Statistical Analysis Plan

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<Protocol number>
RICH-ART
Radiation Induced Cytitis treated with Hyperbaric oxygen – A Randomized Controlled Trial

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Revisions

Version	Description of Changes	Date
1.0	Fist version	2018-04-03
1.1	Review	2018-05-02
1.2	Final version	2018-05-14

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event (Appendix B)
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
HBO	Hyperbaric oxygen
HBOT	Hyperbaric oxygen therapy
IC	Informed Consent
ICH	International Conference on Harmonisation
ISF OAE	Investigator Study File Other Significant Adverse Event (Appendix B)
SAE SMF	Serious adverse event (Appendix B) Study Master File
HRQOL	Health-related Quality of Life

1 STUDY DETAILS

1.1 Study Objectives

The primary objective of this study is to assess the relief of symptoms after HBO therapy in patients with late radiation cystitis by having change in EPIC symptom estimation scale as primary variable.

The secondary objectives for this study are:

To assess health-related quality of life before and after HBO therapy having change SF-36 as the variable

To assess the severity of radiation injury having the RTOG-scale as variable

To investigate the mucosa with respect to functionality by assessment of inflammation activity, quantification of fibrosis, vascular density and the presence of stems cells having histological analysis from biopsies as variable

1.2 Study Design

This is a prospective, randomized, controlled, parallel-group, multicenter study in Sweden, Norway and Denmark to evaluate the effects of hyperbaric oxygen therapy in 80 subjects with symptomatic radio-therapy induced cystitis.

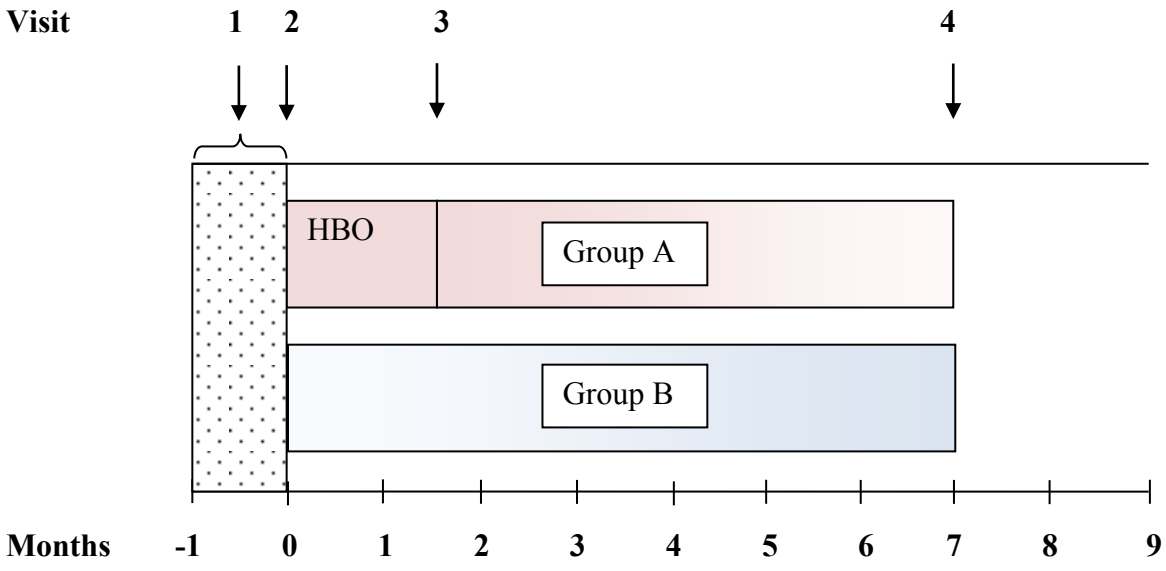

Table 1 Study Activities

Activity	Visit 1		Visit 2	Visit 3	Visit 4
	Screening				
	Within 6 weeks				
Informed consent	X				
Demography	X				
Nicotine	X		X	X	X
Weight, height	X			X[A]	
Medical history and smoking	X				
Pulse, blood pressure	X			X[A]	
Physical examination	X			X[A]	
Blood for laboratory screen	X			X[A]	
Cystoscopy	X				X
Biopsy for histologcal analysis	X				X
Incl/excl criteria	X				
Randomisation	X				
HBO treatment			**X[A]**		**X[B]**
EPIC	X			X[A]	X
SF36	X			X[A]	X
Concomitant medication	X		X[A]	X[A]	X
HBO side effects				X[A]	
SAE	X		X[A]	X[A]	X

X[A] = Group A only X[B] = Group B only

1.3 Treatment Groups

Group A (intervention) has received 30-40 treatments of HBOT in a mono- or multi-place chamber with 100% O2 at 2.4-2.5 ATA, 80-90 minutes each time. Group B (control group) has not received any treatment during the study period. Group A and B are otherwise following the same protocol.

1.4 Sample Size

Using available data from a few similar methodological studies assuming that the symptom reduction has a standard deviation of 23 units and that the expected reduction in urinary EPIC exceeds that of control group by 15 points a parallel group design with 40 patients in each treatment group would have a power exceeding 80% for detecting a statistically difference between the study groups in EPIC (using a two-sample t-test with a 5% significance level). $N=2x(PIxSD/CL)^2$; $N=2x(2,8x23/15)^2$; N=37. In order to have a safety margin, N is rounded up to 40.

2 STUDY POPULATIONS

2.1 Definition of Study Populations

2.1.1 Intent-to-Treat Population (Full Analysis Set)

All randomized subjects will be included in the Intent-to-Treat (ITT) population.

2.1.2 Per-Protocol Population

All randomized subjects with no major protocol violations will be included in the Per Protocol (PP) population. The final decisions regarding the PP population will be taken at the Clean File meeting before the database lock.

2.1.3 Safety Population

All enrolled subjects who received at least one dose of randomised investigational product (IP) will be included in the safety population.

3 STUDY VARIABLES

EPIC and SF-36 are calculated according to their respective instructions. Calculation has been made in the eCRF for the main scale for EPIC and for the main scale and subscale for SF-36. Instructions for calculation of EPIC subscale are included below.

Form "EPIC"
Total EPIC-score is calculated in the eCRF.

EPIC is calculated according to
https://medicine.umich.edu/sites/default/files/content/downloads/Scoring%20Instructions-EPIC.pdf

Likert scale 0-100. Mean value according to following conversion:

EPIC_1, 2, 3, 8, 9:	1=0, 2=25, 3=50, 4=75, 5=100)
EPIC_4:	1=0, 2=33, 3=67, 4=100
EPIC_5:	0=100, 1=67, 2=33, 3=0
EPIC_6a-6f, 7, 14a-14f, 15:	0=100, 1=75, 2=50, 3=25, 4=0
EPIC_10, 11, 12:	1=100, 2=75, 3=50, 4=25, 5=0
EPIC_13:	1=100, 2=50, 3=0

- EPIC Bowel total (EPIC_8 to EPIC_15)
- EPIC Uro Function (EPIC_1 to EPIC_5)
- EPIC Uro Bother (EPIC_6 to EPIC_7)
- EPIC Uro Incontinence (EPIC_1, EPIC_4, EPIC_5, EPIC_6a)
- EPIC Uro Irritable/Obstr (EPIC_2, EPIC_3, EPIC_6a to EPIC_6f)

3.1 Baseline Variables

3.1.1 Demographics and Baseline Characteristics

Age (years)
Gender (m/f)
BMI (kg/m^2)
Smoke (y/n)
Nicotine_use (y/n)

3.1.2 Medical and Surgical History

Intrusive_surgery (y/n)
Type_of _cancer (var)

Cancer_ICD10 (text)
Localization_of_cancer (var)
Chemoterapy (y/n)
Brachyterapy (y/n)
Brachy_energy (##)
Brachy_start (time from start to inclusion)
Exrad_energy (##)
Exrad_start (time from start to inclusion)
Surg_pre_rad (y/n)
Surg_port_rad (y/n)
Debute_y (year from debute to inclusion)
Debute_m (month from debute to inclusion)
Other_disease (y/n)
Other_surg (y/n)

3.1.3 Prior and Concomitant Medications

Prior medication: Table “Medications_on_entry” coded according to ATC
Concomitant medication: Form “Medication during study”, Table “Medications” ATC-code, start_date, stop_date, Reason_for_therapy.

Medication_entry (y/n)

3.2 Efficacy Variables

3.2.1 Primary Efficacy Variable

Absolute change in mean **EPIC Urinary total score** from baseline to visit 4.
- EPIC Urinary total (EPIC_1 to EPIC_7)

3.2.2 Secondary Efficacy Variables

- Relative change in mean **EPIC Urinary total score** from baseline to visit 4.
- EPIC Urinary total (EPIC_1 to EPIC_7)

- Absolute change in **EPIC-subscales** (listed below) from baseline to visit 4 between group A and B
- EPIC Bowel total (EPIC_8 to EPIC_15)
- EPIC Uro Function (EPIC_1 to EPIC_5)
- EPIC Uro Bother (EPIC_6 to EPIC_7)
- EPIC Uro Incontinence (EPIC_1, EPIC_4, EPIC_5, EPIC_6a)
- EPIC Uro Irritable/Obstr (EPIC_2, EPIC_3, EPIC_6a to EPIC_6f)

- Absolute change in **SF-36** (listed below) from baseline to visit 4 between group A and B.

- GH - General Health (GHScore)
- PF - Physical functioning (PFScore)
- RP - Role limitations due to physical health (RPScore)
- RE - Role limitations due to emotional problems (REScore)
- VT - Energy/fatigue (VTScore)
- MH - Emotional well-being (MHScore)
- SF - Social functioning (SFScore)
- BP - Pain (BPScore)

3.2.3 Exploratory Efficacy Variables

- Absolute change in Severity of radiation-injury in bladder **(RTOG)** from baseline to visit 4 between group A and B

3.3 Safety Variables

3.3.1 Exposure of Study Drug

Form Administration of HBO
Exposure: Number of HBO treatments according to protocol (90 min +/- 5 min, ≥2,4 ATA)
Manual variable based on form value "#": HBO_no

Compliance:
Execution of HBO treatments according to protocol (90 min +/- 5 min, ≥2,4 ATA) At least 30 Tx (HBO_no >= 30)

When treatment is administered in hospitals, under the supervision of medical staff, there is no uncertainty about compliance. The HBO administration (pressure, treatment time, any air breaks any other specific conditions) must be recorded in the appropriate sections of the Case Report Forms (CRFs).
The 40 treatments should be given within the framework of 80 days. For longer interruption or discontinuation of treatment, patients should not be regarded as treated according to protocol but monitoring will continue (intention to treat). However, the patient should be considered to be treated as per protocol if at least 30 treatments in the hyperbaric chamber have been given within 60 days.

3.3.2 Adverse Events

Form Adverse Events
While this is a study with a registered product within the terms of the regulatory approval, serious AEs must be collected, registered in the CRFs and an assessment of causality of the SAE should be performed. Also, discontinuations due to AEs will be collected. Non-serious AEs will be collected in the present study only during the HBOT-period.

AE or SAE is defined by variable "Is_SAE" (y/n)
Relationship to TX id defined by variable "Relationship_tx".
Definite, Probably, Possible, Unlikely, Not related, Unknown

3.3.3 Laboratory Measurements

A safety panel of laboratory measurements has been collected.

Clinical Chemistry	Haematology
S/P-Creatinine	B-Haemoglobin (Hb)
S/P -Bilirubin, total	B-Leukocytes, total count (LPC)
S/P -Alkaline phosphatase (ALP)	B-Leukocytes diff.absolute count:
S/P -Alanine aminotransferase (ALAT)	B-Basofila
S/P -Aspartate aminotransferase (ASAT)	B-Eosinof
S/P -Albumin	
S/P -Potassium (K)	B-Lymfocyter
S/P -Sodium (Na)	B-Monocyter
S/P -Glucose	B Neutrofila
S/P – C-Reactive Protein (CRP)	

Urine	
U-Erythrocytes (U-Ery)	
U-Albumin (U-Alb)	
U-Glucose (U-Glu)	
U-pregnancy-test	
U-culture (bacterial)	

Baseline is available for group B. Both baseline and follow up (post treatment) measurements is available for group A. Included time points for analysis of laboratory measurements: Baseline (visit 1) for both group A and B and visit 3 for group A.

Mean values and comparison between baseline and follow up for each analysis will be made for group A. Comparison between baseline values for group A and B will also be made.

Assessment of individual measurements in relation to reference values will be made manually and presented as part of the safety assessment of the treatment.

4 STATISTICAL METHODOLOGY

4.1 General Methodology

The main analyses will be performed on the ITT population and complementary analyses on the PP-population.
Primary efficacy variable will be analysed with two-sample T-test between the two randomised groups.
For comparison of the two randomised groups Fisher's nonparametric permutation test will be used for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables and Fisher's exact test for dichotomous variables.
When possible 95% confidence intervals for the difference between the two groups will be calculated.
All the main analysis will be unadjusted. If clinical relevant statistical differences are found in baseline variables between the two randomised groups complementary analyses adjusted for these variables will be performed.
For continuous outcome variables adjustment will be done by analysis of covariance and for dichotomous outcome variables by multivariable logistic regression.

For analysing change over time within each group Fisher's non-parametric permutation test for paired observation will be used for continuous variables and Sign test for ordered categorical variables.

The distribution of variables will be given as mean, standard deviation, median, minimum and maximum for categorical variables as numbers and percentages.
All results will be presented in tables and selected results in figures.

No imputation will be done to replace missing data.
All tests will be two-tailed and conducted at 0.05 significance level. All analyses will be performed by using SAS® v9.2 (Cary, NC).

4.2 Patient Disposition and Data Sets Analysed

The number of subjects included in each of the ITT, PP and safety populations will be summarized for each treatment group and overall. The number and percentage of subjects randomized and treated will be presented. Subjects who completed the study and subjects who withdrew from study prematurely will also be presented with a breakdown of the reasons for withdrawal by treatment group for the ITT, PP and safety populations.

4.3 Protocol Violations/Deviations

Major protocol deviations are those that are considered to have an effect on the analysis. A list of potential major protocol deviations will be generated programmatically from the data captured before the clean file meeting. The clinical monitors of the study will review the list and the finalisation of the major protocol deviations will be done at the clean file meeting.
The number of patients with major protocol deviations will be summarized per treatment group.

4.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for the ITT and PP populations and analysed according to the methods described in section "General Methodology" above.

4.5 Medical and Surgical History

Medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) for each treatment group for ITT population.

4.6 Prior and Concomitant Medications

Prior and concomitant medication will be summarized by higher level anatomical therapeutic classification (ATC) group and generic term for each treatment group for ITT population.

4.7 Efficacy Analyses

4.7.1 Primary Efficacy Analysis

Primary efficacy analysis (EPIC Urinary total score) will be analysed with two-sample two-sided T-test between the two randomised groups on the ITT population at significance level 0.05. 95% confidence intervals for the difference in primary efficacy variable between the two groups will be presented. Figures will be given as Box-plots both by visit and for change from baseline.
A sensitive analysis will be performed on primary efficacy variable between the two groups with Fisher's non-parametric permutation test and with imputation with stochastic imputation.

4.7.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be the analyses of all secondary efficacy variables see section 3.2.2-3.2.3 according the statistical methods given section 4.1 general methodology on both ITT population and on PP-population.
The primary efficacy analysis will be performed on the PP-population.

4.7.3 Subgroup analyses and Interaction analyses

Baseline variables that could influence the relation between the two groups on primary efficacy variable will be included in linear interaction analyses with treatment. For baseline variables with a p-value for interaction with treatment <0.10 further subgroups analyses will be performed

4.8 Safety Analyses

4.8.1 Exposure of Study Drug

Duration of therapy will be summarized for each treatment. Compliance will be summarized for the HBO treatment at visit 3 for group A.
The summaries will be provided for safety population.

4.8.2 Adverse Events

Only treatment-emergent AEs will be included in the summaries for safety population.

A summary of subjects reporting at least one of the following AEs will be presented in an overview table:

- Any AE
- Any SAE

- Any treatment-related AE
- Any treatment-related SAE
- Any AE leading to discontinuation
- Death

Summaries per SOC and PT presenting n (%) of AEs and n (%) of subjects with at least one AE will be provided for:

- All AEs (includes all serious and non-serious AEs)
- All AEs by maximum reported intensity
- All AEs by causality
- All SAEs
- All AEs leading to discontinuation

4.8.3 Laboratory Measurements

Laboratory measurements for clinical chemistry, haematology and urinalysis will be summarized per treatment group for safety population.

5 LISTING OF TABLE, FIGURES AND LISTINGS

5.1 Listing of Tables

Table Number	Table Title
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14.1.3.1	Demographics and Baseline Characteristics (ITT Population)
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14.2.1.1	Primary Efficacy Analysis (ITT Population)
14.2.1.2	Primary Efficacy Analysis (PP Population)
14.2.1.3	Secondary Efficacy Analysis EPIC subscales (ITT Population)
14.2.1.4	Secondary Efficacy Analysis EPIC subscales (PP Population)
14.2.1.5	Secondary Efficacy Analysis SF-36 and subscales (ITT Population)
14.2.1.6	Secondary Efficacy Analysis SF-36 and subscales (PP Population)
14.2.1.7	Exploratory Analysis – RTOG (ITT Population)
14.2.1.8	Exploratory Analysis – RTOG (PP Population)
14.2.1.9	Subgroup analysis and Interaction analysis (PP Population) (if applicable)
14.3.1.1	Duration of Exposure (Safety Population)
14.3.1.2	Compliance (Safety Population)
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14.3.2.3	Adverse Events, by System Organ Class, Preferred Term and Maximum Reported Intensity (Safety Population)
14.3.2.4	Adverse Events, by System Organ Class, Preferred Term and Causality Assessment (Safety Population)

14.3.2.5	Serious Adverse Events, by System Organ Class and Preferred Term (Safety Population)
14.3.3	Adverse Events Leading to Discontinuation, by System Organ Class and Preferred Term (Safety Population)
14.3.4.1	Descriptive Statistics for Laboratory Variables: Haematology (Safety Population)
14.3.4.2	Descriptive Statistics for Laboratory Variables: Clinical Chemistry (Safety Population)
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5.2 Listing of Figures

Table Number	Table Title
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14.3.3	Change in RTOG at baseline and visit 4 for both groups

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16.2.2	Patients with Important Protocol Deviations
16.2.3	Patients Excluded from the Efficacy Analysis
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2	Medical History
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16.2.4.4	Prior and Concomitant Medications
16.2.5	Compliance and Drug Exposure
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16.2.7	Adverse Events
16.2.8	Laboratory Data
16.2.9	Vital Signs Data
16.2.11	Abnormal Physical Examination Data

6 REFERENCES

7 APPENDIX