In this abbreviated Statistical Analysis Plan (SAP), we present the tables/figures to be produced for TACTILE. We retain the paragraph numbering from the original SAP.

8.1 Patient Accountability

The number and percentage of randomized and withdrawn patients will be presented by treatment group (Table 14.1.1). The number and percentage of enrolled patients prematurely discontinuing the study will also be presented by treatment group together with the reason for withdrawal. Patient accountability will also be presented by site stratified by treatment group (Table 14.1.2).

8.2 Safety Analyses

Descriptive statistics and appropriate tests will be used to summarize and compare the safety parameters between treatment groups. All safety analyses will be performed on the safety population. Treatment group comparisons will assess the significance of the difference between treatment and control groups.

8.2.1 Adverse Events

Adverse events will be coded according to pre-specified Tactile internal codes. Adverse events will be summarized by severity, outcome, causality and seriousness (i.e., SAE) and stratified by treatment group (Table 14.3.1). For subjects with more than one event, the event with the highest level of severity, outcome or causality, seriousness, respectively, will be reported. The number and percentage of subjects with an event by the internal Tactile AE codes will be compared by treatment group (Tables 14.3.2). Subjects with more than one event by internal Tactile code will be counted only once. All AEs will be listed, sorted by treatment group, subject identification, and date of the AE (Table 16.2.7.1). Data presented will include: causality, severity, seriousness, outcome, verbatim description, internal Tactile codes.

8.2.2 Serious Adverse Events

SAEs will be listed, sorted by treatment group, subject identification, and onset date (Table 16.2.7.2). Data presented will include: causality, severity, seriousness, outcome, verbatim description, internal Tactile codes.

8.2.3 Other Safety Analyses

The following analyses will be carried out on the Safety Populations. ACTitouch® treated subjects will be compared with multi-layer bandaging treated subjects in terms of:

- the difference in the incidence of ulcer-related adverse events (defined as ulcer infections, maceration, allergic reaction to dressing, or hospitalization for worsening VLU) at 16 weeks using the Cochrane-Mantel-Haenszel (CMH) test (Table 14.3.3) .

8.3 Efficacy Analyses

All analyses will be carried out on the ITT population.

8.3.1 Primary Efficacy Analysis

The percentage of each subject's ulcer area reduction at 16 weeks will be assessed using a specialized ulcer camera and ulcer imaging system. Images will be centrally read by a qualified independent adjudicator. The percentage of ulcer area reduction for the ACTitouch® treated subjects will be compared with multi-layer bandaging treated subjects using a linear mixed model analysis of covariance (ANCOVA) with the following covariates: treatment group; duration of VLU ([1,6]; (6,24] months); baseline size of VLU, [1.5,12cm], (12,50cm]; history of diabetes; age. The analysis will be conducted on the ITT population (Table 14.2.3).

8.3.2 Secondary Efficacy Analysis

The following analyses will be carried out on all three analysis populations defined above.:

- ACTitouch® treated subjects will be compared with multi-layer bandaging treated subjects in terms of the difference in changes in HRQOL at 16 weeks assessed by the overall score of the Charing Cross Venous Ulcer Questionnaire using a similar ANCOVA model as used in similar to the Primary Endpoint Analysis. If the primary efficacy analysis was significant, then the difference will be tested at the two-sided α=.05 level – Table 14.2.6.

8.3.3 Exploratory Efficacy Analysis

- To compare the difference in ulcer-free days at 16 weeks between ACTitouch® treated subjects with multi-layer bandaging treated subjects based on non-parametric analysis of covariance using the same covariates -Table 14.2.7.
- To compare the difference in changes in HRQOL at 16 weeks compared to baseline between ACTitouch® treated subjects with multi-layer bandaging treated subjects using the overall score of the VCSS and the same method as the Primary Endpoint Analysis -Table 14.2.10
- To compare the difference in the time-to-100% healed VLU between ACTitouch® treated subjects with multi-layer bandages treated subjects using a Cox Proportional Hazard model with the same covariates as above -Table 14.2.12.
- To compare the cumulative incidence graphs of subjects with 100% percent healed VLU between ACTitouch® treated subjects with multi-layer bandaging treated subjects using Kaplan-Meier product-moment estimates and the log rank rest for differences in survival curves - Figure 1.

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APPENDIX: DATA TABLES

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Table 14.1.1 Patient Disposition

ITT sample

	1.5cm<=size<=12cm				12cm<size<= 50cm			
	1<=age<6 months		1<=age<6 months		6<=age<=24 months		6<=age<= 24 months	
	Treatment (N)	Control (N)	Treatment (N)	Control (N)	Treatment (N)	Control (N)	Treatment (N)	Control (N)
Randomized	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
Safety	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
Completed	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
Discontinued	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
Primary Reason for Discontinuation:								
Adverse Event	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
Protocol Violation	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
Lost to Follow-up	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
Other	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)

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Table 14.1.2 Patient Disposition By Site
ITT sample

	Treatment N(%)[b]	Control N(%)[b]	Total N(%)[b]
xxxx	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
xxxx	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
xxxx	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
xxxx	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)
xxxx	xx/xx(xxx.x%)	xx/xx(xxx.x%)	xx/xx(xxx.x%)

Note: denominator of all percentages is number randomized by group

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Table 14.3.1 Safety Analysis: Summary Incidence of Adverse Events
Safety sample

Condition	Treatment N(%)	Control N(%)	P-value
Safety Analysis Set	xx	xx	
Patients with Adverse Events	xx(xxx.x%)	xx(xxx.x%)	x.xxx
Patients with AEs by Severity[a]			
No Event	xx(xxx.x%)	xx(xxx.x%)	x.xxx
Mild	xx(xxx.x%)	xx(xxx.x%)	
Moderate	xx(xxx.x%)	xx(xxx.x%)	
Severe	xx(xxx.x%)	xx(xxx.x%)	
Patients with AEs by Causality[a]			
Definitely related	xx(xxx.x%)	xx(xxx.x%)	x.xxx
Probably related	xx(xxx.x%)	xx(xxx.x%)	
Possibly related	xx(xxx.x%)	xx(xxx.x%)	
Not related	xx(xxx.x%)	xx(xxx.x%)	
No Event	xx(xxx.x%)	xx(xxx.x%)	
Outcome			
No Event	xx(xxx.x%)	xx(xxx.x%)	x.xxx
Resolved	xx(xxx.x%)	xx(xxx.x%)	
Resolved w/ sequelae	xx(xxx.x%)	xx(xxx.x%)	
Continuing	xx(xxx.x%)	xx(xxx.x%)	
Lost to follow-up	xx(xxx.x%)	xx(xxx.x%)	
Death	xx(xxx.x%)	xx(xxx.x%)	

Condition	Treatment N(%)	Control N(%)	P-value
Patients with SAEs	xx(xxx.x%)	xx(xxx.x%)	x.xxx
Patients Discontinued due to AE	xx(xxx.x%)	xx(xxx.x%)	x.xxx

NOTE: P-value based on Kruskal-Wallis test controlling for stratification. Denominator is the number of patients in the Safety Analysis Set.
[a]Patients experiencing more than one adverse event are counted under the maximum severity experienced across events.

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Table 14.3.2 Safety Analysis: Incidence of Adverse Events by Internal AE Code
Safety sample

Internal AE Code	Treatment N(%)	Control N(%)	p-value[a]
Patients with Adverse Events	xx(xxx.x%)	xx(xxx.x%)	xxxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx
AE_CODE XX	xx(xxx.x%)	xx(xxx.x%)	x.xxx

Note: A patient experiencing multiple incidences of an event with the same internal AE code is counted only once.
[a] P-value calculated from CMH Test.

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Table 16.2.7.1 Listing of Adverse Events
Safety sample

Treatment Group	Patient ID	Onset Date (Study Day)	Stop Date (Study Day)	Internal AE Code	Serious	Duration	Severity	Causality	Outcome
xxxx	xx	ddmmyy (xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy (xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy(xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy(xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy(xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy(xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy(xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy(xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx
xxxx	xx	ddmmyy(xx)	ddmmyy(xx)	xx	xx	xx	xx	xx	xx

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Table 14.3.3 Safety Analysis: Incidence of Ulcer-Related Adverse Events at 16 Weeks

Safety sample

Ulcer-related AE	Treatment N(%)	Control N(%)	p-value[a]
Ulcer infecttions	xx/xx(xxx.x%)	xx/xx(xxx.x%)	x.xxx
Ulcer maceration	xx/xx(xxx.x%)	xx/xx(xxx.x%)	x.xxx
Allergic reactions	xx/xx(xxx.x%)	xx/xx(xxx.x%)	x.xxx
Hospitalization for worsening VLU	xx/xx(xxx.x%)	xx/xx(xxx.x%)	x.xxx
All Ulcer-related AEs	xx/xx(xxx.x%)	xx/xx(xxx.x%)	x.xxx

Note: P-value calculated using the CMH test adjusting for ulcer size and duration (stratification)

Table 14.2.3 Primary Efficacy Analysis: Changes in % Wound Area Reduction
Evaluable Available Case Population

		% Wound Area Reduction at Follow-up		Changes in % Wound Area Reduction from Baseline			
Label	Statistic	Treatment Group (N=122)	Control Group (N=128)	Treatment Group	Control Group	[Treatment - Control] Difference (95% CI)[¥]	P-Value[£]
baseline	N	xx	xx				
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)				
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)				
16 weeks	N	xx	xx	xx	xx		
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x, xx.x)[¥]	x.xxx[£]
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)		

NOTES:[¥] Estimates of mean difference between treatment groups, 95% confidence interval and P-value based on a linear mixed model ANCOVA with the following covariates: treatment group; duration of VLU ([1,6]; (6,24] months); baseline size of VLU, [1.5,12cm], (12,50cm]; history of diabetes; age. [¥] The covariate adjusted one-sided lower bound 97.5% confidence interval of the treatment difference in mean percent ulcer area reduction (calculated as mean of ACTitouch® group minus mean of multi-layer bandaging treated group) is compared to the non-inferiority margin (-.125) . If the lower bound exceeds the margin, the null hypothesis is rejected, and ACTitouch® system is deemed non-inferior to multi-layer bandaging[£].

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Table 14.2.6 Secondary Efficacy Analysis: Changes in Charing Cross Scores at 16 Weeks

Evaluable Available Case Population

		% Wound Area at Follow-up		Changes in % Wound Area from Baseline			
Label	Statistic	Treatment Group (N=122)	Control Group (N=128)	Treatment Group	Control Group	[Treatment - Control] Difference (95% CI)¥	P-Value¥
baseline	N	xx	xx				
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)				
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)				
16 weeks	N	xx	xx	xx	xx		
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x, xx.x)	x.xxx
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)		

Note: ¥Estimates of mean difference between treatment groups, 95% confidence interval and P-value based on linear mixed model ANCOVA with the following covariates: treatment group; duration of VLU ([1,6]; (6,24] months); baseline size of VLU, [1.5,12cm], (12,50cm]; history of diabetes; age.

Table 14.2.7 Exploratory Efficacy Analysis: Ulcer Free Days at 16 Weeks

Evaluable Available Case Population

		% Wound Area at Follow-up		Changes in % Wound Area from Baseline			
Label	Statistic	Treatment Group (N=122)	Control Group (N=128)	Treatment Group	Control Group	[Treatment - Control] Difference (95% CI)¥	P-Value¥
baseline	N	xx	xx				
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)				
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)				
16 weeks	N	xx	xx	xx	xx		
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x, xx.x)	x.xxx
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)		

Note: ¥Estimates of mean difference between treatment groups, 95% confidence interval and P-value based on non-parametric ANCOVA with the following covariates: treatment group; duration of VLU ([1,6]; (6,24] months); baseline size of VLU, [1.5,12cm], (12,50cm]; history of diabetes; age.

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Table 14.2.10 Exploratory Efficacy Analysis: Changes in VCSS at 16 Weeks

Evaluable Available Case Population

		% Wound Area at Follow-up		Changes in % Wound Area from Baseline			
Label	Statistic	Treatment Group (N=122)	Control Group (N=128)	Treatment Group	Control Group	[Treatment - Control] Difference (95% CI)[¥]	P-Value[¥]
baseline	N	xx	xx				
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)				
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)				
16 weeks	N	xx	xx	xx	xx		
	Mean(SD)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x, xx.x)	x.xxx
	Median(Min,Max)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)	xx(xx,xx)		

Note: [¥]Estimates of mean difference between treatment groups, 95% confidence interval and P-value based on ANCOVA with the following covariates: treatment group; duration of VLU ([1,6]; (6,24] months); baseline size of VLU, [1.5,12cm], (12,50cm]; history of diabetes; age.

Table 14.2.11. Exploratory Analysis: Cox PH Analysis of the Time to 100% Healed VLU

Variable	Hazard Rate	95% Confidence Interval Hazard Rate	P-value
Treatment Group	x.xxx	(x.xxx, x.xxx)	x.xxx
Ulcer Size	x.xxx	(x.xxx, x.xxx)	x.xxx
Ulcer Duration	x.xxx	(x.xxx, x.xxx)	x.xxx
Diabetes	x.xxx	(x.xxx, x.xxx)	x.xxx
Age	x.xxx	(x.xxx, x.xxx)	x.xxx