseline demographic and clinical characteristics as presented in Table 54.

Table 54: Patient Demographics for mITT Population

	All Patients (N=397)	Augment (N=260)	Autograft (N=137)	P - values
Gender				0.0734
Male	204	125 (48.08)	79 (57.66)	
Female	193	135 (51.92)	58 (42.34)	
Age				0.3321
N		260	137	
Mean		55.83	57.28	
Standard deviation		14.463	13.488	
Median		57.9	58.3	
Min-Max		20.2-86.2	20.3-82.2	
Race				
White		235(90.38)	126(91.97)	0.7142
Black or African American		19(7.31)	6(4.38)	0.2859

	All Patients (N=397)	Augment (N=260)	Autograft (N=137)	P - values
Asian		2(0.77)	0	0.5469
American Indian or Alaska Native		0	0	
Native Hawaiian or Pacific Islander		0	0	
Other		4(1.54)	5(3.65)	0.2853
Missing				
Ethnicity				0.1511
Hispanic or Latino	20	10(3.88)	10(7.30)	
Not Hispanic or Latino	377	250(96.15)	127(92.70)	
Missing				
Occupational Status				
Work Status				0.3738
Employed Full Time	158	98(37.69)	60(43.80)	
Employed Part Time	22	13(5.00)	9(6.57)	
Semi-Retired	5	3(1.15)	2(1.46)	
Retired	137	89(34.23)	48(35.04)	
Unemployed	26	19(7.31)	7(5.11)	
Disabled	49	38(14.62)	11(8.03)	
Missing				
Student Status				0.5293
Full Time	7	6(2.31)	1(0.73)	
Part Time	4	2(0.77)	2(1.46)	
NA	386	252(96.92)	134(97.81)	
Missing				
Living environment				0.9206

	All Patients (N=397)	Augment (N=260)	Autograft (N=137)	P - values
Home(alone)	54	36(13.85)	18(13.14)	
Home(with spouse, family, friend, aide)	342	223(85.77)	119(86.86)	
Being cared for in a facility	1	1(0.38)	0	
Other				
Missing				
Height				0.4581
N		259	137	
Mean		170.42	171.28	
Standard Deviation		10.625	11.475	
Median		170.18	172	
Min-Max		144.78-208.28	134.62-203.2	
Weight				0.1771
N		259	137	
Mean		89.292	92.101	
Standard Deviation		19.386	20.197	
Median		88.0	90.72	
Min-Max		48.99-149.69	47.63-151.5	
BMI(kg/m^2)				0.2463
N		260	137	
Mean		30.615	31.321	
Standard Deviation		5.6669	5.9284	
Median		30	31	
Min-Max		19-45	20-44	

	All Patients (N=397)	Augment (N=260)	Autograft (N=137)	P - values
Smoking History (no year limit)				0.1280
Never	200	133(51.15)	67(48.91)	
Yes, currently	50	38(14.62)	12(8.76)	
Stopped	147	89(34.23)	58(42.34)	
Missing				
No. cigarettes/day				0.0486
N		37	11	
Mean		9.1676	14.818	
Standard deviation		8.1401	8.0476	
Median		57.9	20	
Min-Max		0-25	3-25	
No. cigars/day				0.2526
N		36	11	
Mean		0.4639	0	
Standard deviation		1.3174	0	
Median		0	0	
Min-Max		0-5	0	
No. pipes/day				-
N		35	11	
Mean		0	0	
Standard deviation		0	0	
Median		0	0	
Min-Max		0	0	
Quit				

	All Patients (N=397)	Augment (N=260)	Autograft (N=137)	P - values
No. years ago (approximately)				0.0655
N		80	52	
Mean		17.8	22.212	
Standard deviation		12.816	14.091	
Median		16.5	25.5	
Min-Max		0-48	0-54	
Affected Foot/Ankle				0.2362
Right	201	129(49.62)	72(52.55)	
Left	178	122(46.92)	56(40.88)	
Bilateral	18	9(3.46)	9(6.57)	
Missing				
Foot/Ankle to be treated				0.5973
Right	209	134(51.54)	75(54.74)	
Left	188	126(48.46)	62(45.26)	
Missing				
Age of the Injury/Deformed at Baseline(weeks)				0.1666
N		164	85	
Mean		242.28	321.54	
Standard deviation		96	145.7	
Median		408.58	462	
Min-Max		1.1-2591	3.1-2116.4	
Description of the injury/Deformity				0.2007
Primary Arthritis	143	89(34.23)	54(39.42)	

	All Patients (N=397)	Augment (N=260)	Autograft (N=137)	P - values
Rheumatoid Arthritis	25	20(7.69)	5(3.65)	
Post-traumatic injury/deformity	192	130(50.00)	62(45.26)	
Ankylosing spondylitis				
Other	37	21(8.08)	16(11.68)	
Missing				
Risk Factors				
Smoking history within last five years		64(24.62)	32(23.36)	0.8065
Obesity(BMI>30 kg/m^2)		117(45.00)	74(54.01)	0.0920
Previous revision surgery		60(23.08)	32(23.36)	1.00
Diabetes history (type 1 or 2)		26(59.09)	18(13.14)	0.4067

Review of the demographic data for the mITT population and the p-values relative to the ITT dataset reveal no differences between groups.

Question 22

22) *You report the differences of patient demographic and clinical characteristics and conducted subgroup analyses. The main analyses on the primary and secondary endpoints, however, were based on simple and non-covariate-adjusted hypothesis tests without adjustment for potential confounding effects. Without a control for possibly existing confounding effects, the results can be biased. Please provide in depth analyses for all the main results, evaluating and adjusting for the confounding effects of all covariates included in Table 8 in the Clinical Study Report.*

Response

BMTI modeled the primary results (primary endpoint variable: week 24 CT fusion based on 50% osseous bridging). The data consist of 397 subjects in the mITT population who were credited with 244 successful fusions and 153 failed fusions. These 397 subjects contained 260 Augment Bone Graft subjects and 137 autologous bone graft ("autograft") subjects, with 159 successes in the Augment group (61.15%) and 85 successes in the autograft group (62.04%).

Four logistic regression models were used to examine patient-level CT fusion. A simple model, only employing treatment group as a predictor, was fit as a naive first pass. As requested, a larger model employing the covariates listed in Table 8 of the clinical study report was also fit. A third model, one constructed by simply retaining those factors with Wald Type III p-values significant at the 0.10 level, was then constructed.

Table 8 in the clinical study report included over a dozen factors for consideration in any modeling exercise. Coupled with treatment and interactions with treatment and other factors, such an unrestrained model can easily fall prey to possessing more degrees of freedom than can be adequately supported by the number of events in the data set. As there were a total of 244 successes and 153 failures in the data set, the limiting sample size is the minimum of these two, and a rule of thumb of employing no more than 1 degree of freedom for every 10-20 limiting events caps the number of degrees of freedom in the model to be no higher than approximately 15.

Taking a more scientific-based path to model development, we also fit a fourth model with 14 degrees of freedom, employing domain knowledge surrounding patients typically undergoing foot and ankle arthrodesis.

Models were fit using SAS' GENMOD procedure. The odds of fusion were estimated and contrasts were constructed to examine interesting effects. Results are presented as estimates of odds ratios and corresponding 90% confidence limits. Wald Type 3 statistics are presented as well.

Non-inferiority may be investigated by examining the lower endpoint of the confidence interval. Under a null hypothesis that the fusion rates in the two treatment groups are 75% and 85%, the corresponding odds of fusion can be computed as (.75*.25)/(.85*.15) = 0.53. As such, a rational threshold for a determination of non-inferiority is in the neighborhood of 0.50; non-inferiority is supported by a lower confidence limit greater than 0.50.

Model 1

The first model employed only an intercept and a term for treatment group.

The estimate of the odds of fusion on Augment Bone Graft compared to autologous bone graft was 0.96 with 90% confidence limits of (0.67, 1.38), the corresponding chi-square p-value for a test of unequal odds is 0.86, showing that the treatments are not different.

The lower confidence limit is 0.67, providing support for non-inferiority.

Model 2

Table 8 in the clinical study report exposed subgroup splits based on a number of factors. Based on these subgroup splits, the following main effect factors were included in the logistic regression in model 2: treatment (Augment or autograft), (pooled) investigative site, joint(s) treated, risk factor status, age, gender, smoking, obesity, previous surgery at the fusion site, history of diabetes, concurrent osteotomy procedure, concurrent soft tissue procedure. In addition to the main effects, interactions between treatment and these main effects were also included.

Investigative sites were pooled as in the response to question 15, with the small sites together and those sites with extreme CT outcomes into a group of 'affected sites'.

Single degree-of-freedom dummy variables were set up to indicate whether or not a certain joint was under consideration for each patient. Thus, four binary variables represented the presence of the four joints under consideration in the study. For example, if a patient had an ankle fusion procedure, then the dummy variable for ankle was set to 1, while those for subtalar, calcaneocuboid, and talonavicular were all set to 0. If a patient had a triple hindfoot arthrodesis, then the ankle variable was set to 0 while the other three were set to 1. If a patient had a subtalar and calcaneocuboid, then the ankle and talonavicular variables were set to 0 while the subtalar and calcaneocuboid variables were set to 1. Therefore, each of these four joint variables shows the presence (1) or absence (0) of that particular joint under consideration for that patient.

Risk factor status was coded in binary fashion, with 0 being no risk factors and 1 being at least one risk factor.

Age was also coded in binary form with a split at 65 years old, as in Table 8.

Obesity was coded as binary with the split at BMI of 30.

Smoking was coded as an ordinal outcome with four levels: never smoked, quit more than 5 years ago, quit less than 5 years ago, and current smoker. Thus, the model parameter for smoking category is a slope and represents the change induced by a one-unit change in smoking category.

Neurovascular status (intact or impaired) was included in Table 8 of the clinical study report but was not considered in the modeling exercise since there were only 11 subjects with impaired neurovascular status. Also, age of injury was present in Table 8 but is not included here due to large numbers of missing injury ages; only 249 subjects possess a non-missing age of injury. (Please see the response to question 11 for more details on age of injury and relationship to CT fusion data.)

The Wald Type 3 analysis of variance table is shown below.

Table 55: Model 2 Wald Type 3 GEE Analysis of Variance

Source	Degrees of freedom	Chi-square	P
Treatment	1	0.07	0.79
Pooled site	6	25.36	0.00
Treatment-by-pooled site	6	8.39	0.21
Ankle joint	1	4.19	0.04
Subtalar joint	1	0.97	0.32
Calcaneocuboid joint	1	4.76	0.03
Talonavicular joint	1	0.06	0.81
Treatment-by-ankle	1	1.34	0.25
Treatment-by-subtalar	1	0.03	0.86
Treatment-by-calcaneocuboid	1	2.72	0.10
Treatment-by-talonavicular	1	0.39	0.53
Risk factors	1	0.20	0.66
Treatment-by-risk factors	1	0.27	0.60
Age	1	12.28	0.00
Treatment-by-age	1	8.22	0.00
Gender	1	0.00	0.96

Source	Degrees of freedom	Chi-square	P
Treatment-by-gender	1	0.19	0.66
Smoker category	1	2.54	0.11
Treatment-by-smoker category	1	0.88	0.35
Obese	1	0.33	0.57
Treatment-by-obese	1	0.32	0.57
Previous surgery	1	0.01	0.93
Treatment-by- previous surgery	1	0.02	0.87
History of diabetes	1	0.01	0.94
Treatment-by-history of diabetes	1	1.68	0.19
Osteotomy procedure	1	0.10	0.75
Treatment-by-osteotomy procedure	1	3.52	0.06
Soft tissue procedure	1	1.61	0.20
Treatment-by-soft tissue procedure	1	0.10	0.75

Estimates of odds ratios and corresponding confidence intervals are shown in the following plot. Points of note can be found in the table and the plot.

The main effect for treatment is not significant but interactions with other effects lurk in the model, requiring further exploration. In particular, interactions with site, some of the joints, age, and the osteotomy effect are present.

Sites 42 and 56 have lower odds of fusion than do the small sites but not significant interaction with treatment. Thus, while these sites may have lower odds of fusion, these lower odds are consistent for the two treatment groups.

Odds of fusion on subjects with ankle surgery are greater than on subjects with hindfoot joint surgery, while the odds of fusion for subjects with calcaneocuboid joints in their collection of joints treated had lower odds of fusion compared to those who did not have calcaneocuboids involved. Whether these lower odds are a consequence of the calcaneocuboid joint itself or whether it is due to calcaneocuboid joints often being one of a double or triple fusion (which require more joints to be fused to declare success) is uncertain.

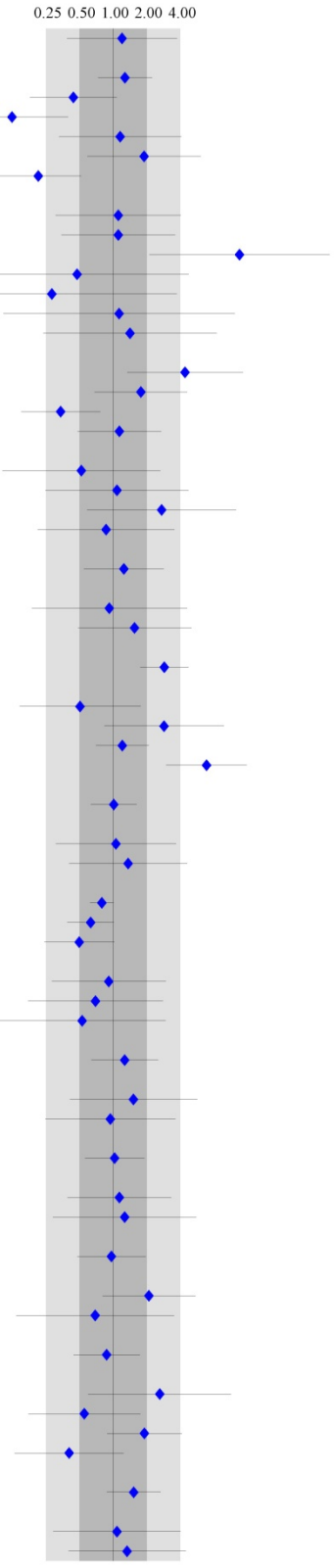
The significant interaction (p=0.10) between treatment and the calcaneocuboid joint points to increased odds of fusion for Augment over autograft in subjects who had a calcaneocuboid joint treated.

Age impacts the odds of fusion, as younger subjects have greater odds of fusion than do older subjects. Furthermore, this impact interacts with treatment, as young people fare especially well compared to older people when being treated with autograft. This disparity is markedly attenuated with Augment.

No main effect for osteotomy is seen, although an interaction with treatment is visible. This interaction presents itself as improved odds of fusion on Augment relative to autograft in subjects with concurrent osteotomies and the reverse when there is no concurrent osetotomy, and as improved odds of fusion for no concurrent osteotomy compared to a concurrent osteotomy when treated with Augment, and the reverse when treated with autograft, although, strictly speaking, no one of these comparisons is significant.

Figure 8: Model 2 odds ratios and corresponding confidence intervals

Comparison	Odds ratio and 90% CI
Augment over autograft - overall	1.20 (0.39,3.74)
Offending sites over small sites	1.28 (0.73,2.24)
Site 41 over small sites	0.44 (0.18,1.07)
Site 42 over small sites	0.12 (0.04,0.39)
Site 45 over small sites	1.16 (0.33,4.07)
Site 47 over small sites	1.89 (0.59,6.10)
Site 56 over small sites	0.21 (0.09,0.52)
Augment over autograft - small sites	1.11 (0.31,4.04)
Augment over autograft - offending sites	1.11 (0.34,3.60)
Augment over autograft - Site 41	13.57 (2.11,87.17)
Augment over autograft - Site 42	0.48 (0.05,4.77)
Augment over autograft - Site 45	0.28 (0.02,3.71)
Augment over autograft - Site 47	1.13 (0.10,12.31)
Augment over autograft - Site 56	1.42 (0.24,8.47)
Ankles over not ankles	4.42 (1.34,14.59)
Subtalars over not subtalars	1.77 (0.68,4.61)
Calcaneocuboids over not ccbs	0.34 (0.15,0.77)
Talonaviculars over not talonavics	1.14 (0.48,2.69)
Augment over autograft - ankles	0.52 (0.10,2.65)
Augment over autograft - subtalars	1.08 (0.25,4.72)
Augment over autograft - calcaneocuboids	2.72 (0.59,12.66)
Augment over autograft - talonaviculars	0.87 (0.21,3.54)
No risk factors over risk factors	1.25 (0.55,2.84)
Augment over autograft - no risk factors	0.93 (0.19,4.60)
Augment over autograft - risk factors	1.56 (0.49,5.02)
Young (< 65 y.o.) over older (>= 65 y.o.)	2.88 (1.75,4.74)
Augment over autograft - young	0.51 (0.15,1.76)
Augment over autograft - older	2.86 (0.84,9.79)
Young over older - Augment	1.21 (0.70,2.10)
Young over older - autograft	6.86 (2.99,15.73)
Women over men	1.02 (0.63,1.63)
Augment over autograft - women	1.06 (0.31,3.66)
Augment over autograft - men	1.36 (0.40,4.62)
One level increase in smoking category	0.79 (0.62,1.01)
Two level increase in smoking category	0.63 (0.39,1.02)
Three level increase in smoking category	0.50 (0.24,1.02)
Augment over autograft - 1 smoke level inc.	0.91 (0.28,2.97)
Augment over autograft - 2 smoke level inc.	0.70 (0.17,2.80)
Augment over autograft - 3 smoke level inc.	0.53 (0.10,2.95)
Not obese over obese	1.27 (0.64,2.53)
Augment over autograft - not obese	1.53 (0.41,5.66)
Augment over autograft - obese	0.95 (0.25,3.63)
No previous surgery over previous surgery	1.03 (0.56,1.90)
Augment over autograft - no previous sx	1.14 (0.39,3.32)
Augment over autograft - previous sx	1.27 (0.29,5.55)
No diabetes history over diabetes history	0.97 (0.48,1.96)
Augment over autograft - no diabetes hx	2.10 (0.81,5.45)
Augment over autograft - diabetes hx	0.69 (0.14,3.52)
No osteotomy over osteotomy	0.88 (0.44,1.73)
Augment over autograft - no osteotomy	2.62 (0.60,11.40)
Augment over autograft - osteotomy	0.55 (0.17,1.76)
No osteotomy over osteotomy - Augment	1.91 (0.88,4.12)
No osteotomy over osteotomy - autograft	0.40 (0.13,1.24)
No soft tissue proc over soft tissue proc	1.53 (0.88,2.67)
Augment over autograft - no soft tiss proc	1.08 (0.29,4.02)
Augment over autograft - soft tiss proc	1.34 (0.40,4.48)



Model 3

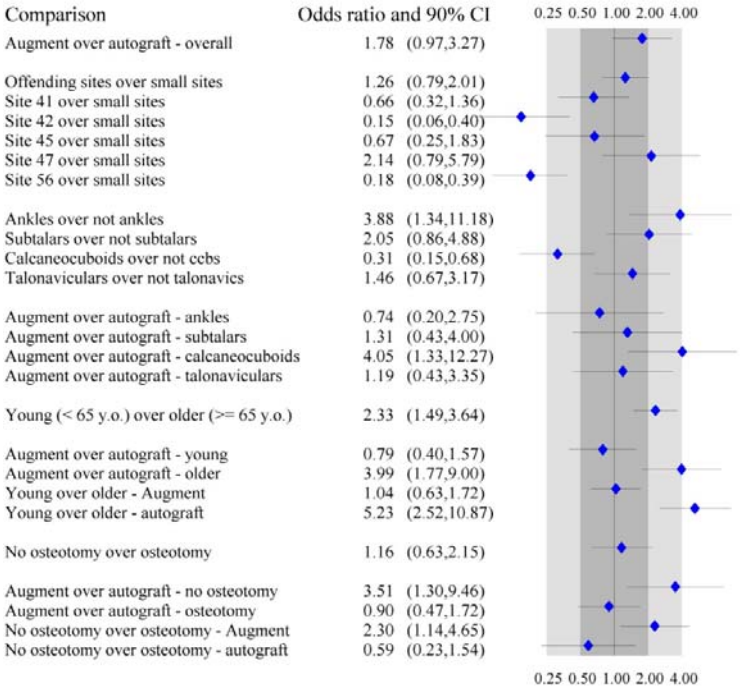
The large model in model2, with its 39 degrees of freedom (plus an intercept) being used to model only 153 events, is most certainly overfit and is therefore likely over-estimating its own worth, prohibiting new observations from agreeing with predictions that may come from the model, and assigning meaningful relationships where only spurious relationships exist. Consequently, reduction of the model should be made.

Model 3 will employ only the significant terms from model 2. The ANOVA table and plot are below.

Table 56: Model 3 Wald Type 3 GEE Analysis of Variance

Source	Degrees of freedom	Chi-square	P-value
Treatment	1	2.40	0.12
Pooled site	6	34.10	0.00
Ankle joint	1	4.43	0.04
Subtalar joint	1	1.83	0.18
Calcaneocuboid joint	1	6.16	0.01
Talonavicular joint	1	0.63	0.43
Treatment-by-ankle	1	1.89	0.17
Treatment-by-subtalar	1	0.33	0.57
Treatment-by-calcaneocuboid	1	3.19	0.07
Treatment-by-talonavicular	1	0.71	0.40
Age	1	9.71	0.00
Treatment-by-age	1	9.02	0.00
Osteotomy procedure	1	0.17	0.68
Treatment-by-osteotomy procedure	1	3.80	0.05

Figure 9: Model 3 odds ratios and corresponding confidence intervals



We kept all the joint effects and all the interactions in this model to keep a full view of the impact of the different sites and their relationship to treatment.

This smaller model contains 19 degrees of freedom (plus an intercept), likely still too many, but the benefit to the model in reduced confidence interval lengths can be seen.

Sites 42 and 56 still possess low odds of fusion relative to the small sites. Ankles still show higher odds and calcaneocuboids lower odds of fusion, with Augment showing benefit particularly in subjects with treated calcaneocuboids.

Younger subjects have greater odds of fusion and young subjects are especially better off than older subjects if autograft is the treatment. This disparity between young and old is not seen in Augment.

The interaction between treatment and concurrent osteotomy status is fueled by a dramatically higher odds of fusion for Augment over autograft in subjects without an osteotomy.

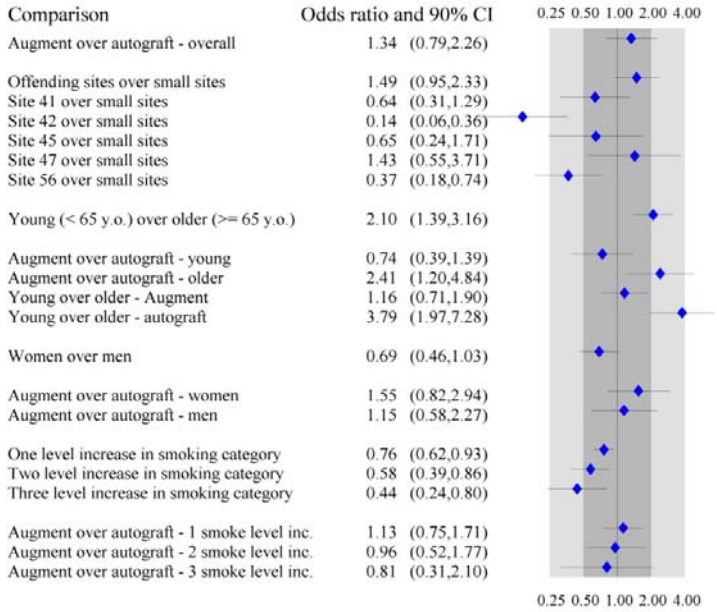
Model 4

A fourth model was fit, using preselected predictors thought to impact the odds of fusion and considered important from an interaction point-of-view: treatment, site, age, gender, smoking, and interactions. This model contains 13 degrees of freedom and is shown in the following table and plot.

Table 57: Model 4 Wald Type 3 GEE Analysis of Variance

Source	Degrees of freedom	Chi-square	P
Treatment	1	0.83	0.36
Pooled site	6	28.76	0.00
Age	1	8.78	0.00
Gender	1	2.30	0.13
Smoking category	1	5.05	0.02
Treatment-by-age	1	5.66	0.02
Treatment-by-gender	1	0.38	0.54
Treatment-by-smoking category	1	0.47	0.49

Figure 10: Model 4 odds ratios and corresponding confidence intervals



We note again results from sites 42 and 56 and the improved odds with being younger. Furthermore, the disparity between young and old with autograft is again highlighted.

Smoking can be seen to be detrimental, as well.

The overall odds of fusion for Augment relative to autograft is estimated at 1.34 with the lower end of the confidence limit at 0.79, a condition indicative of non-inferiority of Augment.

Furthermore, Augment does not show the disparity between ages that autograft produces; the estimated odds of fusion for young relative to old on Augment is 1.16, compared to 3.79 on autograft.

This smaller model provides a concise look at conditions impacting the odds of fusion.

Of all the potential factors influencing the odds of fusion, the treatment used (Augment or autograft) seems to be one of the least important, with the exception that it seems to interact with age: older subjects on autograft do substantially worse than their younger counterparts. One cannot make the same conclusion about Augment. This further reinforces that subjects can expect equivalent effectiveness outcomes with Augment compared to autograft without the co-morbidities associated with autograft.

Question 23

23) You have not analyzed the data with time-to-event measurements. Per the FDA approved protocol, such analyses should be done starting for data at 24 weeks. It is particularly important for the time-to-event occurrence of adverse events. In addition to comparing proportions of

adverse events in the 2 comparison groups, the time of AE occurrence and the incidence of AEs should also be evaluated. Please provide the results based on time-to-event analysis for the data included in the current PMA submission.

Response

Time to event analysis was not submitted with the 24 week clinical study report as not all subjects had completed evaluations to provide time-to-event data. As requested by FDA, these data are reported in the final clinical study report submitted with this response. Comparisons of AE occurrence will also be made as requested. Clinical Study Report dated 17 November 2010 as included (in Exhibit 6). AE comparisons are included in this response (in Exhibit 8).

Question 24

24) You have not described whether the Augment Bone Graft has been approved by countries other than Canada. Please clarify whether this device has been approved in other countries; and if so, please provide the complaint data on the safety profile of the device from those countries and all necessary and known information about the device that is not supplied in the PMA per 21CFR 814.84. 25.

Response

Augment Bone Graft received a device license in November 2009 by Health Canada. Augment Bone Graft is not approved in any other jurisdiction and is considered an investigational device in all other countries.

Since Canadian market approval BioMimetic Therapeutics has sold 50 Augment Bone Graft kits in Canada. BioMimetic Therapeutics has not received any complaints or reports of adverse events related to the use of Augment Bone Graft.

It is also noted that a similar product, GEM 21S, which is comprised of β-TCP (250-1000µm) and 0.3 rhPDGF-BB, is approved in the United States and Canada for treatment of periodontal related defects.

Question 25

25) The PMA submission does not include a Post-Approval Study (PAS) protocol or discussion of post approval plans. You need to propose a post approval study in order to address post approval issues including any cancer that may be detected and/or potential tumor growth that may be associated with the use of any growth factor. If your application is approved, FDA may require you to conduct a post-approval study as a condition of approval. Should a PAS be needed, a PAS protocol or an outline must be agreed upon by you and the Office of Surveillance and Biometrics (OSB) by the time of approval. OSB's Division of Epidemiology, in consultation with the Clinical Reviewer, the Lead Reviewer and other members of the review team will work

interactively with you to develop the PAS protocol. An outline detailing the elements you should include in the post-approval study protocol is provided below.

a Background
b. Objectives
c. Study design
d. Study groups (including description of group)
e. Patient inclusion and exclusion criteria
f. Sample size calculation (based on testable hypothesis)
g. Recruitment strategy (for study sites and subjects)
h. Data collection: Study Endpoints
i. Follow-up schedule and plan to minimize loss to follow-up.
j. Statistical analysis plan
k. Detailed study timeline
l. Reporting requirements (interim and final reports)

Please be sure that the study time-line includes the following information:

- Expected date of study initiation
- Expected monthly number of study sites with IRB approvals
- Expected number of subjects enrolled per month
- Expected date of enrollment completion
- Expected date of study follow-up completion
- Expected date for Final Report submission

FDA would also like to remind you to refer to the guidance document on how to handle post-approval studies imposed by approval orders, located at the following website: http://www.fda.gov/cdrh/osb/guidance/1561.html.

Response

As requested by FDA, BMTI is proposing a study to enroll subjects treated under protocol BMTI-2006-01 to a long-term follow-up study. Subjects and sites would be included based on participation in protocol BMTI-2006-01 and followed up to 5 years from their original study procedure. The study, based on FDA acceptance, is planned to begin activity in January 2011, with initiation of 30 sites (maximum of 37 sites) at an average rate of six (6) sites initiated per month through June 2011, upon receipt of IRB approval. Enrollment of 300 subjects (maximum of 397) patients is planned from January through May of 2011 at an average rate of 2 subjects enrolled per site per month. Follow-up of subjects is expected to continue through January 2015. A final study report is planned for May of 2015. A summary of the proposed study design is included as Exhibit 11.

Question 26

26) FDA is aware of observations of epidemiologic studies wherein the use of the Regranex product, which contains the same rhPDGF-BB protein contained within your product, has been correlated with an apparent increase in cancer mortality in patients treated with the product FDA's Center for Drug Evaluation and Research (CDER) issued an Early Communication (EC)

regarding the observations in order to inform physicians and patients of the potential safety concern. FDA continues to believe that this information should be prominently communicated to physicians and patients. Please review the information contained on FDA's EC weblink http://www.fda.govlDrugs/DrugSafetylPostmarketDrugSafetyInformationforPatientsandProvider slDrugSafetvInformationforHeathcareProfessionals/ucm072148.htm) regarding the Regranex safety information and revise the product and patient information labels accordingly.

Response

Please refer to the response to question 6b for a detailed discussion of the relevance of the referenced Regranex data to Augment.

Since the Regranex data cannot be directly applied to Augment, BMTI does not believe any change to the labeling based on that study is warranted. BMTI does recognize the potential seriousness of a growth factor's effect on cancer rates. This is evidenced in the extensive pre-clinical program that has been developed with the help of the Agency, rigorous reporting of all adverse events in the clinical program and the proposed post-approval study discussed in the response to question 25. Therefore, BMTI respectfully requests that FDA and the company collaborate on any appropriate labeling after FDA has thoroughly reviewed all of BMTI's pre-clinical and clinical data.

The following additional minor deficiencies and advisories were noted in this initial scientific review and the indicated responses should be provided:

Minor Deficiencies

Question 27

27) *In response to FDA's question (deficiency 6) you have asserted that the elevated fibrinogen levels were actually seen across all groups, including the control cohort, and that the "fibrinogen levels for the cohorts that were statistically greater than the untreated controls were within the historical range of 'normal' values". Your analysis of the fibrinogen values, i.e., comparison with statistical analysis, was not provided. Please provide the fibrinogen values for the test article-treated groups and the control cohort, as well as the historical data set for fibrinogen values.*

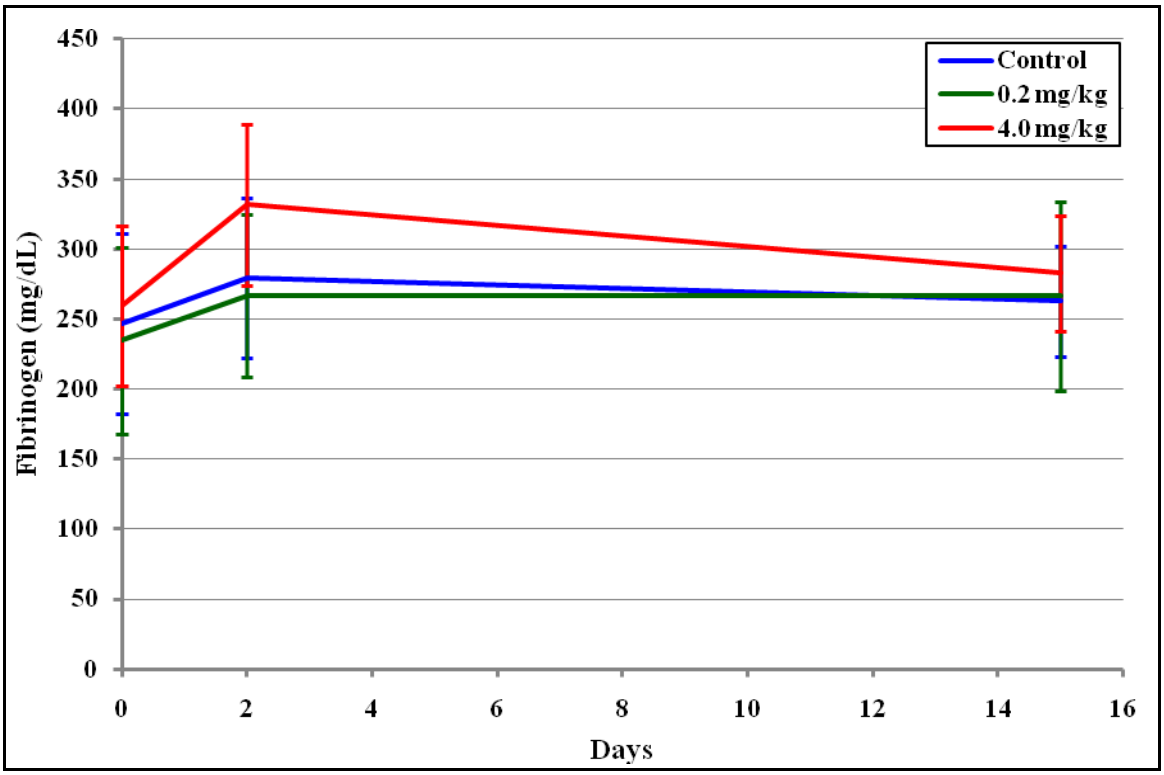
Response

In response to this deficiency and deficiency # 28 the study report has been revised. The report also includes a clarification on the elevated fibrinogen levels seen at Day 2 in the male group of the animals. Both an amended report and a redlined version are found in Exhibit 12.

The elevations in fibrinogen levels at Day 2 reached statistical significance only in male rats in the high dose treatment group. Because the fibrinogen changes in the males were dose related, they were considered test article related, but because of the small magnitude of the increases, and because these differences were not observed in the females, they were not considered toxicologically meaningful.

As indicated in our previous response, Day 2 fibrinogen levels were elevated in all groups relative to the Day 0 levels. It is possible that these changes are due, at least in part, to the stress inflicted on the animals by the Day 0 blood draw, article injection and Day 2 blood draw all taking place in a 48-hour window. The increase in fibrinogen levels reached significance only in the males that received the highest dose of the test article (4.0 mg/kg). Importantly, this elevation was transient with a trend towards normalization by Day 15 (Figure 11). It is unclear why the same response was not observed in the females.

Figure 11: Fibrinogen levels as a function of time in the three treatment groups.



The mean fibrinogen value on Day 0 (pre-treatment) for the animals included in this study was 246.7 ± 62.7 mg/dL with a minimum value of 60.0 mg/dL and a maximum value of 324.0 mg/dL. The means and ranges for all the animals and segregated by sex are displayed in the table below. All the raw data for each individual animal and time point can be found in the study report (Exhibit 12).

Table 58: Fibrinogen Values by All Animals and Segregated by Sex

	Mean	Std. Deviation	Minimum	Maximum
All Animals	246.7	62.7	60.0	324.0
Males	252.5	83.2	60.0	324.0
Females	241.2	34.9	160.0	308.0

Because of the uncertainty on the significance of these findings brought by the differences in the responses observed in male versus female rats, BioMimetic Therapeutics, Inc. has initiated a new acute toxicity study with larger sample size (10 animals per sex and time point in each group) that will serve to verify or refute these findings. This Acute Toxicity study is expected to start in the first week of December 2010 at the CRO Ricerca in Cleveland. The draft study protocol is found in Exhibit 12.

Question 28

28) Upon review of the individual line listings in the single dose intravenous toxicity study with rhPDGF-BB in rats conducted by WuXi AppTec, it appears that summary data from the low and high dose groups were transposed in summary tables 9 and 10. If this is correct, please amend the study report should be amended, checked for any other discrepancies, and resubmitted with a summary of all changes (red-lined).

Response

BMTI has reviewed the tables with WuXi AppTec and apologizes for the transposed data in the summary tables. The study report has been revised and the redlined version with all corrections is provided in Exhibit 12. The revised sections of the report are the following:

Replace Executive Summary, Page 9, Second Paragraph Sentences 5, 6, & 7 with the following:

"On Day 2, fibrinogen levels increased from baseline in a dose-dependent manner for test article-treated males. The fibrinogen levels for high-dose males were significantly greater than controls; however, there were no observed differences between treated and control females on Day 2. On Day 15, fibrinogen levels for the high-dose males had decreased but remained significantly greater than controls. On Day 15, fibrinogen levels for the low-dose females were significantly greater than controls; however, there was no difference between the controls and the high-dose group. Because the fibrinogen changes in the males were dose related, they were considered test article related, but because of the small magnitude of the increases, were not considered toxicologically meaningful. Because the fibrinogen changes in the Day-15 females were not dose related and were not preceded by any changes on Day 2, a relationship to test article administration could be established."

Replace in Section 17.4, Hematology and Coagulation, Paragraph 2, Sentences 2 and 3 with the following:

"Fibrinogen levels were increased in males terminated on Day 2, with levels in the high-dose males significantly greater than controls."

Replace in Section 17.4, Hematology and Coagulation, Paragraph 3, Sentence 1 with the following:

"On Day 15, significantly increased fibrinogen was still observed in the high-dose males. Fibrinogen levels in the low-dose females were also significantly increased with no changes in the high-dose females. In the males, these changes were considered test article-related but not toxicologically important. No clear relationship between fibrinogen levels and treatment in the females could be established."

Replace Discussion and Summary, Paragraph 1, Sentences 10, 11, and 12 (Sentence 10 to the end of the paragraph) to the following:

"Dose-related increases in fibrinogen levels were observed only in males. On Day 2 and Day 15, fibrinogen levels for the high-dose males were significantly greater than the controls. These changes were considered test article related. This mild response was not considered toxicologically relevant. In the females, there was a significant increase in fibrinogen in the low-dose group on Day 15. The increase was not dose related, was small in magnitude, and was well within the historical reference range; therefore, a clear relationship to test article administration could not be determined. Per the Sponsor, the low and high doses of rhPDGF-BB test article administered to the animals in this study exceeded the maximum human critical dose by 5- and 100-fold, respectively, on a per kilogram body weight basis."

Reasons for change: a re-evaluation of the data by the study director following changes in the data tables, correction of an error in Section 17.4, and clarification of sex differences for fibrinogen analysis in Section 17.4.

Question 29

29) *In response to FDA's deficiency regarding the reproductive toxicity assessment (#11), you have noted that the study has been completed (the draft report was provided; the complete final report is pending)). With respect to FDA recommendations to revise the route of exposure, the timing of the exposure to the protein, and the dose of rhPDGF-BB used in the investigation, you have provided rationales for the protocol choices made. Until this information is provided, FDA is not able to provide feedback about whether additional investigation, e.g., F1 developmental growth prior to sacrifice, F2 reproductive toxicology evaluation, is necessary. Review of the study's findings may clarify whether additional investigation is warranted.*

Response

The reproductive toxicity of rhPDGF-BB was studied by daily intravenous administration of rhPDGF-BB in gravid rats over 21 days of gestation. The conclusions of this GLP study entitled Recombinant Human Platelet-derived Growth Factor-BB (rhPDGF-BB): an Intravenous Injection Teratology Study in the Rat (Charles River Lab Study No. 901703) is summarized below. The study report is attached.

Conclusions of the reproductive toxicity study:

The administration of rhPDGF-BB at 40 µg/kg and 400 µg/kg by daily intravenous injection to female rats from Gestation Days 0 to 20 resulted in neither maternal toxicity nor adverse effects on embryo-foetal development in this study. Toxicokinetic analysis of plasma at Day 21 gestation, indicated no detectable rhPDGF-BB (consistent with a very short half-life systemically) and there were no detectable binding or neutralizing antibodies against rhPDGF-BB after dosing. Based on these results, the NOAEL for maternal toxicity and the NOAEL for embryo foetal development is 400 µg/kg/day, the highest dose tested in the study. The highest dose corresponds to approx. 10x the maximum clinical dose, and 21 days of repeated administration corresponds to 210x the maximum clinical dose. Therefore, it can be stated that there are no toxicity concerns with the proposed clinical dose.

Evaluations of the F1 group:

As shown in the reproductive toxicology report, the F1 fetuses were evaluated grossly and microscopically for visceral and skeletal development anomalies. Data indicated no visceral anomalies in F1 fetuses. There were trends indicating accelerated ossification of the intraparietal lobes and reduced incidence of the 14th rib in F1 fetuses from dams receiving the highest dose of rhPDGF-BB.

Reproductive function consequences:

The trend for accelerated ossification of the intraparietal lobes and reduced incidence of the 14th rib would neither affect fetal viability nor reproductive capacity. No visceral or skeletal anomalies were observed in the control or the low dose rhPDGF-BB groups.

Question 30

30) *In response to FDA's deficiency regarding a neutralizing antibody repro tox study (deficiency #13), you have indicated that attempts to develop a rabbit neutralizing antibody have failed and therefore you propose to use the commercially available goat antibody in a rodent placental transfer assessment. If the antibody passes through the placenta, you then propose to conduct PK evaluations based on a 7 day time frame for exposure. You have stated that guidance would be welcomed. The information provided does not appear to indicate that your attempts to develop a neutralizing antibody in rabbits have been exhaustive; however FDA believes the proposed approach of the first phase of experiments has merit. One recommendation would be to radio-label the goat antibody prior to injecting into the pregnant dams for increased potential to detect placental transfer to the fetal circulation. The dosing/7day time frame for assessment of 'some' type of toxicity proposal is not detailed sufficiently for critical comment. Various doses should be considered, i.e., a dose range in hope of eliciting a dose response, and should have some basis on what would theoretically be expected clinically. Beyond these 2 considerations, the other standard repro tox elements should be incorporated into the study, e.g., number of animals, types of evaluations, F1 evaluation and F1 development prior to sacrifice, potential to conduct an F2 study. We are available to discuss your proposed protocols and recommend that you set up a conference call in this regard with the review team.*

Response

To date, our efforts to develop neutralizing anti-hPDGF-BB antibodies in rabbits have not been successful. To our knowledge, there is only one commercially available anti-hPDGF-BB antibody with neutralizing activity. This antibody is a goat IgG produced by R&D Systems.

BMTI proposed to perform a study in rats with this commercially available anti-hPDGF-BB IgG antibody because such a study in rabbits presented significant challenges in terms of material availability and time. The proposed studies (in the rat) would necessitate 200-400 milligrams of the antibody; performing these same studies in a rabbit model would necessitate 12 - 16 times more if we accept that the average weight of a rat is 250 g and the average weight of a rabbit is

between 3 and 4 kg. R&D Systems can provide the goat anti-hPDGF-BB IgG antibody from a single lot in sufficient quantities to complete the proposed rat studies. Obtaining the amount of goat anti-hPDGF-BB IgG antibody necessary for rabbit studies may not be feasible.

The goals of the initial PK studies are:

1. To confirm that the goat anti-rhPDGF-BB IgG antibody crosses the placental barrier.
2. To assess the serum levels of anti-rhPDGF-BB IgG antibody in maternal and fetal blood.
3. To determine the exposure levels of the anti-hPDGF-BB IgG antibody in maternal and fetal blood.

The first study will serve to assess points 1 and 2 above. It will be a pilot study performed in pregnant rats. A high dose of the antibody (0.1 - 1 mg) will be administered IV to pregnant rats in late gestation (day 18 -19) with collection of maternal and fetal blood 24 hours after administration of the goat anti-hPDGF-BB IgG antibody.

If the goat anti-hPDGF-BB IgG antibody is detected in fetal flood, point 3 will be assessed in a second study which will be a formal PK study performed in pregnant rats. This PK study will serve to determine the exposures and the residence time of the goat anti-hPDGF-BB IgG antibody in the rat circulation.

The data from these studies will be used to design the actual reproductive toxicity/teratology study. These studies will determine the frequency of dosing necessary to achieve and maintain appropriate exposures throughout the gestation period.

The timeframe for obtaining the quantities of Goat NAb needed and completion of the initial two proposed studies before entering into the Ab teratology study is 6-9 months depending on CRO availability and R&D Systems schedule for antibody production. In the mean time BMTI also commits to initiate a strong effort to generate anti-rhPDGF-BB antibodies in rabbits as well as in rodents.

List of Exhibits

Exhibit	Volume	Page
Exhibit 1		
Final Report RD-072809-01P: rhPDGF-BB: An Intravenous Injection Teratology Study in Rat	2	1
Final Report 1524-03: Evaluation of the Chronic Toxicity and Carcinogenicity of Recombinant Human Platelet-Derived Growth Factor-Bb (rhPDGF-BB) Mixed With β-Tricalcium Phosphate (β-TCP) Matrix (Augment Bone Graft) Implanted in a Rat Model	3	1
Appendix A: Control & Test Article Information	4	1
Appendix B: Record of Animal Fate & Disposition	4	9
Appendix C: Individual Detailed Clinical Observations	4	20
Appendix D: Individual Mass Findings	4	65
Appendix E: Individual Body Weight Findings	4	89
Appendix F: Individual Food Consumption Values	4	150
Appendix G: Individual Ophthalmoscopic Exam Findings	4	211
Appendix H: Serological Health Screen	4	238
Appendix I: Clinical Pathology Interpretation	4	257
Appendix J: Individual hematology Values	4	260
Appendix K: Individual Coagulation Values	4	389
Appendix L: Individual Clinical Chemistry Values	5	1
Appendix M: Individual Urinalysis Values	5	105
Appendix N: Individual Bone Marrow Values	5	251
Appendix O: Serum Test Article Antibody Analysis Report	5	432
Appendix P: Pathology Interpretation	5	465
Appendix Q: Tissues & Organs-collected, weighed, examined	5	469
Appendix R: Individual Organ Weight Values	6	1
Appendix S: Individual Animal Data Record-Pathology	6	66
Appendix S: Ind. Animal Data-Pathology (cont'd)	7	1
Appendix S: Ind. Animal Data-Pathology (cont'd)	8	1
Appendix S: Ind. Animal Data-Pathology (cont'd)	9	1
Appendix T: Protocol & Amendments	9	136
Appendix U: Deviations	9	173
Exhibit 2 – Intentionally Left Blank		
Exhibit 3		
Millipore Validation Report 07-129	10	1
Qualification Report A Radioimmunoassay to detect	10	78

Exhibit	Volume	Page
neutralizing antibodies against rhPDGF-BB in Human Serum Rnd-0008-RDR		
Qualification Report An Enzyme-Linked Immunoabsorbent Assay to Detect Human Antibodies against Recombinant Human Platelet Derived Growth Factor B-homodimer (rhPDGF-BB) in Human Serum Rnd-0009-RDR	10	89
Exhibit 4		
Summary report on development of anti-rhPDGF-BB Neutralizing Antibody assay based on human neonatal dermal fibroblast cells RnD-102110-01R	10	112
Summary report on development of anti-rhPDGF-BB Neutralizing Antibody assay based on rat lung fibroblast cells RnD-102110-02R	10	120
Qualification of an analytical method to detect neutralizing antibodies to recombinant Human PDGF-BB in rat serum by western blotting. Inhibition of recombinant human PDGF-BB induced phosphorylation of PDGF receptor beta in RFL-6 cells. RnD-062110-1P	10	126
Related communications	10	141
Exhibit 5		
Raw Data – Pivotal	10	146
Raw Data – Canada (pilot)	10	192
Amended Report to RnD-082109-01R: Screening of Serum Samples from Clinical Study BMTI-2006-01-US for the Presence of Human Anti-rhPDGF-BB Antibodies	10	196
Assessment of Changes to Amended Immunogenicity Report RnD-102810-1R	10	209
Exhibit 6		
Event Summaries for Neoplasms	10	217
Luitpold MDR20090420 (carcinoma)	10	400
52-Week Clinical Study Report: BMTI-2006-01 Version 2.0 – Nov. 17, 2010	11	1
Appendices to CSR	11	307
Patient Profiles	12	1
Exhibit 7		
Secondary Procedures Table	13	1
24-week protocol deviations	13	8

Exhibit	Volume	Page
52-week protocol deviations	13	9
Coughlin, MJ et al. Comparison of Radiographs and CT Scans in the Prospective Evaluation of the Fusion of Hindfoot Arthrodesis. Foot & Ankle Intl 27:780-787, 2006.	13	10
Dorsey, ML et al. Correlation of Arthrodesis Stability with Degree of Joint. AJR 192:496-499, 2009.	13	18
Infections and Infestations by Treatment Group	13	22
Exhibit 8		
DMC Charter	13	26
DMC Members – CV's	13	59
Vascular Disorders by Treatment Group	13	135
124 AD Events between 6 and 12	13	136
AE Timeline by SOC	13	139
Operative Systemic Events	13	141
Positive subjects profiles	13	148
Exhibit 9		
Patient Accounting Table	13	195
Patient Withdrawals Table	13	196
Exhibit 10		
Financial Certification & Disclosures	13	199
Exhibit 11		
Pivotal Clinical Trial Extension Study Design Summary	13	215
Exhibit 12		
Amended Final Report 109720: Evaluation of the Acute Toxicity of Recombinant Human Platelet-Derived Growth Factor-BB (rhPDGF-BB) Administered Intravenously in a Rat Model	14	1
Amended Final Report 109720: (Red-lined Version)	14	215
Draft Protocol: Intravenous Toxicity Study following a Single Administration of rhPDGF-BB in Rats at Fourteen Days (Study 026691-0)	14	443