Observational Study of the GORE® TAG® Thoracic Endoprosthesis in the treatment of diseases of the thoracic aorta

Protocol number: FPR 12-03

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W. L. Gore & Associates, Inc.
Medical Products Division

[redacted]

STATISTICAL ANALYSIS PLAN

Gore-TAG_SAP_V2.2

Sponsor: W.L. GORE & ASSOCIATE

Device: GORE TAG

Protocol Nr: FRP 1203

[redacted]

Observational Study of the GORE® TAG® Thoracic Endoprosthesis in the treatment of diseases of the thoracic aorta

Statistical Analysis Plan

Versions	Date	Documents used / Comments	Author	Validation
Version 2.2	24/02/2017	- Gore-TAG_SAP_V2.1 (secondary procedures = re-interventions)	[redacted]	[redacted]
Version 2.1	31/03/2016	- Gore-TAG_SAP_V2.0 + Comments from WL Gore following SAR V2.0 review	[redacted]	[redacted]
Version 2.0	21/03/2016	- Gore-TAG_SAP_V1.3 + Comments from WL Gore following SAR V1.0 review + Titles/wording updates to be consistent with the English version of the CRF	[redacted]	[redacted]
Version 1.3	01/12/2015	- Gore-TAG_SAP_V1.2 + Comments from WL Gore (30NOV2015) + Call (30NOV2015)	[redacted]	[redacted]
Version 1.2	25/11/2015	- Gore-TAG_SAP_V1.1 + Addition of life-threatening emergency definition	[redacted]	[redacted]
Version 1.1	02/11/2015	- Gore-TAG_SAP_V1.0 + Addition of derived criteria calculation	[redacted]	[redacted]
Version 1.0	22/10/2015	- Gore-TAG_SAP_V0.4 + Comments from WL Gore (06OCT2015) + mails from W L Gore on secondary endpoints (07, 08, 09 and 12OCT2015)	[redacted]	[redacted]

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STATISTICAL ANALYSIS PLAN

Gore-TAG_SAP_V2.2

Sponsor: W.L. GORE & ASSOCIATE

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[redacted]

Versions	Date	Documents used / Comments	Author	Validation
Version 0.4	20/08/2014	- Gore-TAG_SAP_V0.3 + Comments from WL Gore (19AUG2015)	[redacted]	[redacted]
Version 0.3	13/08/2015	- Gore-TAG_SAP_V0.2 + Comments from WL Gore (13AUG2015)	[redacted]	[redacted]
Version 0.2	17/07/2015	- Gore-TAG_SAP_V0.1 + List of tables, graphs and listings + Layout of table	[redacted]	[redacted]
Version 0.1	08/07/2015	- PROT 14-10-03 FPR 12-03 FR final EN-US - Annotated CRF	[redacted]	[redacted]

SIGNATURE PAGE

OBSERVATIONAL STUDY OF THE GORE® TAG® THORACIC ENDOPROSTHESIS IN THE TREATMENT OF DISEASES OF THE THORACIC AORTA

Version 2.2

W.L. GORE & ASSOCIÉS

Name	Position	Date	Signature
Abe Letter	Clinical Biostatistician	27-FEB-2017	
Alexandre Figard	Clinical Study Manager	27-FEB-2017	

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CT-scan	Computed Tomography scan
FUP	Follow-up
LPPR	Liste des Produits et Prestations Remboursables (List of Reimbursable Products and Services)
MRI	Magnetic resonance imaging
SAP	Statistical Analysis Plan

1. OVERVIEW

This statistical analysis plan (SAP) describes the planned statistical analyses of the data collected in the course of the observational study of the GORE® TAG® thoracic endoprosthesis in the treatment of diseases of the thoracic aorta.

This SAP provides additional details concerning the statistical analyses outlined in the protocol (version dated 21SEP2015). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data.

1.1. Study Objective

The objective of this study is to evaluate the usefulness of the technique in terms of efficacy and safety of use of the GORE® TAG® and Conformable GORE® TAG® thoracic endoprosthesis at 5 years, on a cohort of patients representative of the population treated in real life conditions.

1.2. Study Design

This study is an observational, prospective, multicenter, non-randomized, single-arm and open-label which 160 patients will be enrolled from approximately 30 investigational French sites.

1.3. Study Plan

[redacted]

1.3.2. Study duration

The duration of the study will be determined by the duration of recruiting 160 consecutive patients within 30 potential investigation centers.

- Enrollment period for the 160 patients: 24 months
- Follow-up period for each patient: 5 years
- Total duration of the study: 7 years (84 months)

1.3.3. Study Device

The study devices are the GORE® TAG® and Conformable GORE® TAG® thoracic endoprosthesis including any newer models [redacted]

1.3.4. Study Assessments

The following flowchart applies to the study:

Data	CRF Pré-op.	CRF Treat-ment	CRF Post-op.	CRF Follow-up	CRF AE	CRF Re-intervention	CRF Study Exit
Consent	X						
Eligibility criteria	X						
Imaging tests	X		X	X			
Clinical history	X						
Assessment of disease(s) and diagnosis(es)	X						
Implantation		X					
Information on the device used		X					
Post-operative assessment			X				
Post-operative follow-up at D1-D30, 1, 2, 3, 4 and 5 years				X			
Onset of complications		X	X	X	X		
Repeat vascular intervention						X	
Surgical conversion						X	X
Lost to follow-up							X
Death					X		X

2. STATISTICAL METHODS

2.1. General Statistical Considerations

2.1.1. Descriptive Statistics in Summary Tables

- *Continuous variables* will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations will also be specified.
- *Categorical variables* will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Percentages will be calculated on the number of non-missing observations and will be displayed using one decimal, the corresponding bilateral 95% CI will be presented if appropriate. The number of missing observations will also be specified.

2.1.2. Inferential Analysis

Differences between groups in survival analysis will be addressed by the log-rank test.

2.1.3. Handling Missing Data

No replacement of missing data is planned.

If a patient interrupts the study before the end of study, he/she will be considered as missing from his/her last follow-up.

Patients will be considered as censored at the date of the last observation in survival analyses.

2.1.4. Data Listings

Patient data listings will be selected data supportive of summary statistical tables, including derived/calculated data from statistical process. These key data listings will be performed on selected analysis sets according to the focus of the listings.

[redacted]

2.3. Analysis Sets

2.3.1. Definition of patient populations

2 populations will be defined:

- The "included" population will include all patients enrolled in the study.
- The Per Protocol (PP) population will include all "included" patients for whom the GORE® TAG® and Conformable GORE® TAG® thoracic endoprosthesis were introduced through surgical or percutaneous approach, and who fulfill the eligibility criteria.

2.4. Statistical Analyses

All analyses will be conducted on the PP population.

The "included" populations defined in section 2.3.1 will only be used to list the patients who do not fulfill the eligibility criteria.

2.4.1. Patient Disposition

The following items will be presented:

- The number of included and PP patients (globally and by center) as well as a listing of non-included patients and patients excluded from the PP population
- A study flowchart table will be presented on the PP population and the reasons of interruption will be specified.
- Study duration:
  - The total study duration (between procedure and study exit) will be presented globally.
  - The study follow-up duration (between procedure and the last available follow-up) will also be presented in intermediary report(s).

2.4.2. Patient Characteristics

Descriptive statistical data will be used to draw up a recapitulation of PP patients at baseline, procedure and follow-up.

2.4.2.1. Baseline

- Demographics
- Medical condition (Medical history / risks factors, patient symptoms)
- Patient participation in another W.L. Gore study
- Life-threatening emergency
- Main indication for implantation
- Dissections and trauma patients characteristics
- Procedure planning

2.4.2.2. Procedure

- Implantation parameters
- Procedure evaluation and results
- Device used
- Imaging abnormalities
- Time spent in ICU

2.4.2.3. Follow-up

The following items will be presented at each visit:

- Measurements and dissections characteristics
- Imaging abnormalities

2.4.3. Endpoints Analyses

2.4.3.1. Primary Analysis

The primary endpoint is the all-cause mortality rate over the long term, which is 5 years.

The 5-year mortality is defined for all deaths occurring between the time of surgery when the endoprosthesis was inserted into the arterial access and the last follow-up visit at 5 years.

It will be presented as a categorical variable (with the corresponding 95% bilateral CI), overall and by visit, and described over time by a survival curve as per the Kaplan-Meier method together with the associated estimators.

The primary endpoint will also be analyzed depending on the life-threatening emergency and by main indication for implant (aneurysm, dissection, ulcer and trauma).

2.4.3.2. Secondary Analyses

The secondary endpoints for assessing the usefulness of the technique will be:

- The exclusion rate of the aneurysm, the false lumen, the penetrating aortic ulcer or rupture site, with no type I or III endoleak (overall and by main indication for implantation)

It will be presented as categorical variables (with the corresponding 95% bilateral CI) by time-point, starting at 30 days.

- The rate of neurological complications
- The rate of cardiac, renal and pulmonary complications
- The rate of device-related complications
- The rate of surgical conversion
- The rate of secondary procedures (re-interventions)
- The rate of mortality related to the disease

They will be presented as categorical variables (with the corresponding 95% bilateral CI) by time-point and described over time by a survival curve as per the Kaplan-Meier method together with the associated estimators.

2.4.4. Safety Analyses

The safety will also be assessed by the analysis of secondary procedures and adverse events.

2.4.4.1. Secondary procedures

- Secondary procedure rate and reasons
- Endovascular/surgical treatment details
- Imaging abnormalities

2.4.4.2. Adverse events

The adverse events analysis will present the number of event of each following category, the number of patients with at least one event of each category and the corresponding percentage:

- Adverse events (overall, serious, device-related and procedure-related)
- Reasons of SAE seriousness.

2.5. Derived Criteria Calculation

- A patient will be considered as fulfilling the eligibility criteria if:
  - Inclusion criterion 1 is ticked YES
  - Inclusion criterion 2 is ticked YES or date of informed consent is filled
  - Inclusion criterion 3 is ticked YES
  - Exclusion criterion 1 is ticked NO
  - Exclusion criterion 2 is ticked NO
- Total study duration will be calculated as:
  Total study duration = study exit date - procedure date +1
  If the procedure date is not available, the baseline date will be used instead.
- Study follow-up duration will be calculated as:
  Study follow-up duration = last FUP date available - procedure date +1
  If the procedure date is not available, the baseline will be used instead.
  If the visit date is not available, the corresponding last imaging date will be used instead.
- Body Mass Index will be calculated as:
  BMI = weight (kg) / (height (m))²
- Derived criterion "life-threatening emergency" will be derived as follows:
  - if vital urgency specify is "Aortic rupture" then life-threatening emergency will be "Yes: Aortic rupture"
  - else if vital urgency specify is "Dissection complicated by malperfusion" then life-threatening emergency will be "Yes: Dissection complicated by malperfusion"
  - else if vital urgency specify is "Other" then life-threatening emergency will be "Yes: Other"
  - else if vital urgency is "No" then life-threatening emergency will be "No"
- Derived criterion "procedure duration" will be calculated as follows:
  Procedure duration = procedure end time – procedure start time
- Derived criterion "exclusion of the aneurysm without endoleak" will be defined as follows:
  No maximum diameter of the aneurysm sac increase > 5 mm (compared to 1st post-op exam) and no type I or type III endoleak

- Derived criterion "exclusion of the false lumen without endoleak" will be defined as follows:

  "Exclusion of the main entry of the dissection" will be YES if:
  - no false lumen perfusion type Ia, Ib, III is ticked
  - and "Incorrect Deployment" is not ticked or "false lumen perfusion through a tear proximal to the device in an untreated segment (not an endoleak)" is not ticked
  - and "Status of false lumen located opposite the treated part of the aorta" is "Complete thrombosis"

  If the perfusion status is unknown or if the false lumen thrombosis status is unknown then "exclusion of the false lumen without endoleak" will be missing.
- Derived criterion "exclusion of the penetrating aortic ulcer without endoleak" will be defined as follows:

  No maximum aortic diameter of the ulcer increase > 5 mm (compared to 1st post-op exam) and no type I or type III endoleak
- Derived criterion "exclusion of the rupture site without endoleak" will be defined as follows:

  No type I or type III endoleak
- Mortality from thoracic disease is defined as any death occurring as a result of complication of aortic disease (rupture, conversion, etc.) or following any surgery intended to treat the aortic disease. It will be derived as follows:
  - If the death occurs within 30 days after the initial procedure or any re-intervention or
  - If the death is related to the disease

  Then mortality from thoracic disease will be "YES"
- An adverse event (or any other parameter that is not reported in a follow-up CRF) will be considered as having occurred
  - "at 1 month" if it occurs between the procedure (included) and 30 days after the procedure
  - "at 1 year" if it occurs between the procedure (included) and 365 days after the procedure
  - "at 2 year" if it occurs between the procedure (included) and 731 days after the procedure
  - "at 3 year" if it occurs between the procedure (included) and 1096 days after the procedure
  - "at 4 year" if it occurs between the procedure (included) and 1461 days after the procedure
  - "at 5 year" if it occurs between the procedure (included) and 1826 days after the procedure

3. STATISTICAL SOFTWARE

All statistical outputs (summary tables, data listings and graphs) will be generated using SAS® version 9.4 or later.

4. STATISTICAL TABLES, GRAPHS AND LISTINGS (TABLE OF CONTENTS)

4.1. Statistical Tables

Patient Disposition

Table 1: Number of PP patients overall and by site (Type 4)

Table 2: Study flowchart and study exit reasons (Type 6)

Table 3: Study durations (days) (Type 1)

Patient Characteristics

Baseline

Table 4: Age at surgery (years) (Type 1)

Table 5: Sex (Type 3)

Procedure

Follow-up

Endpoints Analyses

Primary Analysis

Secondary Analyses

Safety

Secondary procedures

Adverse events

4.2. Graphs

4.3. Listings

Patient Disposition

Listing 1: Reasons of non-inclusion in the study or exclusion from PP population
Listing 2: Patient follow-up, study durations and reasons of study exit and

Patient Characteristics

Baseline

Listing 3: Demographics
Listing 4: Medical history / risks factors
Listing 5: Patient symptoms related to the disease at hospitalization time
Listing 6: Patient participation in another W.L. Gore study
Listing 7: Life-threatening emergency and main indication for implantation
Listing 8: Initial evaluation characteristics for dissection patients
Listing 9: Injury severity of trauma patients
Listing 10: Procedure planning

Procedure

Listing 11: Implantation parameters
Listing 12: Devices used details
Listing 13: Successful deployment of endoprosthesis, failure details and additional procedure(s) conducted before/during the endovascular surgery
Listing 14: Imaging abnormalities observed following the procedure
Listing 15: False lumen perfusion following treatment for dissection
Listing 16: Persistent endoleak details following the procedure
Listing 17: Migrations details (deployment inaccuracy) identified following the procedure

Follow-up

Listing 18: Measurements and dissection characteristics – by visit
Listing 19: Imaging abnormalities observed – by visit
Listing 20: Dissection false lumen perfusion characteristics – by visit
Listing 21: Endoleak details – by visit
Listing 22: Migrations details – by visit

Endpoints Analyses

Listing 23: Primary and secondary endpoints

Safety

Listing 24: Secondary procedures
Listing 25: Adverse events

5. LAYOUT OF THE STATISTICAL TABLES

5.1. Continuous variables

5.1.1. No group (Type 1)

Variable	N	Missing	Mean	S.D.	Median	Min, Max	Q1-Q3	95% CI*
Variable label	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	[XX,X ; XX,X]

*If needed

5.1.1. With groups (Type 2)

Variable	Group label	N	Missing	Mean	S.D.	Median	Min, Max	Q1-Q3	95% CI*
Variable label	Group 1	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	[XX,X ; XX,X]
	Group 2	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	[XX,X ; XX,X]
	...	...	...	...	...	...	...	...	...
	Group g	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	[XX,X ; XX,X]
	Total*	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	[XX,X ; XX,X]

*If needed

5.2. Categorical variables

5.2.1. No group (Type 3)

		Population (N=XX)
Variable label	N	XX
	Variable 1	XX (XX.X%)
	95% CI (Variable 1)*	[XX.X% - XX.X%]
	Variable 2	XX (XX.X%)
	95% CI (Variable 2)*	[XX.X% - XX.X%]
	...	...
	Variable n	XX (XX.X%)
	95% CI (Variable n)*	[XX.X% - XX.X%]
	Missing	XX

*If needed

5.2.2. With groups (Type 4)

		Group label				
		Group 1 (N=XX)	Group 2 (N=XX)	....	Group n (N=XX)	Total* (N=XX)
Variable label	N	XX	XX	...	XX	XX
	Variable 1	XX (XX.X%)	XX (XX.X%)	...	XX (XX.X%)	XX (XX.X%)
	95% CI (Variable 1)*	[XX.X% - XX.X%]	[XX.X% - XX.X%]	...	[XX.X% - XX.X%]	[XX.X% - XX.X%]
	Variable 2	XX (XX.X%)	XX (XX.X%)	...	XX (XX.X%)	XX (XX.X%)
	95% CI (Variable 2)*	[XX.X% - XX.X%]	[XX.X% - XX.X%]	...	[XX.X% - XX.X%]	[XX.X% - XX.X%]
	...	...	...	...	...	...
	Variable n	XX (XX.X%)	XX (XX.X%)	...	XX (XX.X%)	XX (XX.X%)
	95% CI (Variable n)*	[XX.X% - XX.X%]	[XX.X% - XX.X%]	...	[XX.X% - XX.X%]	[XX.X% - XX.X%]

		Group label				
		Group 1 (N=XX)	Group 2 (N=XX)	....	Group n (N=XX)	Total* (N=XX)
	Missing	XX	XX	...	XX	XX

*If needed

5.3. Others

5.3.1. Several variables or variables with more than one modality by patient (Type 5)

Variable 1 / Variable 2	Population (N=XX)	95% CI
Variable 1 modality 1	XX (XX.X%)	[XX.X% - XX.X%]
Variable 1 modality 2	XX (XX.X%)	[XX.X% - XX.X%]
...	...	...
Variable 1 modality n	XX (XX.X%)	[XX.X% - XX.X%]

(sum of all modality ≥ total number of patient)
*If needed

5.3.2. Conditional variables (Type 6)

Variable 1 / Variable 2	Population (N=XX)	95% CI*
Variable 1 modality 1	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 1	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 2	XX (XX.X%)	XX (XX.X%)
...	...	...
Variable 2 modality n	XX (XX.X%)	XX (XX.X%)
Variable 1 modality 2	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 1	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 2	XX (XX.X%)	XX (XX.X%)
...	...	...
Variable 2 modality n	XX (XX.X%)	XX (XX.X%)
...	...	...
Variable 1 modality n	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 1	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 2	XX (XX.X%)	XX (XX.X%)
...	...	...
Variable 2 modality n	XX (XX.X%)	XX (XX.X%)

*If needed

5.3.1. Conditional variables with groups (Type 7)

Variable 1 / Variable 2	Group 1 (N=XX)	95% CI* (Group 1)	Group 2 (N=XX)	95% CI* (Group 2)	...	Group n (N=XX)	95% CI* (Group n)
Variable 1 modality 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	...	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	...	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	...	XX (XX.X%)	XX (XX.X%)
...	...	...	...	...	...	...	...

Variable 1 / Variable 2	Group 1 (N=XX)	95% CI* (Group 1)	Group 2 (N=XX)	95% CI* (Group 2)	…	Group n (N=XX)	95% CI* (Group n)
Variable 2 modality n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
Variable 1 modality 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
…	…	…	…	…	…	…	…
Variable 2 modality n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
…	…	…	…	…	…	…	…
Variable 1 modality n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
Variable 2 modality 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)
…	…	…	…	…	…	…	…
Variable 2 modality n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	…	XX (XX.X%)	XX (XX.X%)

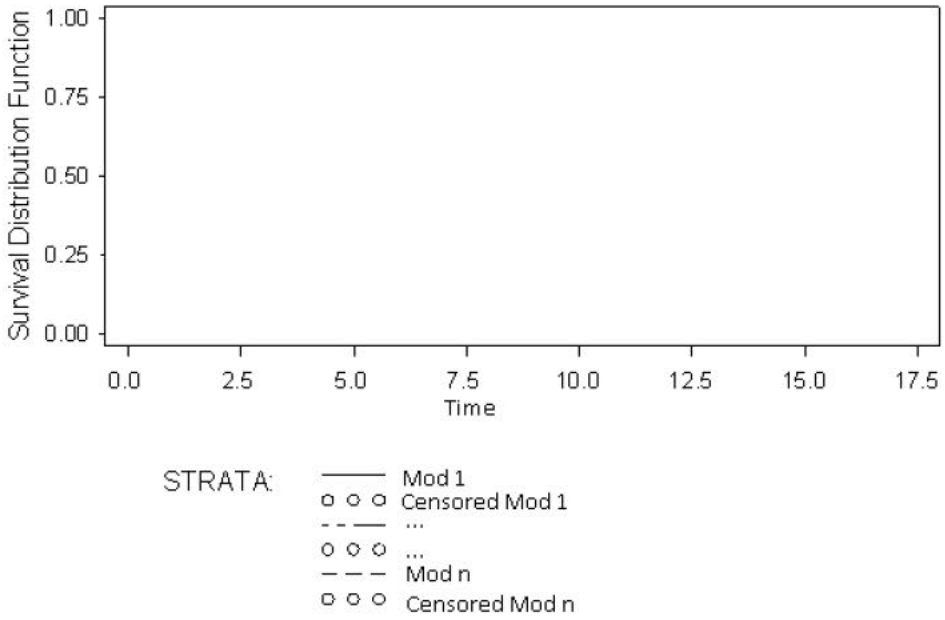
*If needed

5.3.1. Adverse events (Type 8)

	Population (N=XX)		
Adverse events	NAE (1)	n (2)	% (3)
ALL	XX	XX	XX.X
Type 1	XX	XX	XX.X
Type 2	XX	XX	XX.X
…	…	…	…
Type n	XX	XX	XX.X

(1): Number of adverse events/medication of a given type of adverse event/medication
(2): Number of patients with at least one adverse event of a given type of adverse event
(3): (n / N)*100 (N: total number of patients)

5.3.2. Survival curve (Type 9)



Summary table

	Mod 1 (n=X)	...*	Mod n* (n=X)	Log-Rank test
Nb of patients	X	...	X	
Nb of patients with an event	XX (XX.X%)	...	XX (XX.X%)	0.xxx
Nb of patients without an event	XX (XX.X%)	...	XX (XX.X%)	
Survival rate	XX%	...	XX%	
Progression-Free survival (days)		...		
Median	XX	...	XX	
(95% CI)	(XX.X, XX.X)	...	(XX.X, XX.X)	
25th-75th percentile	XX.X – XX.X	...	XX.X – XX.X	
Range	XX.X – XX.X	...	XX.X – XX.X	

* If any