RGnCON

Pilot clinical investigation evaluating the safety and performance of RGn550 in treating sportspeople suffering from acute concussion syndrome

A prospective, comparative, randomized, simple-blinded, monocentric investigation

STATISTICAL ANALYSIS PLAN

Version 2.0 – 03/08/2022

Written by [redacted]

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1. STATISTICAL ANALYSIS PLAN - APPROVAL FORM

REGENLIFE

Function	Name	Signature	Date
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		

Function	Name	Signature	Date
[redacted]	[redacted]		

2. VERSION HISTORY

Version	Date	Author	Comment / changes
0.1	25/10/2022	[redacted]	Initial draft version (based on protocol version 2.0, dated 11/08/2022)
0.2	08/03/2023	[redacted]	Comments from RGnCON
1.0	05/05/2023	[redacted]	First approved and signed version (based on protocol version 2.0, dated 11/08/2022)
1.1	31/07/2023	[redacted]	Draft version after data review
2.0	03/08/2023	[redacted]	Second approved and signed version (based on protocol version 2.0, dated 11/08/2022)

3. ABBREVIATIONS

List all abbreviations used in the SAP.

Abbreviation	Description
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
eCRF	Electronic case report form
FAS	Full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
MD	Missing data
Q1	First quartile
Q3	Third quartile
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SCR	Screened set
SD	Standard deviation
SOC	System organ class
WHO-DD	World Health Organization drug dictionary

4. PROTOCOL

Please refer to protocol version 2 dated of 11/08/2022 for the overall study design, plan description, study objectives, inclusion and exclusion criteria and sample size calculation.

5. ANALYSIS SETS AND SUBGROUPS

The analysis sets are defined below.

- **Screened set (SCR):** The SCR population consists of all patients who provided a written inform consent.
- **Full Analysis Set (FAS):** All patients of SCR population who have been treated at least once with RGn550 device.

Note : Patients will be analyzed as treated, i.e. according to the device actually used (either RGn550 5Hz or RGn550 10Hz). It is not planned to provide statistical analysis as randomized. If any, potential randomization errors (for example, patients who would be randomized to RGn550 5Hz but received RGn550 10Hz) will be listed.

The following subgroups will also be defined :

- **Measure of the Near Point of Convergence (NPC)** at D0 before treatment : NPC > 5
- **Maddox rod horizontal** at D0 before treatment : Horizontal deviation
- **Maddox rod vertical – Left eye** at D0 before treatment : Vertical deviation
- **Maddox rod vertical – Right** eye at D0 before treatment : Vertical deviation
- **Maddox rod vertical – Both eyes** at D0 before treatment : Vertical deviation on at least one eye.
- **Number of previous concussions** : <3 concussions vs ≥3 concussions

6. ENDPOINTS

6.1. Primary safety endpoint

The primary safety endpoint is the proportion of patients with at least one Adverse Device Event (ADE) after use of RGn550 in acute concussion syndrome, either at a frequency of 5 or 10 Hz.

Primary endpoint will be computed as following:

- Presence of at least one Adverse Device Event ADE (yes / no)

6.2. Secondary endpoints

6.2.1. Secondary safety endpoints

The following secondary safety endpoints will be computed using data recorded in the "Adverse Event (AE)" Form:

- Proportion of patients with at least one mild ADE
- Proportion of patients with at least one moderate ADE
- Proportion of patients with at least one severe ADE
- Proportion of patients with at least one adverse event (AE)
- Proportion of patients with at least one device deficiencies (DDs)

Notes / definitions:

- AEs will be coded using the MedDRA dictionary version 25.0.
- Adverse Device Effects (ADE) are defined as all AEs recorded in the eCRF with a possible, probable or causal relationship to RGn550.
- ADE occurring during the first session (at D0) are defined as all ADE with a start date equal to the date of D0.
- ADE occurring during the second session (at D7) are defined as all ADE with a start date equal to the date of D7.

6.2.2. Secondary performance endpoints

According to section 9.5.4.2 of the Protocol, the following endpoints will be used to address Secondary performance objectives:

- Automated oculomotor and oculopostural functions will be used as recorded in the eCRF, before and after treatment session at D0 and D7 and then at D52:
    - Convergence, evaluated with the measure of the Near Point of Convergence (NPC)
    - Deviations:
        - Cover test
            - Normal fixation of both eyes
            - Abnormal with at least one eye
        - Maddox rod test:
            - Horizontal deviation (yes/no)
            - Vertical deviation right eye (yes/no)
            - Vertical deviation left eye (yes/no)
- Balance function will be used as recorded in the eCRF, before and after treatment session at D0 and D7 and then at D52:
    - Patient's eyes opened

- Statokinesigram area (mm²)
- Left distribution (%)
- Right distribution (%)

- Patient's eyes closed
  - Statokinesigram area (mm²)
  - Left distribution (%)
  - Right distribution (%)
- Rombert quotient (RQ)

The Romberg quotient is the ratio between the statokinesigram area (mm2) with closed eyes (CE) and the statokinesigram area (mm2) with opened eyes (OE), it will be calculated as follow :

RQ = CE/OE.

- Statokinetic distribution index (SKDI)

The stato-kinetic distribution index (SKDI) is the result of the STGK area multiply by the ratio of support distribution it will be calculated as follow:

SKDI (mm2) = STKG area (mm2) x (D/d*)
*D : Highest distribution value (%)
d : Lowest distribution value (%)

- TMT A&B before treatment session at D0 and after treatment session at D7:
  - TMT – A
    - Time to perform the task will be derived as:

      Time to perform the task (in second) = minutes * 60 + second.

    - Number of errors (will be used as recorded in the eCRF)
  - TMT –B
    - Time to perform the task will be derived as:

      Time to perform the task (in second) = minutes * 60 + second.

    - Number of errors (will be used as recorded in the eCRF)
  - TMT – B - A
    - Time to perform the task will be derived as:

      Time to perform the task (in second) = Time to perform the task B - Time to perform the task A

    - Number of errors will be derived as:

      Number of errors = Number of errors B - Number of errors A

- Concussion syndrome symptoms (SCAT5) will be used as recorded in the eCRF at D0 before treatment, D7 before treatment, D14 and D52
  - Symptom severity score
  - The total number of symptoms
- Blood markers at D0 before treatment to D52 will be used as recorded in the eCRF
  - Anti-inflammatory cytokines InterLeukin (IL)-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11 and IL-13
  - S100 calcium binding protein B (S100B)

- Glial Fibrillary Acidic Protein (GFAP)
- Ubiquitin C-terminal Hydrolase-L1 (UCH-L1).

6.3. Other endpoints and variables

6.3.1. Demographic data and other baseline characteristics

The following standard characteristics (gender, Practiced sport leading to investigation concussion, etc.) will be used as recorded in the eCRF:

- Demographic and clinical data
- Concussion History

In addition, the following endpoints will be derived:

- Age (years) = (date of informed consent – date of birth) / 365.25
- BMI (kg/m²) = weight/ height²
- Time since concussion (days) = date of informed consent – date of investigation concussion
- Duration of previous concussion (days) = Recovery date - Onset date

6.3.2. Concomitant therapies

Concomitant therapies will be coded with WHO-DD version B3 Sept 2019.

7. DATA ANALYSIS CONSIDERATIONS

7.1. Statistical software

The statistical analysis will be performed using SAS® VIYA v9.4 (or a more recent version).

7.2. Type I error, handling of multiplicity issues and alpha adjustement procedures

The global significance level (type I error rate) is set to $\alpha = 0.05$. No adjustment of alpha level will be done.

7.3. Centre effect and pooling of centres

This section is not applicable because there is only one center in this trial.

7.4. Descriptive analyses of quantitative and qualitative variables

Quantitative variables will be described by: N (number of patients with non-missing data), mean, standard deviation (SD), minimum, maximum, median, first quartile (Q1) and third quartile (Q3).

Categorical variables will be described by frequency and percentage of patients in each category. Percentages will be expressed with one decimal place.

7.5. Handling of missing data and outliers

Handling of missing AE attributes:

AEs with missing relationship, missing seriousness, and/or missing severity will be considered as related to study drug, serious, and severe for the analysis, respectively.

Onset date of AE will be imputed as below. The objective is to maximize the probability the AE is considered as treatment emergent.

Onset date of AE	Imputed AE onset date
Completely missing	Date of first treatment sessions with RGn550
Day is missing	First day of the month. If imputed date is prior to first treatment sessions with RGn550, then replace with date of first treatment sessions with RGn550.
Day and month are missing	First of January. If imputed date is prior to first treatment sessions with RGn550, then replace with date of first treatment sessions with RGn550.

End date of AE will not be imputed.

Handling of completely or partially missing dates:

For the date of birth, we collect only the month and year, the day of birth will be replaced by the 1st day of the month.

For completely missing dates of performed visits:

- If D0 date is missing, then replace with date of first treatment sessions with RGn550.

- If D7 date is missing, then replace with date of first treatment sessions with RGn550 + 7.
- If D52 date is missing, then replace with date of first treatment sessions with RGn550 + 52.

Other missing data will not be replaced.

8. PLANNED STATISTICAL ANALYSES

Please note that templates presented in this section are only examples. The final statistical outputs that will be provided may be slightly different (in terms of style, font size, column size, etc.). These templates have been designed using labels of variables from blank CRF. Label of variables in final statistical outputs may be slightly different from those presented here.

8.1. Disposition of patients

The following will be provided by randomization arm and overall:

- Number of screened patients
- Number of eligible patients (patients who met all inclusion criteria and no exclusion criteria)
- Number of treated patients
- Among treated patients:
    - Number of patients who completed the Investigation
    - Number of patients who Withdrew
    - Number and percentage of patients who performed each visit

The following template will be used.

	All **N=XX**
Patients screened	XX (100.0%)
Patients eligible	XX (XX.X%)
Patients treated	XX (XX.X%)
Among patients treated:	
Patients who completed the Investigation	XX (XX.X%)
Patients who Withdrew	XX (XX.X%)
Reason (s) for Withdrawal:	
Consent Withdrawal	XX (XX.X%)
Adverse Event	XX (XX.X%)
Clinical Investigation Plan Deviation	XX (XX.X%)
Lost to Follow-up	XX (XX.X%)
Death	XX (XX.X%)
Other	XX (XX.X%)

In addition, the following data will be provided:

- Date of first patient randomized
- Date of last patient randomized
- Date of last patient out (i.e. last visit performed)
- Study duration (days) = date of last patient last visit - date of first patient randomized

8.2. Analysis sets

Frequency and percentage of patients included in each analysis sets defined in Section 5 will be provided.

	Total N=XX
Population SCR [n (%)]	XX (100.0%)
Population FAS [n (%)]	XX (XX.X%)
Group of treatment	
RGn550 5Hz [n (%)]	XX (XX.X%)
RGn550 10Hz [n (%)]	XX (XX.X%)
Analysis subgroups:	
NPC>5 at D0 before treatment [n (%)]	XX (XX.X%)
Maddox rod horizontal deviation at D0 before treatment [n (%)]	XX (XX.X%)
Maddox rod vertical deviation on left eye at D0 before treatment [n (%)]	XX (XX.X%)
Maddox rod vertical deviation on right eye at D0 before treatment [n (%)]	XX (XX.X%)
Maddox rod vertical: at least one deviation (left and/or right eye) at D0 before treatment [n (%)]	XX (XX.X%)
Number of previous concussions	
< 3 [n (%)]	XX (XX.X%)
≥ 3 [n (%)]	XX (XX.X%)

8.3. Demographic data and baseline characteristics, including medical history and therapies

Descriptive analyses will be provided for all data listed in section 6.3.1, by randomization arm and overall, on the FAS population.

The following templates will be used.

8.3.1. Visit at screening

8.3.1.1. Inclusion criteria

	Total N=xx
Male or female aged at least 18 years old [n (%)]	xx.x (xx.x)
Suffering from a concussion syndrome resulting from a shock that occurred during sport practice less than 72h ago, as confirmed by neurological examination via the Head Injury Assessment - Form 3 (HIA3) tool	xx.x (xx.x)
Affiliated to French social security	xx.x (xx.x)
Who provided a dated and signed informed consent form	xx.x (xx.x)

8.3.1.2. Non-inclusion criteria

<same template as above>

8.3.1.3. Demographic data

	RGn550 5Hz N=xx	RGn550 10Hz N=xx	Total N=xxx
Age (years) <example of continuous data>			
non-missing	xxx	xxx	xxx
mean (sd)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
median	xx.x	xx.x	xx.x
q1;q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
min;max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
missing			
Gender [n (%)] <example of categorical data>			
non-missing	xxx	xxx	xxx
Female	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Male	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
missing			

8.3.1.4. Concomitant therapies by ATC3 and pharmaceutical substance

	Group of treatment								
	RGn550 5Hz N=xx			RGn550 10Hz N=xx			Total N=xx		
ATC3 / Pharmaceutical substance(s)	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat
ANY TREATMENTS	6	6	3.8	12	10	6.3	18	16	5.1
OTHER ANALGESICS AND ANTIPYRETICS	2	2	1.3	7	7	4.4	9	9	2.9
- Metamizole sodium	1	1	0.6	6	6	3.8	7	7	2.2
- Paracetamol	1	1	0.6	1	1	0.6	2	2	0.6
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	3	3	1.9	2	2	1.3	5	5	1.6
- Ibuprofen	3	3	1.9	2	2	1.3	5	5	1.6
ADRENERGICS, INHALANTS	.	.	.	1	1	0.6	1	1	0.3
- Salbutamol	.	.	.	1	1	0.6	1	1	0.3
ANTIHISTAMINES FOR SYSTEMIC USE	1	1	0.6	.	.	.	1	1	0.3
- Cetirizine	1	1	0.6	.	.	.	1	1	0.3
DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE	.	.	.	1	1	0.6	1	1	0.3
- Betamethasone	.	.	.	1	1	0.6	1	1	0.3
PROPULSIVES	.	.	.	1	1	0.6	1	1	0.3

	Group of treatment								
	RGn550 5Hz N=xx			RGn550 10Hz N=xx			Total N=xx		
ATC3 / Pharmaceutical substance(s)	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat	Nb TRT	Nb pat	% pat
- Metoclopramide	.	.	.	1	1	0.6	1	1	0.3

8.4. Safety analysis

8.4.1. Analysis of the primary safety endpoint: proportion of patients with at least one ADE after use of RGn550

The proportion of patients with at least one ADE after use of RGn550 in acute concussion syndrome, either at a frequency of 5 or 10 Hz, will be calculated along with its 95% confidence interval (using exact Clopper-Pearson method). This analysis will be performed on the FAS population, by treatment groups and overall.

The following template will be used.

	RGn550 5Hz N=xx	RGn550 10Hz N=xx	Total N=xx
At least one ADE			
Non-missing	xx	xx	xx
Yes [n (%) 95% CI]	xx (xx.x) xx.x ; xx.x	xx (xx.x) xx.x ; xx.x	xx (xx.x) xx.x ; xx.x
No [n (%) 95% CI]	xx (xx.x) xx.x ; xx.x	xx (xx.x) xx.x ; xx.x	xx (xx.x) xx.x ; xx.x
missing	xx	xx	xx

Note: a lost to follow-up rate of 10% is anticipated. If this rate is higher, an analysis of the primary endpoint using percentage of patient-years will be considered.

Note: at the time of writing this SAP version, a data review has been performed showing that the lost-to-follow-up rate is 0%.

8.4.2. Analysis of the secondary safety endpoints / overall summary of adverse events

For all secondary safety endpoints listed in Section 6.2.1, a descriptive analysis will be provided. Table will summarize the number and percentage of patients experiencing the event and the 95% CI. The same analysis will be performed for SAE and SADE.

All AEs collected in the eCRF will be used for the analysis.

The following template will be used.

	RGn550 5Hz N=xx	RGn550 10Hz N=xx	Total (N=XX)
Secondary safety endpoints:			
At least one AE - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
At least one ADE - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x

	RGn550 5Hz N=xx	RGn550 10Hz N=xx	Total (N=XX)
At least one mild ADE - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
At least one moderate ADE - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
At least one severe ADE - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
At least one DD - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
Other categories of AEs:			
At least one SAE - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
At least one SADE - N (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
95% CI	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x

8.4.3. Adverse events by MedDRA SOC and MedDRA PT

For all AEs, a descriptive analysis will be provided by MedDRA SOC and MedDRA PT, by randomization arm and overall. All AEs collected in the eCRF will be used for the analysis. The following template will be used.

	Group of treatment								
	RGn550 5Hz N=xx			RGn550 10Hz N=xx			Total N=xx		
System Organ Class / Preferred Term	Nb Med Hist	Nb pat	% pat	Nb Med Hist	Nb pat	% pat	Nb Med Hist	Nb pat	% pat
ANY ADVERSE EVENT	13	11	7.0	18	15	9.5	31	26	8.3
Infections and infestations	7	7	4.5	12	10	6.3	19	17	5.4
- Bronchitis	2	2	1.3	4	4	2.5	6	6	1.9
- Gastroenteritis	1	1	0.6	.	.	.	1	1	0.3
- Influenza	1	1	0.6	.	.	.	1	1	0.3
- Laryngitis	1	1	0.6	.	.	.	1	1	0.3
Gastrointestinal disorders	3	3	1.9	.	.	.	3	3	1.0
- Gastrooesophageal reflux disease	2	2	1.3	.	.	.	2	2	0.6
- Inguinal hernia	1	1	0.6	.	.	.	1	1	0.3

8.4.4. Adverse device events by MedDRA SOC and MedDRA PT

For all ADEs, a descriptive analysis will be provided by MedDRA SOC and MedDRA PT, by randomization arm and overall.

For all ADEs occurring during the first session (at D0), a descriptive analysis will be provided by MedDRA SOC and MedDRA PT, by randomization arm and overall.

For all ADEs occurring during the second session (at D7), a descriptive analysis will be provided by MedDRA SOC and MedDRA PT, by randomization arm and overall.

The same template as above (i.e. for Adverse events) will be used.

8.5. Efficacy analysis

8.5.1. Analysis of the secondary performance endpoints

The secondary performance endpoints will be analyzed in the FAS population by treatment groups, excluding data that would be collected after the following intercurrent event: treatment group switch during follow-up.

8.5.1.1. Automated oculomotor and oculopostural functions and balance function

For the evolution of parameters of oculomotor and oculopostural functions and balance function defined in Section 0, the following timepoints will be compared: (D0 after treatment - D0 before treatment, D7 before treatment - D0 before treatment, D7 after treatment - D0 before treatment, and D52 – D0 before treatment). A mixed effect regression model (logistic model for a categorical parameters and a linear model for continuous parameters) will be used with a patient random effect. Group effects (5 Hz vs 10Hz), period effects (D0 before, D0 after, D7 before, D7 after and D52) and the group-by-period interaction will be added as fixed effects. The stratification variable gender (male/female) will be added in the model as covariates.
Note: the stratification variable concussion history within 6 months prior to inclusion (yes/no) will not be added in the model as too few patients had concussion history (cf. data review minutes of 18/07/2023).

The following template will be used for continuous parameters.

	Group of treatment		
Ref = D0 before treatment	**RGn550 5Hz N=xx**	**RGn550 10Hz N=xx**	**Difference**
Endpoint XXX at D0 after treatment			
Adjusted mean	x.xx	x.xx	x.xx
95% CI	x.xx ; x.xx	x.xx ; x.xx	x.xx ; x.xx
p-value	.	.	0.xxx
Endpoint XXX at D7 before treatment			
Adjusted mean	x.xx	x.xx	x.xx
95% CI	x.xx ; x.xx	x.xx ; x.xx	x.xx ; x.xx
p-value	.	.	0.xxx
Endpoint XXX at D7 after treatment			
Adjusted mean	x.xx	x.xx	x.xx
95% CI	x.xx ; x.xx	x.xx ; x.xx	x.xx ; x.xx
p-value	.	.	0.xxx
Endpoint XXX at D52			

	Group of treatment		
Ref = D0 before treatment	**RGn550 5Hz N=xx**	**RGn550 10Hz N=xx**	**Difference**
Adjusted mean	x.xx	x.xx	x.xx
95% CI	x.xx ; x.xx	x.xx ; x.xx	x.xx ; x.xx
p-value	.	.	0.xxx
From an mixed model including treatment (p=0.xxx), visit (p=0.xxx), treatment-by-visit interaction (p=0.xxxx) as fixed effects and variable xxx as random effect, variable yyy (p=0.xxx) as baseline covariate.			

The following template will be used for categorical parameters.

	RGn550 10Hz vs RGn550 5Hz at visit 1	**RGn550 10Hz vs RGn550 5Hz at visit 2**	**visit 2 vs visit 1 at RGn550 10Hz**	**visit 2 vs visit 1 at RGn550 5Hz**
Endpoint XXX				
Odds ratio	X.X	X.X	X.X	X.X
95% CI	[X.X ; X.X]	[X.X ; X.X]	[X.X ; X.X]	[X.X ; X.X]
From an mixed model including treatment (p=0.xxx), visit (p=0.xxx), treatment-by-visit interaction (p=0.xxxx) as fixed effects, variable xxx as random effect and variable yyy (p=0.xxx) as baseline covariate.				

In addition, the following analyses will be performed for exploratory purpose:

- The NPC measurement will also be analyzed in the subgroup “NPC > 5 at D0 before treatment”.
- The Maddox rod horizontal will also be analyzed in the subgroup “Horizontal deviation at D0 before treatment”.
- The Maddox rod vertical - left eye will also be analyzed in the subgroup "Vertical deviation at D0 before treatment”
- The Maddox rod vertical - both eyes will also be analyzed in the subgroup “Vertical deviation at least one eye at D0 before treatment”.

Note: the Maddox rod vertical – right eye will not be analyzed in the subgroup “Vertical deviation at D0 before treatment” as too few patients were included in this subgroup (cf. data review minutes document of 18/07/2023).

8.5.1.2. Executive function (TMT A&B)

For the evolution of executive functions defined in Section 0, the following timepoints will be compared: (D0 before treatment – D7 after treatment) and a mixed effect regression model (logistic model for a categorical parameter and a linear model for continuous parameter) will be used with a patient random effect. Group effects (5 Hz vs 10Hz), period effects and group-by-period interaction will be added as fixed effects. The stratification variable gender (male/female) will be added in the model as covariates.
The same template as above (i.e. for continuous parameters) will be used.

8.5.1.3. Concussion syndrome symptoms (SCAT5)

For concussion syndrome symptoms (SCAT5) functions defined in Section 0, the following timepoints will be analyzed (D0 before treatment, D7 before treatment, D14 and D52), a mixed linear regression model will be used with a patient random effect. Group effects (5 Hz vs 10Hz), period effects and

group-by-period interaction will be added as fixed effects. The stratification variables and SCAT5 baseline will be added in the model as covariates.

The same template as above will be used.

In addition, for exploratory purpose, the concussion syndrome symptoms (SCAT5) will also be analyzed in the subgroup “Number of previous concussions”.

Note:

An additional analysis for oculomotor and oculopostural functions, balance function, executive function (TMT A&B) and concussion syndrome symptoms (SCAT5) will be performed on all patients to evaluate the change between D0 and D52. A mixed effect regression model (logistic model for a categorical parameter and a linear model for continuous parameters) will be used with a patient random effect and a period effect (D0 and D52) will be added as fixed effects.

8.5.1.4. Blood markers

A descriptive analysis of blood markers defined in Section 0, at each time point and the change from baseline will be assessed by randomization arms and overall.

The following template will be used.

		Value at visit									Change from baseline						
		Missing	**N**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**Min**	**Max**
RGn550 5Hz	**Baseline**	xx	xx	xx	xx	xx	xx	xx	xx	xx							
	D52	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
RGn550 10Hz	**Baseline**	xx	xx	xx	xx	xx	xx	xx	xx	xx							
	D52	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Total	**Baseline**	xx	xx	xx	xx	xx	xx	xx	xx	xx							
	D52	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx

In addition, for exploratory purpose, the Blood markers will also be analyzed in the subgroup “Number of previous concussions”.

8.5.1.5. Sensitivity analysis

A sensitivity analysis will be conducted on the secondary performance endpoints (oculomotor and oculopostural functions, balance function, executive function (TMT A&B) , concussion syndrome symptoms (SCAT5) and blood markers) in the FAS without excluding any data that would be collected after intercurrent events.

Of note, data of patients with a second concussion that occurred after RGn550 first treatment session will be considered before the onset of the concussion. Similarly, data of patients with a contraindication to RGn550 that occurred after RGn550 first treatment session will be considered before the onset of the contraindication.

This sensitivity analysis will be performed only if the proportion of excluded patients exceeds 10% (at least 5 patients excluded).

8.6. Exploratory analyses

Exploratory analyses will be performed on the potential relationship between drowsiness (AE) and concussion severity parameters (measured by the SCAT5 score) using a chi-square or Fisher exact test, for the qualitative variables, and a Student or Mann Whitney (Kruskal-Wallis) test, depending on the normality of parameters, for the quantitative variables.

9. INDIVIDUAL DATA LISTINGS

All data collected in the eCRF will be listed. Individual data listings will be provided in an excel file, with one tab for each form. In addition, analysis sets, and randomization arm of each patient will be added in each tab. MedDRA and WHO-Drug coding will be listed in the corresponding tabs.

10. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

This SAP is based on protocol version 2.0 and CRF version 2.0.

Changes in the statistical methods compared with those stated in the protocol are the following.

Add analysis subgroups:

- Subgroups analysis (“NPC > 5 at D0 before treatment”, “Horizontal deviation at D0 before treatment”, “Vertical deviation at D0 before treatment” (Maddox rod vertical – Left eye) and “Vertical deviation on at least one eye at D0 before treatment” (Maddox rod vertical – Both eyes), “number of previous concussions”).

Add secondary endpoints:

- Rombert quotient and Statokinetic distribution index calculation.

Add analysis of:

- NPC measurement in the subgroup “NPC > 5 at D0 before treatment”.
- Maddox rod horizontal score in the subgroup “Horizontal deviation at D0 before treatment”.
- Maddox rod vertical left eye in the subgroup "Vertical deviation at D0 before treatment”
- Maddox rod vertical both eyes in the subgroup “Vertical deviation at least one eye at D0 before treatment”.

Add descriptive analysis of ADE occurring during the first session (D0) and during the second session (at D7).

Add Exploratory analyses: study of potential relationship between drowsiness and concussion severity parameters.

There were no other changes in the statistical methods from those stated in the protocol.

11. QUALITY CONTROL

A self-validation will be performed by the statistician in charge of the analysis as follows: each derived variable will be validated exhaustively (i.e. on all patients) whenever possible. Exhaustive controls can be performed using either contingency tables (i.e. displaying all qualitative variables and minimum/maximum values of quantitative variables involved in the derivation rules) or individual data listings that are considered as not too large (i.e. no more than 50 rows). An exhaustive control is considered possible when the corresponding output contains up to 50 rows. For validation outputs considered as too large (i.e. more than 50 rows), the validation can be performed on a minimum of 5% patients randomly drawn. If the validation output is still too large (i.e. more than 50 rows), the validation will be performed on a subset of 50 rows (minimum).

Validation outputs will be reviewed by a third party (i.e. head of biostatistics or another statistician).

Derivation of the primary endpoint will be double-checked by a third party (i.e. head of biostatistics or another statistician).