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Intramuscular Administration of Autologous Bone Marrow Cells for Limb Salvage in Critcial Limb Ischemia:

Results of the Phase III MOBILE Trial*

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* (MarrOwStim Treatment of LimB IschemIa in Subjects With Severe Peripheral ArterialL DiseasE)

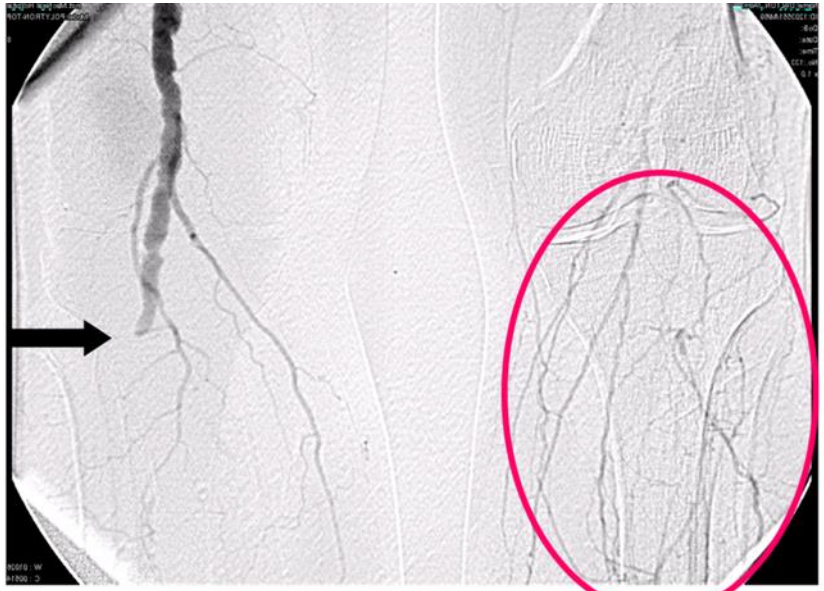
Rationale for MOBILE

Critical Limb Ischemia:

- End stage of peripheral arterial disease
- 53,300 amputations each year

Convincing results from a Phase I trial demonstrating safety and suggesting efficacy of concentrated bone marrow cells in preventing amputation in "no option" CLI

Murphy, et al. *J Vasc Surg* 2011;53:1565-74

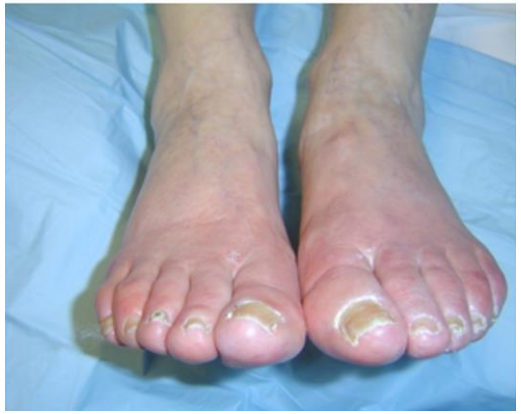


30% CLI patients "*No Option for Revascularization*"

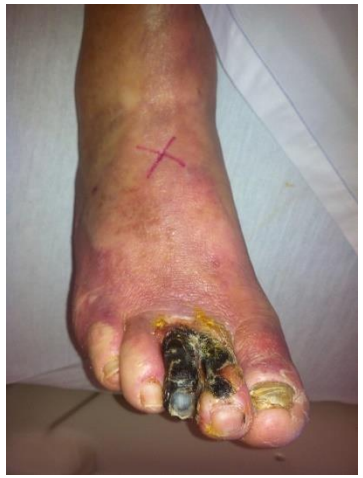
The MOBILE Trial Design

Inclusion Criteria

- Not a candidate for revascularization.
- Ankle Brachial Index < 0.60, TBI < 0.40
- **Rutherford 4** and **Rutherford 5** Disease



Rest Pain



Tissue Loss

Exclusion Criteria

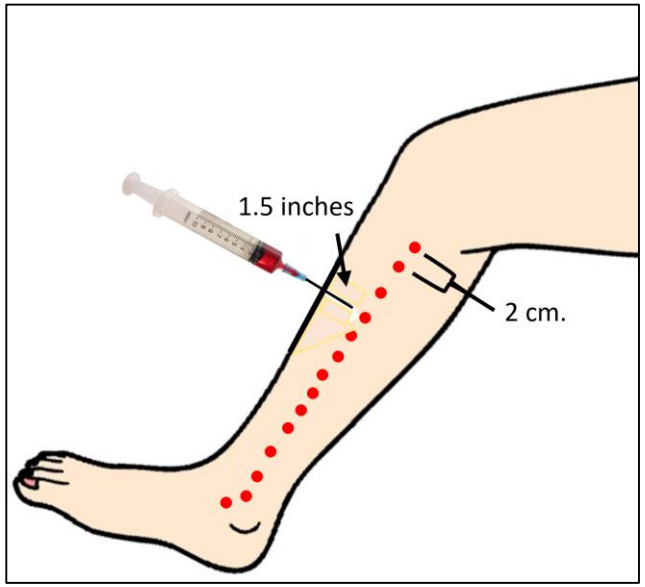
- HbA_1C> 10%
- CHF: NYHA Class IV
- Creatinine > 2.5 mg/dl or on Hemodialysis
- Amputation < 30 days from enrollment

The MOBILE Trial Design:
Study Product and Administration

1. Aspirated bone marrow is placed in centrifuge tube.

2. Marrow is concentrated with centrifugation (15 min).

3. Concentrated bone marrow cells are collected.



4. 0.75 cc's of cBMA is injected IM 1.5 inches deep at 35-40 sites in the index limb.

The MOBILE Trial:
Randomization and Endpoints

- Double-blinded, placebo-controlled trial at 24 centers in the U.S.
- Randomization: 3:1 (cBMA: placebo)…ethical concerns and enrollment.
- Stratified by **Rutherford class** and **Diabetes**

- **Primary Endpoint**:

  Regulatory: Amputation Free Survival (AFS) at 52 weeks

  AFS = all cause mortality + amputation

- **Secondary Endpoints**:

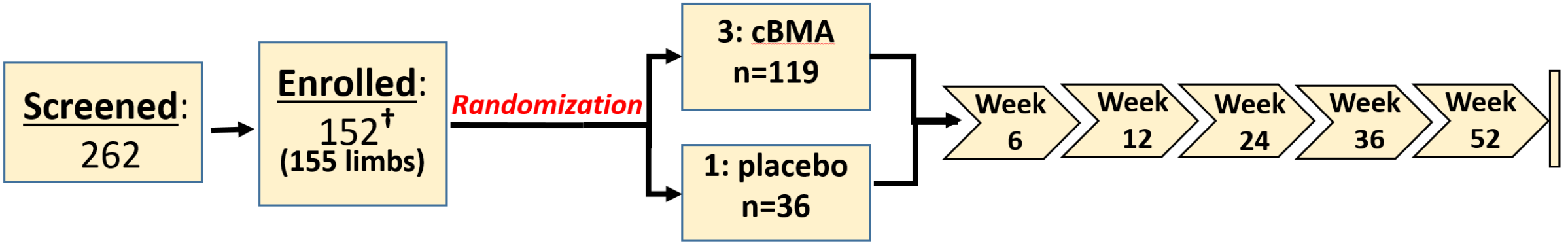
  1.**Therapeutic**: Incidence of ***major amputation*** at 52 weeks

  2. Ankle-Brachial Index, Toe-Brachial Index, Transcutaneous oxygen measurements

  3. 6 minute walk test (6 MWT)

The MOBILE Trial:Results

Enrollment (5/10/2010 – 5/4/2016)



		Placebo	cBMA	P-value
Rutherford	4	19 (52.8%)	65 (54.6%)	.851
	5	17 (47.2%)	54 (45.4%)	
Diabetes	No	22 (61.1%)	70 (58.8%)	.849
	Yes	14 (38.9%)	49 (41.2%)	

† 80% power to detect 60% reduction of risk for major amputation/death.
Based on 40% failure rate for control and 20% for cBMA groups (*Norgren L, et al. J Vasc Surg. 2007;45(Suppl S):S5-S67).*

The MOBILE Trial:Results

Safety Analysis: *no significant differences in SAE or AE between study groups.*

AE Category	Population (includes long term follow-up as of 6/22/2016)	Placebo (n=36)	cBMA (n=119)	P-Value
SAE	Any SAE	25 (69.4%)	70 (58.8%)	.329
	Death	4 (11.1%)	5 (4.2%)	.214
	Respiratory Failure	4 (11.1%)	2 (1.7%)	.026*
AE	Any AE	35 (97.2%)	117 (98.3%)	.550
	Fever	4 (11.1%)	2 (1.7%)	.026*
	Low RBC Related Level†	13 (36.1%)	82 (68.9%)	<.001*

†No negative sequelae reported – Lower RBC related level expected with large volume bone marrow aspiration.

Results:

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Death *Plus* Amputation (AFS)– All Randomized Subjects (N=155)*

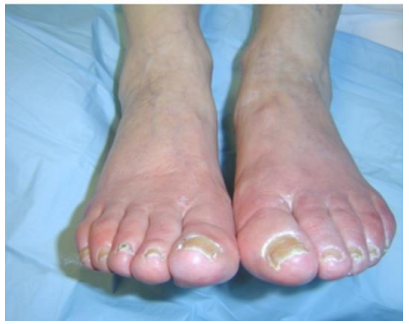
	Placebo (N=36)	cBMA (N=119)	P-value	Estimate
Subjects with Events (%)	11 (**30.56%**)	24 (20.17%)		
Hazard ratio (95% CI)			.224	0.64 (0.31 – 1.31)

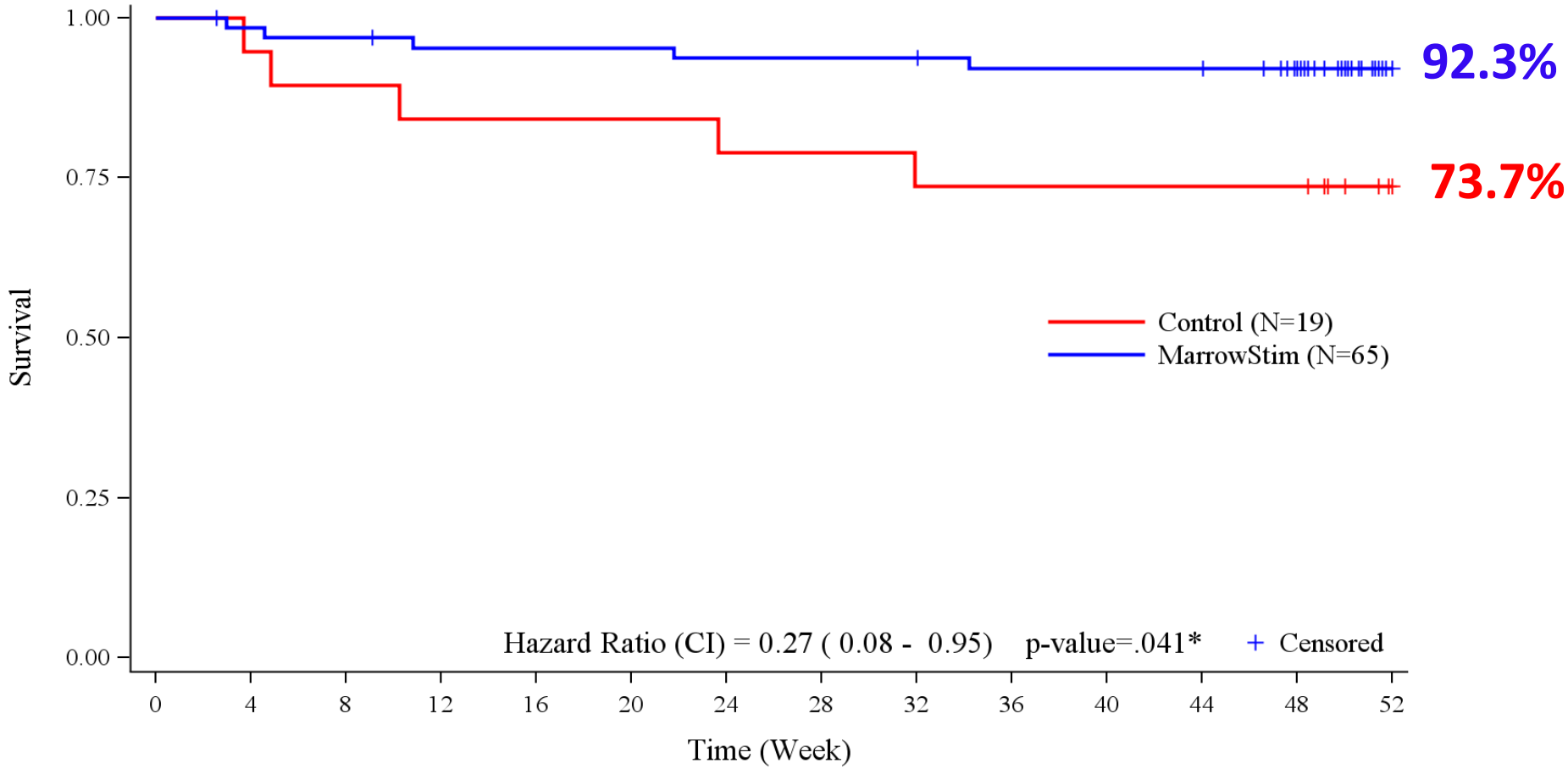
Major Amputation – All Randomized Subjects (N=155)

	Placebo (N=36)	cBMA (N=119)	P-value	Estimate
Subjects with Events (%)	8 (22.22%)	19 (15.97%)		
Hazard ratio (95% CI)			.392	0.70 (0.30 - 1.59)

Major Amputation: Rutherford 4 (N=84) [*Rest Pain*]

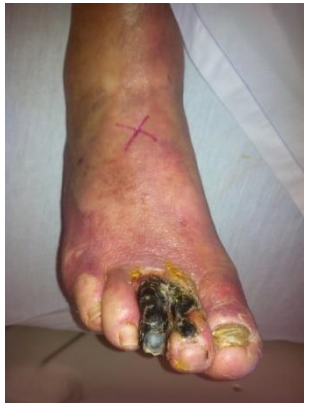
	Placebo (N=19)	cBMA (N=65)	P-Value	Estimate
Subjects with Events (%)	5 (26.32%)	5 (7.69%)		
Hazard ratio (95% CI)			.041*	0.27 (0.08 - 0.95)

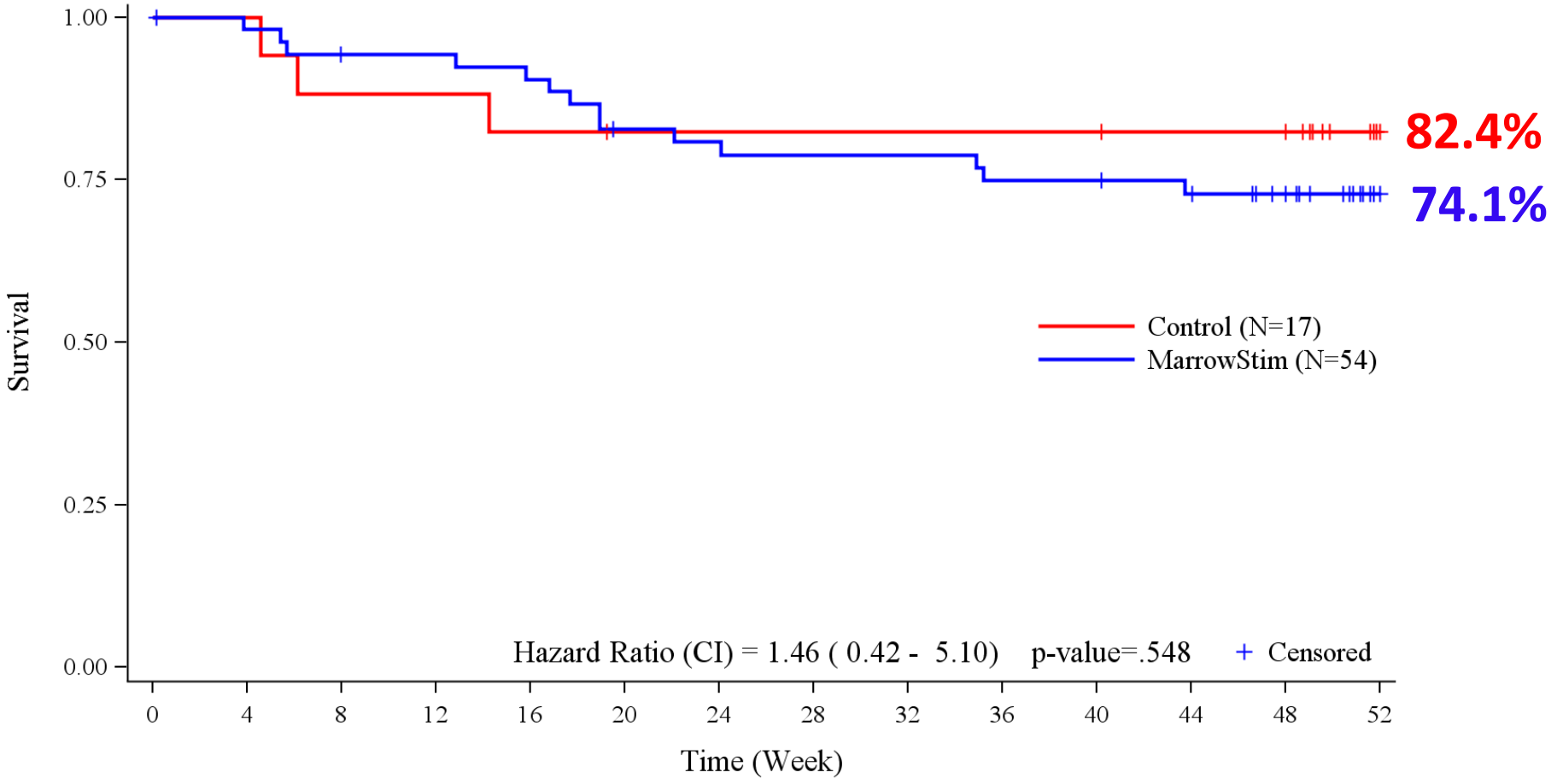




Major Amputation: Rutherford 5 (N=71) [*Tissue Loss*]

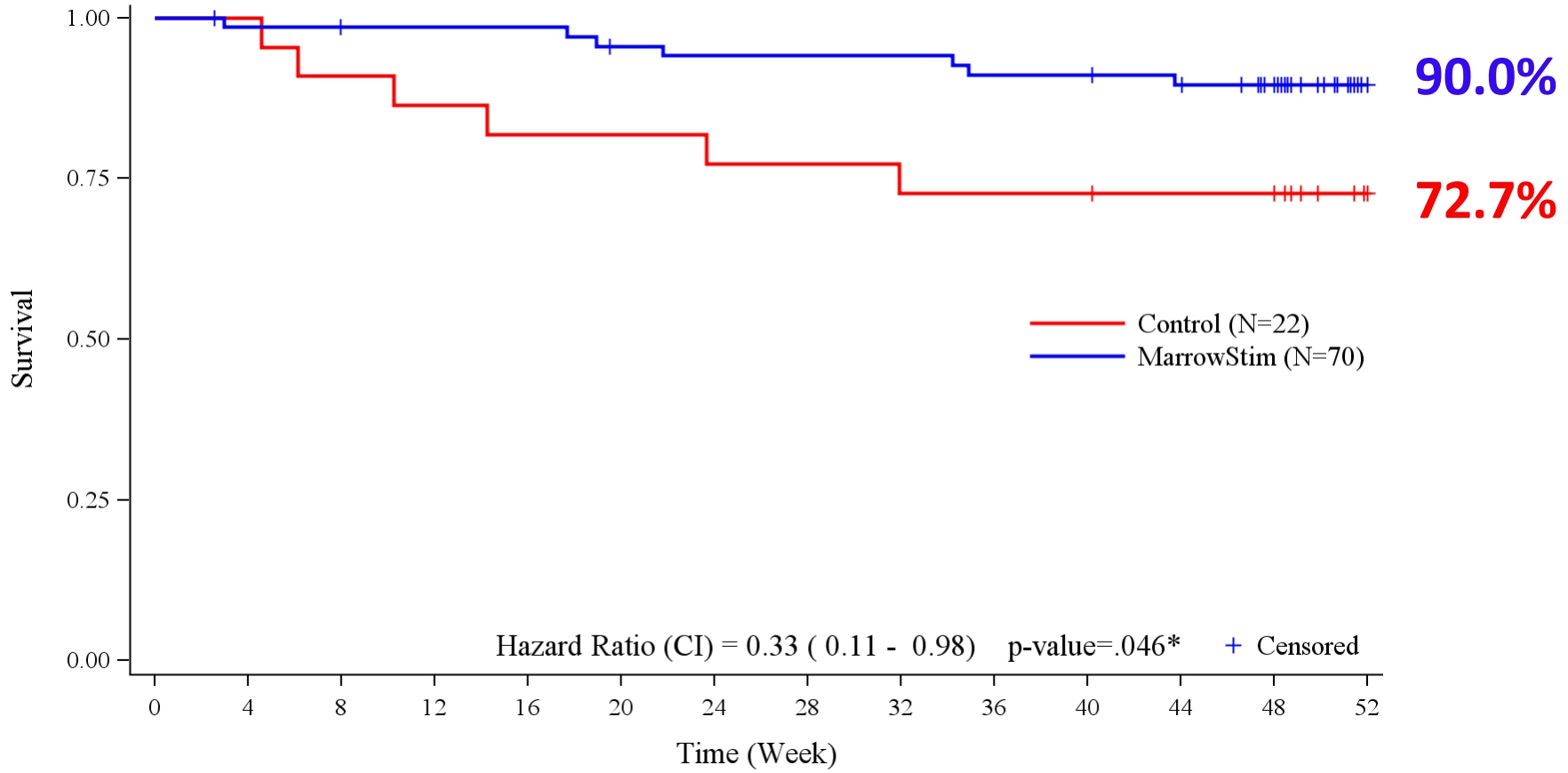
	Placebo (N=17)	cBMA (N=54)	P-Value	Estimate
Subjects with Events (%)	3 (17.65%)	14 (25.93%)		
Hazard ratio (95% CI)			.548*	1.46 (0.42 - 5.10)





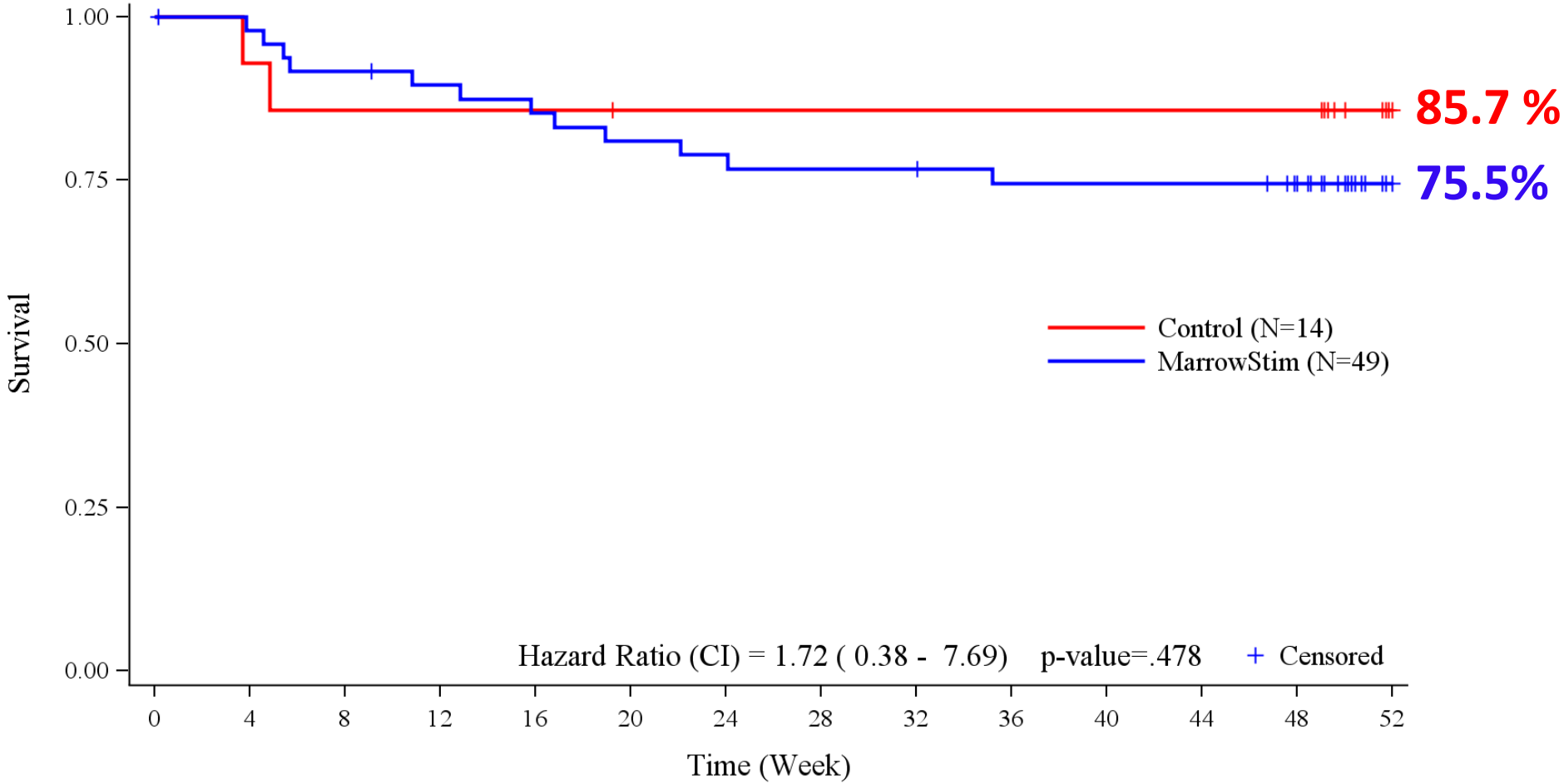
Major Amputation: Non-Diabetic (N=92)

	Placebo (N=22)	cBMA (N=70)	P-Value	Estimate
Subjects with Events (%)	6 (27.27%)	7 (10.00%)		
Hazard ratio (95% CI)			.046*	0.33 (0.11 - 0.98)



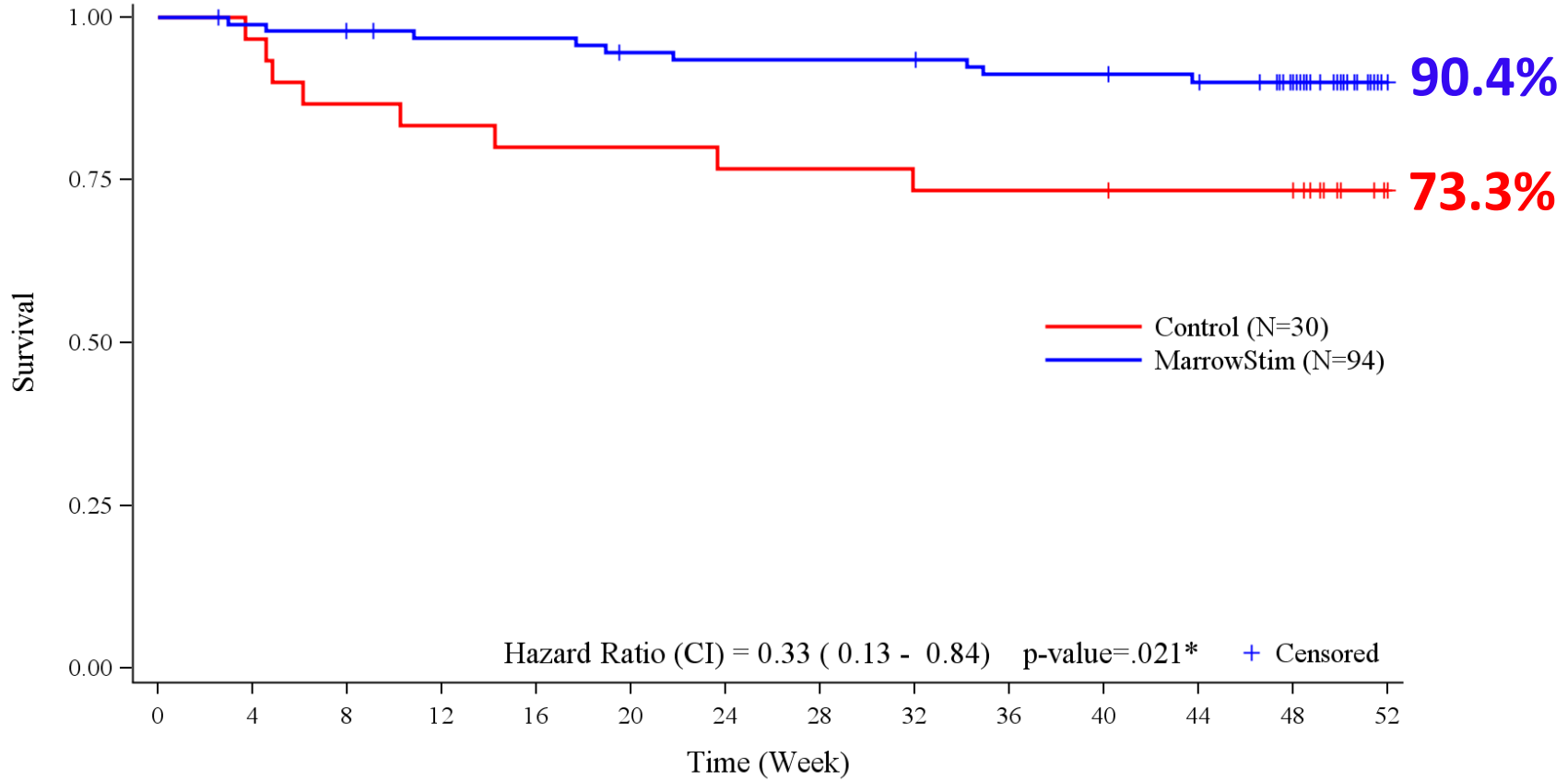
Major Amputation: Diabetic (N=63)

	Placebo (N=14)	cBMA (N=49)	P-Value	Estimate
Subjects with Events (%)	2 (14.29%)	12 (24.49%)		
Hazard ratio (95% CI)			.478	1.72 (0.38 - 7.69)



Major Amputation: All Subjects Excluding Rutherford 5 Diabetics (N=124)

	Placebo (N=30)	cBMA (N=94)	P-Value	Estimate
Subjects with Events (%)	8 (26.67%)	9 (9.57%)		
Hazard ratio (95% CI)			.021*	0.33 (0.13 - 0.84)



Conclusions:

- Excellent safety profile compared to placebo; no statistical difference in total SAEs/AEs between study groups.
- Autologous cBMA improved Amputation Free Survival compared to placebo but not significantly.
  - Statistical power limited by small control population in Rutherford 5 diabetics
  - Actual event rate in control group was 30% vs. predicted 40%
- Post-hoc analyses demonstrate:
  - Significant reduction in major amputation rates in study population when Rutherford 5 diabetics are excluded.