RGnCON INVESTIGATION

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

CLINICAL INVESTIGATION PLAN

Version 2.0 - 11 August 2022

Written by [redacted]

N° ID-RCB: 2022-A01319-34

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1. APPROVAL FORM

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2. INVESTIGATOR SIGNATURE PAGE

Having read this Clinical Investigation Plan, I hereby agree to conduct this investigation in compliance with the plan requirements and all applicable laws and regulations.

Clinical Investigation Title: "RGnCON INVESTIGATION - 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" **Clinical Investigation Plan Version**: Version 2.0 - 11 August 2022
Principal Investigator Name: Date: Signature:

3. TABLE OF CONTENTS

4. LIST OF FIGURES

5. LIST OF TABLES

6. VERSION HISTORY

Version	Date	Author	Description of main modifications – amendments
1.0	17 June 2022	[redacted]	Initial version of the Clinical Investigation Plan
2.0	11 August 2022	[redacted]	Update of the Clinical Investigation Plan to address Ethics Committee's comments: • Description of patient's usual care pathway and link with investigation information and inclusion process (section 9.5.3.1) • Addition of a pregnancy test for women of childbearing potential (sections 8, 9.5.5.1 and 9.5.5.5).

7. ABBREVIATIONS

Abbreviation	Description
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADE	Adverse Device Effect
AE	Adverse Event
ANSM	*Agence Nationale de Sécurité des Médicaments et produits de santé* - French National Agency for the Safety of Medicines and health products
ATC	Anatomical Therapeutic Chemical
ASADE	Anticipated Serious Adverse Device Effect
BD	Base Down
BI	Base In
BO	Base Out
BU	Base Up
CIP	Clinical Investigation Plan
CNIL	*Commission Nationale de l'Informatique et des Libertés* - French National Commission on Informatics and Freedoms
DD	Device Deficiency
eCRF	electronic Case Report Form
FAS	Full Analysis Set
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFAP	Glial Fibrillary Acidic Protein
HIA3	Head Injury Assessment - Form 3
IEC	International Electrotechnical Commission
IFU	Instruction For Use
IL	InterLeukin
ISO	International Organization for Standardization
IWRS	Interactive Web Response System
LED	Light Emitting Diode
LH	Left Hyperphoria
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable

Abbreviation	Description
NPC	Near Point of Convergence
PBM	PhotoBioModulation
PT	Preferred term
Rh	Right hypophoria
RH	Right Hyperphoria
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCAT5	Sport Concussion Assessment Tool - 5th edition
SMS	Static Magnetic Stimulation
SOC	System Organ Classes
TBI	Traumatic Brain Injury
TMT A&B	Trail Making Test part A and B
UCH-L1	Ubiquitin C-terminal Hydrolase-L1
USADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organization

8. SYNOPSIS

Title	Pilot clinical investigation evaluating the safety and performance of RGn550 in treating sportspeople suffering from acute concussion syndrome (RGnCON)
ID-RCB Number	2022-A01319-34
Investigational Medical Device	RGn550 is a reusable non-invasive class IIa electromedical device that is manufactured by REGEnLIFE and not CE-marked yet. The device combines two technologies: • PhotoBioModulation (PBM), which involves exposure to directional low-power and high-fluence monochromatic or quasi-monochromatic light from the red to near-infrared wavelengths (λ = 600-1,100 nm) using lasers and Light Emitting Diodes (LEDs) • Static Magnetic Stimulation (SMS), which consists in the application of a static magnetic field using a neodymium magnet. [redacted] The device is intended, on medical opinion, to treat acute concussion syndrome (inferior or equal to 72h). It is intended for use by physicians and nurses trained in the use of RGn550 on adult patients. The treatment area is the head.
Investigation Rationale	Considering: • The promising results of transcranial PBM in concussion that were published in the literature, • The effect of a previous version of the device on neuroinflammation demonstrated pre-clinically and the fact that a neuroinflammatory response is involved in concussion's physiopathology, • The good safety results obtained in Alzheimer's Disease (AD) patients in the pilot clinical investigation on a previous version of the device, REGEnLIFE wishes to conduct a pilot clinical investigation on RGn550 to evaluate its safety and explore its performance in treating patients with acute concussion syndrome.
Overall Design	RGnCON is a prospective, comparative, randomized, simple-blinded, monocentric, pilot clinical investigation. It involves two parallel groups differing in terms of treatment frequency: half of the patients will be treated with 5 Hz, the other half with 10 Hz.
Objectives	**<u>Primary objective</u>**: • To evaluate the incidence of RGn550's Adverse Device Effects (ADEs) in acute concussion syndrome, when used to deliver, either at a frequency

	of 5 or 10 Hz, two 20-min treatment sessions at 1 week apart. **Secondary objectives**: • To evaluate the incidence of RGn550's ADEs per severity, Adverse Events (AEs) and Device Deficiencies (DDs) • To evaluate the effect of RGn550, after the first and second treatment sessions and then 45 days after the second treatment session, on: o Automated oculomotor and oculopostural functions o Balance function o Executive function • To assess the effect of RGn550 on concussion syndrome symptoms 7 days after the first treatment session as well as 7 and 45 days after the second treatment session • To evaluate the effect of RGn550 on blood markers that are involved in the pathogenesis of concussion 45 days after the second treatment session.
Investigation Population	Adult sportspeople with acute concussion syndrome resulting from sport practice who can participate in a clinical investigation per the law and are able to meet treatment sessions and complete requested assessments will be included. **Inclusion criteria**: • Male or female aged at least 18 years old • Suffering from 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 • Affiliated to French social security • Who provided a dated and signed informed consent form. **Non-inclusion criteria**: • Patient protected by a French legal measure ("sauvegarde de justice", "tutelle" or "curatelle") • Patient not able to express his/her consent • Patient deprived of liberty or hospitalized without consent • Woman who is pregnant or breastfeeding, or who plans to become pregnant or breastfeeding during the investigation, or who has the capacity to conceive but is not using a reliable contraceptive method as deemed by the investigator • Patient living in a medical facility • Patient who experienced a surgery at the treatment application area (head) within 3 months prior to inclusion • Patient with skin lesions on the treatment application area (head) • Patient with a short-term life-threatening pathology (e.g., evolving cancer; non-stable heart failure; severe hepatic, renal or respiratory failure, etc.) • Patient diagnosed with a heart attack within 3 months prior to inclusion • Patient implanted with ferromagnetic material • Patient implanted with a pacemaker • Patient with a risk of epileptic seizure or other non-degenerative central

	nervous system diseases • Patient with major physical or neurosensorial disorders that may interfere with assessments • Patient with chronic psychosis or psychotic episodes • Patient addicted to alcohol or drugs • Patient treated with antidepressant or benzodiazepine • Patient who participated to another investigation/study involving the use of an investigational medical device/drug within the 30 days prior inclusion • Patient not able to meet treatment sessions as deemed by the investigator • Patient not able to complete requested investigation assessments as deemed by the investigator.
Investigation Conduct	Three onsite visits will be performed at the following timepoints: • Day 0 (D0): Inclusion, randomization (to the 5 Hz or 10Hz treatment group) and first treatment session • Day 7 (D7): Second treatment session • Day 52 (D52): Evaluation 45 days after the last treatment session. In addition, at Day 14 (D14), the patient will be asked to remotely assess his/her concussion syndrome symptoms. The overall investigation duration, which corresponds to the inclusion period and the follow-up period, will be of 6 months approximately (4 months of inclusion and 52 days of follow-up).
Endpoints	**<u>Primary endpoint</u>**: • Incidence of RGn550's ADEs throughout the investigation **<u>Secondary endpoints</u>**: • Incidence of RGn550's ADEs per severity (mild, moderate and severe) throughout the investigation • Incidence of RGn550's AEs throughout the investigation • Incidence of RGn550's DDs throughout the investigation • Evolution, before and after treatment session at D0 and D7 and then at D52, of: o Automated oculomotor and oculopostural functions, as assessed through: ▪ Convergence, evaluated with the measure of the Near Point of Convergence (NPC) ▪ Deviations, evaluated with the cover test and Maddox rod test o Balance function, as assessed through the following static stabilometric parameters: ▪ Statokinesigram area ▪ Left/right distribution • Evolution, before treatment session at D0 and after treatment session at D7 of executive function, as assessed with the Trail Making Test part A and B (TMT A&B) • Evolution of concussion syndrome symptoms as assessed by the patient

	with the Sport Concussion Assessment Tool – 5th edition (SCAT5) symptom evaluation tool at D0 before treatment, D7 before treatment, D14 and D52 • Evolution from D0 before treatment to D52 of the concentration of the following blood markers: o Anti-inflammatory cytokines InterLeukin (IL)-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11 and IL-13 o S100 calcium binding protein B (S100B) o Glial Fibrillary Acidic Protein (GFAP) o Ubiquitin C-terminal Hydrolase-L1 (UCH-L1).
Sample Size Justification	It is planned to include 50 patients in this investigation. For such a sample size, the probability of observing at least one ADE will be 0.87 considering a probability of ADE of 0.04.
Statistical Analysis	All analyses will be performed in the Full Analysis Set (FAS), which will comprise all included patients who have been treated at least once with RGn550 device. Patients will be assigned to the treatment group as treated. The global significance level (type I error rate) will be set at $\alpha = 0.05$ (two-sided). Adjustment for multiplicity in not applicable for the primary endpoint and no adjustment for multiplicity is planned for secondary endpoints. **Primary endpoint analysis** The proportion of subjects with at least one ADE will be calculated along with the 95% exact Clopper-Pearson confidence interval in the FAS, by treatment groups and overall. **Secondary endpoints analysis** For ADEs per severity, a descriptive analysis with 95% exact Clopper-Pearson confidence interval of mild, moderate and severe ADEs will be provided in the FAS, by treatment groups and overall. All AEs will be described in the FAS, for each System Organ Class (SOC) and Preferred Term (PT) class using MedDRA (Medical Dictionary for Regulatory Activities) terminology, by treatment groups and overall. All DDs will be described in the FAS, by treatment groups and overall. The secondary performance analyses will be performed in the FAS by treatment groups, excluding data that would be collected after the following intercurrent event: treatment group switch during follow-up. Imputation of missing data will be handled by the mixed model (details will be provided in the Statistical Analysis Plan). A sensitivity analysis will be conducted on the secondary performance endpoints in the FAS without excluding any data collected after intercurrent events.
Provisional timelines	• Regulatory submission: June 2022 • Site initiation: August-September 2022 • Patient recruitment: September 2022 (first patient first visit) - December 2022 (last patient first visit) • Last visit last patient: February 2023 • Database lock: March-April 2023

	• Statistical analysis and clinical investigation report: May-July 2023

	D0		D7		D14 (remote)	D52
	Before treatment	**After treatment**	**Before treatment**	**After treatment**		
Patient information / Informed consent	X					
Eligibility criteria	X					
Pregnancy test for women of childbearing potential	X					
Randomization	X					
Demographic and clinical data	X					
NPC	X	X	X	X		X
Cover test	X	X	X	X		X
Maddox rod test	X	X	X	X		X
Stabilometric test	X	X	X	X		X
TMT A&B	X			X		
SCAT5 symptom evaluation tool	X		X		X	X
Blood sampling	X					X
20-min treatment session	X		X			
Collection of AEs and DDs that previously occurred		X	X	X		X

9. CLINICAL INVESTIGATION PLAN

9.1. Investigational Medical Device

9.1.1. Identification

RGn550 is a reusable non-invasive class IIa electromedical device that is manufactured by REGEnLIFE and not CE-marked yet.

The current valid versions of RGn550's:

- Instructions for Use (IFU) is version 1 dated 07 April 2022
- Investigator brochure is version 1 dated 02 June 2022.

9.1.2. Description

A summarized description of RGn550 is provided below. For further details on the device, please refer to the IFU or investigator brochure.

9.1.2.1. Overall Description

RGn550 combines two technologies:

- **PhotoBioModulation (PBM)**, which involves exposure to directional low-power and high-fluence monochromatic or quasi-monochromatic light from the red to near-infrared wavelengths (λ = 600-1,100 nm) using lasers and Light Emitting Diodes (LEDs)
- **Static Magnetic Stimulation (SMS)**, which consists in the application of a static magnetic field using a neodymium magnet.

Further information on these two technologies is provided in section 9.2.1.2.

[redacted]

[redacted]

[redacted]

[redacted]

9.1.6. Training or Experience Needed to Use the Device

As mentioned in RGn550's investigator brochure:

A 2-hour theoretical and practical training, provided by REGEnLIFE's staff at the time RGn550 is delivered to the users, is required before using RGn550.

9.1.7. Specific Medical or Surgical Procedures Involved in the Use of the Device

No specific medical nor surgical procedures are involved in the use of RGn550.

9.2. Background, Rationale and Justification of the Clinical Investigation Design

9.2.1. Background

9.2.1.1. Concussion

9.2.1.1.1. Definition

Concussion is characterized by an immediate, transient and spontaneously reversible alteration of mental function, ranging from confusion to loss of consciousness, as a result of direct or indirect trauma with impulsive force to the head [1].

The following consensus definition was reached during the 5th international conference on concussion in sport held in Berlin in 2017 [2]:

> Concussion is a traumatic brain injury induced by biomechanical forces. There are several common features that clinically define the nature of a concussive head injury:
>
> - Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head.
> - Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, signs and symptoms evolve over several minutes to hours.
> - Concussion may result in neuropathological changes, but the acute clinical signs and symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies.
> - Concussion results in a range of clinical signs and symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive features typically follows a sequential course. However, in some cases symptoms may be prolonged.
>
> The clinical signs and symptoms cannot be explained by drug, alcohol, or medication use, other injuries (such as cervical injuries, peripheral vestibular dysfunction, etc.) or other comorbidities (e.g., psychological factors or coexisting medical conditions).

It should be noted that the terms “mild Traumatic Brain Injury (TBI)” and “concussion” are often used interchangeably. In the broadest clinical sense, concussion is often defined as representing the immediate and transient symptoms of TBI. One key unresolved issue is whether concussion is part of TBI spectrum associated with lesser degrees of diffuse structural changes than are seen in severe TBI, or whether the concussive injury is the result of reversible physiological changes [2]. The term “concussion” is used throughout this document.

9.2.1.1.2. Physiopathology

As stated above, the concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an “impulsive” force transmitted to the head [2]. This blow can be received in various situations including falls, traffic accidents and sport practice [3, 4]. Sports at risk include hockey, American football, team sports, boxing and winter sports [1].

The pathogenesis of concussion has not been fully elucidated yet, but it is becoming increasingly clear that biomechanical forces lead to an energy crisis, neuroinflammation, cerebral blood flow changes, and pathological cascades, as detailed below and summarized in Figure 7 [5]:

- Biomechanical forces generate disruptions of neuronal cell membranes and axonal stretching, triggering indiscriminate flux of ions through previously regulated ion channels. This ions

imbalance causes neuronal depolarization, near-complete loss of electrochemical energy, and neuronal swelling.

- The adenosine triphosphate-dependent Na+/K+ pumps attempt to restore ionic homeostasis, and hyperglycolysis rapidly depletes energy stores, resulting in lactic acid buildup, and ultimately, the development of cerebral edema. In addition to the ionic flux, there is a hyperacute release of glutamate, the brain's primary excitatory neurotransmitter. Excessive glutamate receptor binding can activate calcium-dependent proteases and phospholipases, uncouple mitochondrial adenosine triphosphate synthesis, promote oxidative stress produce reactive oxygen species, deplete glutathione levels, and increase cellular energy demands.
- Concussion-induced disruption of the blood-brain barrier exacerbates the neuroinflammatory response mediated by immune cells, microglia, cytokines, and other inflammatory mediators. Blood-brain barrier dysfunction contributes to oxidative stress, inflammation, brain swelling, increased intracranial pressure, and ischemia.
- Shearing forces from a direct blow to the head or acceleration-deceleration transmitted through the neck interrupt axonal transport resulting in accumulation of transported materials in injured regions. Axonal dysregulation and accumulation of transport products lead to axonal swelling, secondary disconnection, and Wallerian degeneration (an active, cell-autonomous death pathway as a consequence of the axonal transport system's inability to deliver essential biosynthetic enzymes).

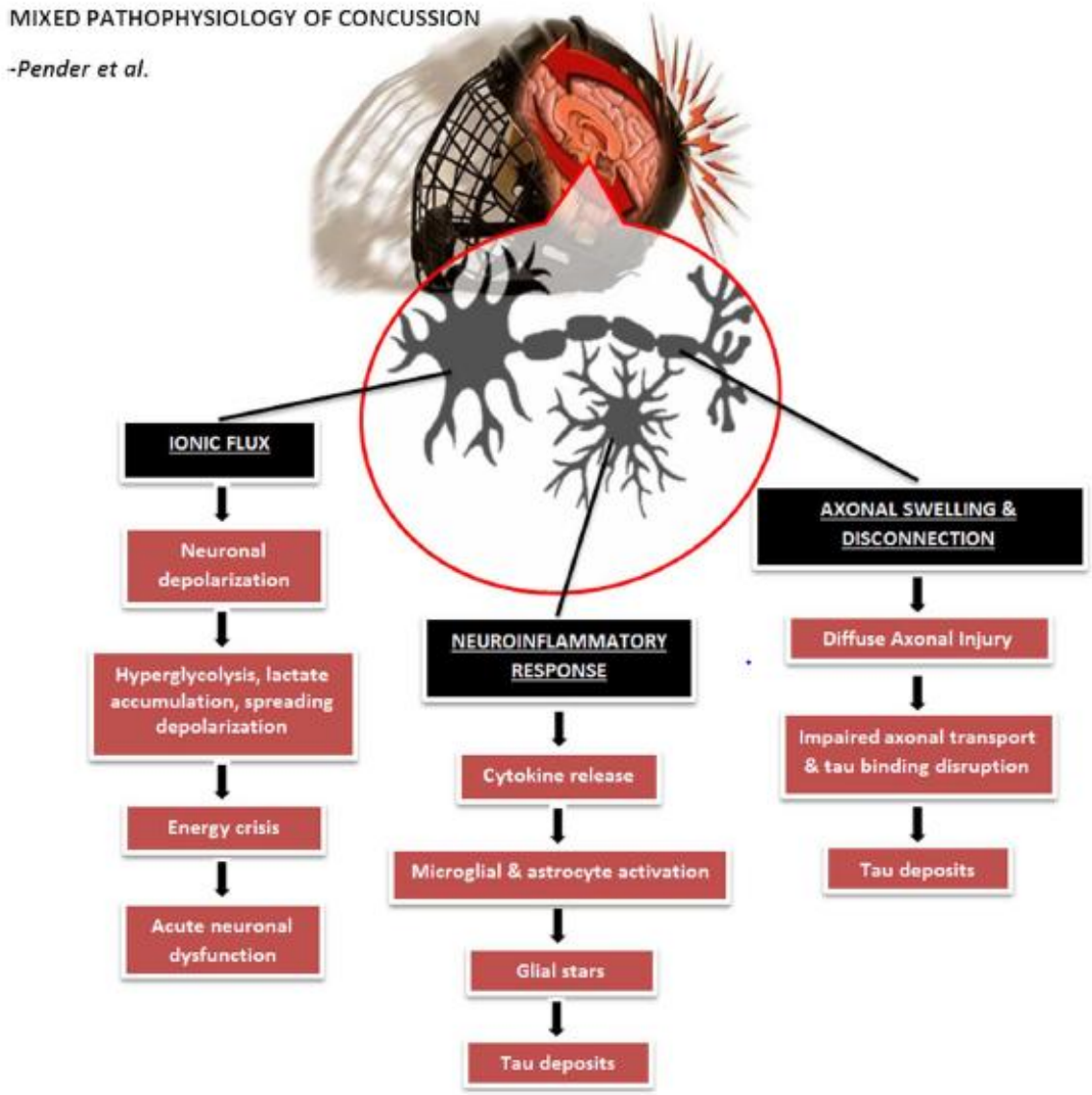

Figure 7: Physiopathology of concussion [5]

9.2.1.1.3. Symptoms

In the acute phase, concussion is an evolving injury with rapidly changing clinical signs and symptoms [2].

These symptoms can be categorized into [1–3, 6, 7]:

- Somatic symptoms, such as:
  - Headache
  - Vision changes including blurred vision, light sensitivity, difficulty reading and convergence dysfunction
  - Coordination disorders
  - Disturbance in balance
  - Insomnia
  - Somnolence
  - Drowsiness

- Cognitive impairment, such as:
    - Feeling like in a fog
    - Disorientation
    - Difficulty concentrating
    - Slowed reaction time
    - Loss of consciousness
    - Amnesia
    - Neurological deficit
- Emotional / behavioral changes such as:
    - Irritability
    - Lability

Altogether, this set of symptoms is called **concussion syndrome** [1, 6].

In adults, symptoms typically resolve in 10 to 14 days [2]. However, some may linger for weeks. Persistent post-concussion syndrome occurs when symptoms persist beyond 3 months [6].

Of note, well-trained and well-prepared sportspersons are thought to heal more rapidly [1, 4].

9.2.1.1.4. Complications

Although the short-term vital prognosis is very good (mortality < 1%), the functional prognosis in the mid- and long-term is more uncertain. Indeed, approximately 10-20% of the patients will have long-lasting effects [3].

The literature on neurobehavioral sequelae and long-term consequences of exposure to recurrent head trauma is inconsistent. However, reported potential long-term problems include [1, 2]:

- Cognitive impairment
- Depression
- Chronic traumatic encephalopathy (although a cause-and-effect relationship has not yet been demonstrated between chronic traumatic encephalopathy and concussion).

Of note, well-trained and well-prepared sportsperson are thought to have less complications. Interestingly, concussions have been reported to be more severe in sportswomen than sportsmen [1].

9.2.1.1.5. Management

Most consensus and agreement statements for managing concussion recommend that patients rest until they become symptom-free. Accordingly, prescribed rest is one of the most widely used interventions. The basis for recommending physical and cognitive rest is that rest may ease discomfort during the acute recovery period by mitigating concussion symptoms and/or that rest may promote recovery by minimizing brain energy demands following concussion. After a brief period of rest during the acute phase (24–48 hours) after injury, patients can be encouraged to become gradually and progressively more active while staying below their cognitive and physical symptom-exacerbation thresholds (i.e., activity level should not bring on or worsen their symptoms). It is reasonable for athletes to avoid vigorous exertion while they are recovering. The exact amount and duration of rest is not yet well defined in the literature and requires further study [2].

No pharmacological therapies are available specifically for concussion; therefore, medications for symptom management can be used (e.g., nonsteroidal anti-inflammatory drugs or amitriptyline for headaches, sleep aids, anxiolytics) [8].

Sunglasses can be used in case of photophobia, and earplugs or noise-canceling headphones can be used in case of phonophobia [8].

9.2.1.1.6. Epidemiology and Burden

Epidemiological data suggest that 50 to 60 million people suffer from craniocerebral trauma in the world every year, including 60% to 95% of concussions. Men are more affected than women, with an overall relative risk close to 2 [3].

In France, there is a high prevalence of concussion: about 150,000 cases per year [3].

Of note, the OMS highlights that the incidence of concussions caused by rugby, American football, soccer and hockey are similar (from 0.6 to 0.8/1,000 athlete-game-hour) while, for combat sports, it is higher (e.g., 7-15/athlete-exposition in taekwondo) [4].

Due to its frequency and the significant risk of an unfavorable evolution (10-20% of cases), the concussion is considered a public health problem [3].

9.2.1.2. Photobiomodulation and Static Magnetic Stimulation

9.2.1.2.1. Photobiomodulation

PBM is a technique that was discovered more than 50 years ago, and that involves exposure to directional low-power and high-fluence monochromatic or quasi-monochromatic light from the red to near-infrared wavelengths (λ = 600-1,100 nm) using lasers or LEDs [9–11].

Of note, PBM also used to be called “low-level laser therapy” but the term “photobiomodulation” was chosen in 2015 as standard because the term “low” was deemed too vague and lasers are not absolutely required [9].

Photons generated by the lasers or LEDs are absorbed by molecules present in the cells, called photoacceptors. The molecule targeted by the light reaches an electronically excited state that temporarily changes its conformation and function, thereby triggering signaling pathways that affect cellular metabolism [9–11]. PBM is thought to stimulate healing, reduce inflammation, relieve pain, and prevent tissue from dying [9].

Transcranial PBM has been widely used in conditions such as wound healing, musculoskeletal pain, and arthritis, and is currently being tested for applications in aging-related neurocognitive decline, depression, and anxiety as well as various neurological disorders, including concussion [12].

In vivo studies have provided promising findings on the effects of transcranial PBM in concussion. Indeed, in animal models, transcranial PBM has been shown to:

- Reduce levels of pro-inflammatory cytokines [13, 14]
- Decrease levels of pro-apoptotic markers [15]
- Reduce the size of brain injury [16]
- Decrease neurological severity [17, 18]
- Improve neurological performance [16]
- Improve behavioral performance [15, 19].

Transcranial PBM was also evaluated across various devices at various parameters and treatment durations through several **clinical investigations** involving people with concussion or TBI, as fully described in the investigator brochure. Overall, transcranial PBM improved cognition, sleep disorders and quality of life and decreased headache, depression, anxiety and insomnia in these investigations. No side effects related to PBM were evidenced. However, since none of these investigations were

controlled nor randomized, there is a risk that such results were obtained because of coincidence only. Controlled randomized clinical investigations are necessary to reach conclusions [20].

9.2.1.2.2. Static Magnetic Stimulation

SMS is a non-invasive stimulation technique that consists of the application of a static magnetic field using a cylindrical neodymium magnet [21, 22].

Static magnetic fields have a constant intensity and direction over time, along with a frequency of 0 Hz. They are different from electromagnetic fields, which vary over time and are associated with induced electric currents [22, 23].

Non-invasive brain stimulation techniques, such as SMS, are becoming increasingly popular for treating a variety of neurological and neuropsychiatric disorders [22].

At the cellular level, **transcranial SMS** is thought to act primarily at the synapse and alter the function of membrane phospholipids and ion channels [22, 23]. It induces changes in voltage-gated calcium channels, intracellular calcium flow, and membrane depolarization [23].

At the systems level, transcranial SMS was demonstrated through **clinical investigations** to **modulate membrane excitability** for up to a few minutes after the end of stimulation:

- Application over the motor cortex was demonstrated to:
  - Reduce motor cortex excitability [21, 22, 24]
  - Reduce somatosensory cortex excitability (N33 component) [21]
  - Modulate intracortical excitability: enhanced facilitation and decreased inhibition [24].
- Application over the sensorimotor cortex was shown to reduce the somatosensory cortex excitability (N20 component) [21] and alter normal somatosensory processing [23]
- Finally, application over the visual cortex increases alpha oscillations and slows visual search abilities [21].

Although conventional non-invasive brain stimulation techniques have some undesirable side effects, such as itching, tingling, headache, and discomfort, these are not observed with transcranial SMS [21].

9.2.2. Rationale

Pre-clinical and clinical investigations were conducted by REGEnLIFE on the previous versions of RGn550 device (RGn500 and RGn530). Although some of these investigations relate to Alzheimer's Disease (AD) rather than concussion syndrome, they are presented below to:

- Testify that the device was previously used in animal models and humans
- Demonstrate that the device's use was safe
- Picture what could be the device performance in concussion syndrome, especially considering its effect on inflammation.

All these investigations are summarized below. For further details, please refer to RGn550's investigator brochure.

9.2.2.1. Pre-Clinical Investigation on RGn500 in Alzheimer's Disease

RGn500 was the first device used in a pre-clinical investigation involving animal models.

[redacted]

[redacted]

A **pre-clinical investigation** in an animal model of AD was conducted to evaluate RGn500's effects in a functional context [25].

The amyloid β 25-35 mouse model of AD was used: male Swiss mice were intracerebroventricularly injected with amyloid β 25-35 peptide. This model was chosen since it has been described as reproducing some of the features of AD. Indeed, this model has been repeatedly shown to result in neuroinflammation and reactive gliosis, pro-apoptotic caspases activity enhancement, oxidative stress, endogenously produced amyloid protein deposition, tau protein hyperphosphorylation, and increase of kinases, a reduction in the number of neurons measured in hippocampal pyramidal cell layers, loss of cholinergic neurons, and memory deficits.

[redacted]

Results showed a neuroprotective effect when treatment was applied both on the head and the abdomen. Protection was statistically significantly demonstrated through:

- Memory restoration
- Normalization of key markers of AD (amyloid β 1-42, pTau)
- Reduction of oxidative stress (lipid peroxidation)
- Normalization of apoptosis (Bax/Bcl2)
- Decrease in neuroinflammation.

When the treatment was localized only on the head or abdomen, RGn500 failed to yield beneficial effects.

[redacted]

Although this rodent model was far from reproducing the complexity of the physiopathological characteristics of AD dementia in humans, these results on RGn500 were promising, especially considering the extremely severe phenotype of amyloid β 25-35 mouse model of AD.

9.2.2.2. Pre-Clinical Investigations on RGn530 in Alzheimer's Disease

Following the preclinical investigation on RGn500, a new version of the device was created: **RGn530**.

[redacted]

[redacted]

Two pre-clinical investigations were conducted on RGn530 using the amyloid β 25-35 mouse model of AD.

[redacted] Results showed that, depending on the parameters used, RGn530 treatment significantly:

- Alleviated memory deficits (spatial working memory, contextual long-term memory)
- Reduced oxidative stress (lipid peroxidation)
- Decreased key markers of AD (amyloid β 1-42, pTau)
- Decreased neuroinflammation (TNFα).

[redacted]

In the second pre-clinical investigation, [redacted] Results showed full and highly significant reversal of memory deficits. No effects on the locomotor activity were observed.

9.2.2.3. Pre-Clinical Investigations to Validate RGn530's Security

Additional **pre-clinical investigations** were conducted on **RGn530** to validate its security. [redacted]

9.2.2.4. Pilot Clinical Investigation on RGn530 in Alzheimer's Disease

Following pre-clinical investigations on RGn530, the clinical safety and performance of the device on cognition in mild-to-moderate AD was evaluated for the first time in a **pilot clinical investigation** [redacted]

[redacted]

In conclusion, this investigation proved RGn530 treatment feasibility and safety in mild-to-moderate AD patients. Although no statistically significant difference in ADAS-cog score after 8 weeks of treatment was observed, results evidenced encouraging performance trends to be evaluated in investigations with a larger sample size. Of note, statistical power was reduced due to the premature end of the investigation associated with the COVID-19 pandemic

9.2.2.5. RGn550

Considering:

- The promising results of transcranial PBM in concussion that were published in the literature
- The effect of RGn500 on neuroinflammation demonstrated in the above-described pre-clinical investigation and the fact that a neuroinflammatory response is involved in concussion's physiopathology
- The good safety results obtained in AD patients in the pilot clinical investigation on RGn530

REGEnLIFE decided to create a new version of the device, named **RGn550**, designed to be used in concussion syndrome.

[redacted]

Of note, REGEnLIFE reviewed the differences between RGn530 and RGn550 and investigated their impact to determine whether pre-clinical investigations that validate RGn530's security [redacted] can validate RGn550's security as well. In this impact analysis [redacted] REGEnLIFE concluded that these pre-clinical investigations indeed validate RGn550's security. [redacted]

In this context, REGEnLIFE wants to conduct a pilot clinical investigation on RGn550 to evaluate its safety and explore its performance in treating patients with acute concussion syndrome.

9.2.3. Justification of the Clinical Investigation Design

RGnCON is a prospective, comparative, randomized, simple-blinded, monocentric, pilot clinical investigation:

- A **prospective** design has been chosen since no data on the use of RGn550 in sportspeople suffering from acute concussion syndrome were previously collected.
- This investigation is **comparative**. It involves two parallel groups differing in terms of treatment frequency: half of the patients will be treated with 5 Hz, the other half with 10 Hz. This will allow to determine which frequency is optimal for the patient both in terms of safety and performance.
- Patients will be assigned to one of these two groups through **randomization** (1:1 ratio).
- Patients will not be aware of the group they were assigned to (**simple blinded**).
- A **monocentric** design has been chosen because RGnCON is a pilot investigation.

Various methodological aspects will prevent investigation bias:

- The presence of two groups will allow to take into consideration all confounding factors, apart from placebo effect.
- The unpredictable randomization will spread all known and unknown confounding factors (apart from placebo effect) within the two groups, resulting in comparable groups, and will prevent selection bias.

- Patients will be stratified based on gender (male/female) and concussion history (history/no history of concussion within 6 months prior to inclusion) as such parameters are known to influence current concussion symptoms and complications.
- The analysis will be performed in the Full Analysis Set (FAS) population without methods to replace missing data. However, some of the used models take into consideration missing data.

Of note, the following bias will remain present:

- The follow-up bias and evaluation bias since investigators will not be blinded
- The site effect since only one site will be recruited.

Nevertheless, the primary purpose of this investigation is to evaluate, for the first time, the safety of RGn550 in sportspeople suffering from acute concussion syndrome and explore its performance in this population. In case this investigation demonstrates RGn550's safety in this population, further investigation(s), using a double-blinding design versus sham, and involving more sites, will be conducted to demonstrate RGn550's safety and performance.

9.2.4. Investigation Classification per European Regulation 2017/745

According to European Regulation 2017/745, RGnCON is a clinical investigation conducted to establish the conformity of a non-CE marked non-invasive class IIa medical device, referred to in Articles 62 and 70.7 a) of the Regulation (case 1 per the French National Competent Authority (ANSM) classification).

9.3. Benefits and Risks of the Investigational Device, Clinical Procedure and Clinical Investigation

9.3.1. Anticipated Clinical Benefits

The potential clinical benefits anticipated to result from the use of RGn550 in patients with acute concussion syndrome are:

- Improvement of automated oculomotor / oculopostural functions,
- Improvement of balance function,
- Improvement of executive function,
- Decrease of concussion syndrome symptoms
- Reduction of neuroinflammation.

These potential benefits are investigated in RGnCON.

9.3.2. Anticipated Adverse Device Effects

The following Adverse Device Effects (ADEs) were observed during the pilot investigation on RGn530 (previous version of the device) and are thus considered as anticipated ADEs of RGn550:

[redacted]

Per RGn550's investigator brochure, the ADEs anticipated to result from the use of RGn550 are:

[redacted]

[redacted]

No severe ADEs are expected.

9.3.3. Risks Associated with the Participation in the Clinical Investigation

Compared to standard clinical practice, additional risks associated with the participation in RGnCON are risks related to:

- **The use of RGn550**
  Anticipated ADEs of RGn550 are described above (section 9.3.2).
  Moreover, as mentioned in RGn550's investigator brochure, a risk management process specific to RGn550 was put in place by REGEnLIFE in accordance with NF EN ISO 14971-2019.

- **The automated oculomotor/oculopostural tests and the TMT A & B**
  Identified risks related to the conduct of such tests are symptoms such as fatigue, headache and dizziness, which are related to the fact that treated patients have a concussion. These symptoms remain acceptable as they are usual symptoms of concussions, expected to remain minor within this context.

- **The stabilometric test**
  The only risk that has been identified as related to the use of the stabilometry platform is a risk of stumble/fall of the patient. However, this risk remains very unlikely considering the reduced height of the platform and the fact that investigators, which are healthcare professionals, will help and support patients during the whole stabilometric process.

- **The blood sampling procedure**
  Risks related to the blood sampling procedure are pain, hematoma at the puncture site, lack of blood reflux, reflex syncope as well as contamination by hepatitis C, C or HIV for the person performing the sampling. These risks are mitigated by the fact that a nurse will be perform the sampling.

No risks were identified as being related to the use of the Sport Concussion Assessment Tool – 5th edition (SCAT5) symptom evaluation tool.

9.3.4. Possible Interactions with Concomitant Treatments

As mentioned in the IFU, RGn550 should not be used in:

- Patients with recent major surgery at the treatment application area (head) within 3 months
- Patients with ferromagnetic material
- Patient with a pacemaker.

No interactions with pharmacological treatments are mentioned in the IFU.

9.3.5. Steps Taken to Control or Mitigate Risks and Benefit-Risk Ratio Rationale

All risks identified during RGn550's risk analysis were mitigated as far as possible. It was concluded that anticipated benefits outweigh residual risks and the overall residual risk is acceptable.

Risks related to investigation procedures mentioned in section 9.3.3 are mitigated by the fact that healthcare professionals will help and support patients during the whole investigation. Investigators will conduct all evaluations while a nurse will perform the blood sampling.

A risk analysis specific to RGnCON will be put in place. This risk analysis will take into consideration any risks associated with each step of the investigation. Associated documentation will describe all steps taken to control and mitigate these risks.

9.4. Clinical Investigation Objectives and Hypotheses

As a pilot investigation, the objective of RGnCON is to demonstrate RGn550's safety and explore its performance in treating adult sportspeople with acute concussion syndrome.

9.4.1. Primary Objective

The primary objective of this investigation is to evaluate the **incidence of RGn550's ADEs** in acute concussion syndrome, when used to deliver, either at a frequency of 5 or 10 Hz, two 20-min treatment sessions at 1 week apart.

9.4.2. Secondary Objectives

The secondary objectives of this investigation relate to both the **safety** and **performance** of RGn550 in acute concussion syndrome, when used to deliver, either at a frequency of 5 Hz or 10 Hz, two 20-min treatment sessions at 1 week apart.
These objectives are:

- To evaluate the **incidence of RGn550's ADEs per severity**, **AEs** and **Device Deficiencies (DDs)**

- To evaluate the effect of RGn550, after the first and second treatment sessions and then 45 days after the second treatment session, on:
    - **Automated oculomotor and oculopostural functions**
    - **Balance function**
    - **Executive function**

- To assess the effect of RGn550 on **concussion syndrome symptoms** 7 days after the first treatment session as well as 7 and 45 days after the second treatment session

- To evaluate the effect of RGn550 on **blood markers** that are involved in the pathogenesis of concussion 45 days after the second treatment session.

These secondary objectives have been chosen as they will allow to evaluate RGn550's safety and determine whether:

- RGn550 could improve important functions that are impacted in acute concussion syndrome, i.e., automated oculomotor/oculopostural, balance and executive functions
- RGn550 could decrease acute concussion syndrome symptoms
- RGn550 could impact the concentration of blood markers involved in acute concussion syndrome

9.5. Clinical Investigation Design

9.5.1. Investigational Medical Devices

Two RGn550 devices producing a 5 Hz frequency and two producing a 10 Hz frequency will be provided by REGEnLIFE to the investigational site. Provided devices will be tracked, during and after the investigation, with assigned serial numbers.

The principal investigator will be trained in the use of RGn550 by REGEnLIFE before the inclusion of the first patient.

Each patient will be treated with the same device throughout the investigation. For a given patient, the other device of the same type (5 Hz or 10 Hz) may only be used in case of malfunction of the initial device.

To maintain simple blinding, the devices will be visually identified as follows:

- The RGn550 devices producing a 5 Hz frequency will be labeled as: Device A1 and Device A2
- The RGn550 device producing a 10 Hz frequency will be labeled as: Device B1 and Device B2.

To track the use of the devices, the principal investigator will mention in the electronic Case Report Form (eCRF) which RGn550 device was used at each treatment session of each patient. In parallel, he will fulfil a treatment sheet associated with the device in question and write down the number of the treated patient, date of treatment, number of treatment session and duration of treatment.

The maximal overall exposure of patients to RGn550 will be of 1 week, since the second, and last, treatment session is planned at Day 7. Exposure during a treatment session will be of 20 min.

9.5.2. Investigation Population

Adult sportspeople with acute concussion syndrome resulting from sport practice who can participate in a clinical investigation per the law and are able to meet treatment sessions and complete requested assessments will be included.

9.5.2.1. Inclusion Criteria

- Male or female aged at least 18 years old
- Suffering from 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
- Affiliated to French social security
- Who provided a dated and signed informed consent form.

9.5.2.2. Non-Inclusion Criteria

- Patient protected by a French legal measure (“sauvegarde de justice”, “tutelle” or “curatelle”)
- Patient not able to express his/her consent
- Patient deprived of liberty or hospitalized without consent
- Woman who is pregnant or breastfeeding, or who plans to become pregnant or breastfeeding during the investigation, or who has the capacity to conceive but is not using a reliable contraceptive method as deemed by the investigator
- Patient living in a medical facility

- Patient who experienced a surgery at the treatment application area (head) within 3 months prior to inclusion
- Patient with skin lesions on the treatment application area (head)
- Patient with a short-term life-threatening pathology (e.g., evolving cancer; non-stable heart failure; severe hepatic, renal or respiratory failure, etc.)
- Patient diagnosed with a heart attack within 3 months prior to inclusion
- Patient implanted with ferromagnetic material
- Patient implanted with a pacemaker
- Patient with a risk of epileptic seizure or other non-degenerative central nervous system diseases
- Patient with major physical or neurosensorial disorders that may interfere with assessments
- Patient with chronic psychosis or psychotic episodes
- Patient addicted to alcohol or drugs
- Patient treated with antidepressant or benzodiazepine
- Patient who participated to another investigation/study involving the use of an investigational medical device/drug within the 30 days prior inclusion
- Patient not able to meet treatment sessions as deemed by the investigator
- Patient not able to complete requested investigation assessments as deemed by the investigator.

9.5.3. Conduct

9.5.3.1. Patient Inclusion

It is planned to include 50 patients in this investigation (refer to section 9.6.1 for sample size justification).

Based on this number and considering that the site estimated that it would be able to include approximately 3 patients per week, a 4-month inclusion period is planned: from September 2022 to December 2022.

The recruited site will be the Hôpital européen Georges-Pompidou located in Paris. The principal investigator will be a neurologist specialized in sport concussions and the coinvestigator will be a sport physician and posturologist.

In current clinical practice, following a shock, a sportsperson with obvious signs of concussion is examined by a physician within 72 hours after the shock to establish the diagnosis of concussion. For example, in the context of professional rugby, the French federation's regulation requires to follow HIA protocol immediately after the shock and the appearance of such signs. This protocol, composed of three steps, is performed by a physician within 48 hours after the shock:

- Step 1: Assessment during the match using HIA1
- Step 2: Post-match assessment, the same day, using HIA2
- Step 3: 36-48 hours post-injury assessment using HIA3.

The subjects of RGnCON investigation will be identified among sportspersons examined by the principal investigator within 72 hours after the shock. They will be included if they meet eligibility criteria and agree to participate in the investigation. Of note, HIA3 is mentioned in the eligibility criteria as the diagnostic tool for concussion. Indeed, as the principal investigator is the referring neurologist for a lot of rugby clubs and several sports federations, it is expected that most subjects will be professional rugby players for whom this protocol is implemented in current clinical practice. Nevertheless, subjects practicing other sports may be included as well if they have a diagnosis of concussion confirmed by the HIA3, meet the eligibility criteria and agree to participate.

All potential subjects will be informed about the investigation as soon as possible after the shock in order to give them adequate time to think about the investigation and their potential participation. During the consultation with the principal investigator, all the information will be reexplained to the patients, who will then be able to ask the investigator any questions they may have. After that, patients will have as much time as needed to provide an answer regarding their participation. If the answer is provided within 72 hours after the shock, then the patient will be included.

9.5.3.2. Visits

Three onsite visits will be performed at the following timepoints:

- Day 0 (D0): Inclusion, randomization (to the 5 Hz or 10Hz treatment group) and first treatment session
- Day 7 (D7): Second treatment session
- Day 52 (D52): Evaluation 45 days after the last treatment session.

In addition, at Day 14 (D14), the patient will be asked to remotely assess his/her concussion syndrome symptoms.

9.5.3.3. Investigation Duration

The investigation duration per subject will be of 52 days.

The overall investigation duration, which corresponds to the inclusion period and the follow-up period, will thus be of 6 months approximately (4 months of inclusion and 52 days of follow-up).

9.5.3.4. Prohibited/Restricted Treatments

Other treatments involving **PBM** or **magnetic fields** will be prohibited during the investigation in order to evaluate RGn550's effects only.

The following pharmacological treatments will be prohibited as well as during the investigation in order to evaluate RGn550's effects only: **benzodiazepine** and **antidepressants**.

In addition, any patients who have a **head surgery** or get implanted with **ferromagnetic material** or a **pacemaker** between the first and second RGn550 treatment sessions will not undergo the second treatment session because RGn550 is contraindicated in these conditions.

Of note, the same will apply to patients who meet **other contraindications** between the two treatment sessions, i.e.:

- Patients with skin lesions on the head
- Patients with short-term life-threatening pathologies (e.g., evolving cancer, non-stable heart failure, severe hepatic, renal or respiratory failure, etc.)
- Patients with a heart attack
- Patients with a risk of epileptic seizure
- Pregnant women.

9.5.3.5. End of Investigation

The end of the investigation is defined as the completion of the last patient last visit. The last patient last visit will occur when the last patient either completes the 52-day follow-up visit or prematurely terminate the investigation.

A patient may prematurely terminate the investigation for the following reasons:

- Screen failure

- Withdrawal
- Lost to follow-up
- Death.

For each patient, an end-of-investigation form will be filled in within the eCRF by the investigator, whether or not they have completed the investigation. In case of premature termination, the date and reason will be collected.

Screen failure

A screen failure occurs when a patient was included while he/she has one or several non-inclusion criteria and/or does not have one or several inclusion criteria.

In that case, the investigators must ensure that the reason for screen failure is adequately documented in the patient's medical file and the eCRF.

Withdrawal

Patients may voluntarily withdraw from the investigation at any time. A patient may also be withdrawn from the investigation at the investigators' discretion.

In case of withdrawal, the investigators must ensure that the date and reason for the withdrawal is adequately documented in the patient's medical file and the eCRF.

Data from all patients who left the investigation prematurely will be analyzed until the date of withdrawal.

Lost to Follow-Up

When investigators do not have any news from a patient, they will make at least three attempts to contact the patient as well as the patient's general practitioner and/or a family member if known. If all these attempts fail, the investigators can then declare the patient as "lost to follow-up". In that case, every effort will be made to obtain necessary information to complete the eCRF.

Each attempt should be documented in the patient's medical file with the date, description of the three unsuccessful contacts along with the contact method (e.g., telephone, letter with acknowledgement of receipt).

Of note, to prevent lost-of follow-up patients, automatic alerts will be sent via emails to the site to remind them of upcoming visits with their patients.

Data from patients who were lost to follow-up will be analyzed until the date of loss to follow-up.

Death

Should it be discovered that the patient is dead, an investigation regarding the cause of death will be conducted by the investigator. The date and cause of death will be recorded in the eCRF and the patient's medical file.

Data from dead patients will be analyzed until the date of death.

9.5.4. Endpoints

9.5.4.1. Primary Endpoint

The primary endpoint of this investigation is the **incidence of RGn550's ADEs** throughout the investigation.

9.5.4.2. Secondary Endpoints

The secondary endpoints are:

- The **incidence of RGn550's ADEs per severity** throughout the investigation:
  - Incidence of mild ADEs
  - Incidence of moderate ADEs
  - Incidence of severe ADEs
- The **incidence of RGn550's AEs** throughout the investigation
- The **incidence of RGn550's DDs** throughout the investigation.
- The evolution, before and after treatment session at D0 and D7 and then at D52, of:
  - **Automated oculomotor and oculopostural functions**, as assessed through:
    - Convergence, evaluated with the measure of the Near Point of Convergence (NPC)
    - Deviations, evaluated with the cover test and Maddox rod test
  - **Balance function**, as assessed through the following static stabilometric parameters:
    - Statokinesigram area
    - Left/right distribution
- The evolution, before treatment session at D0 and after treatment session at D7 of **executive function**, as assessed with the TMT A&B
- The evolution of **concussion syndrome symptoms** as assessed by the patient with the SCAT5 symptom evaluation tool at D0 before treatment, D7 before treatment, D14 and D52
- The evolution from D0 before treatment to D52 of the concentration of the following **blood markers**:
  - 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).

These secondary endpoints have been chosen since:

- Convergence insufficiency is an emerging oculomotor-related outcome after a sport-related concussion [26] and the NPC is one of the primary diagnostic tests used to assess convergence insufficiency. Of note, convergence insufficiency rate following concussion was reported to range from 42% to 55% [7].
- The cover and Maddox rod tests are recognized tests to assess ocular deviations [27, 28]. In particular, the Maddox rod test has been used for more than a century in ophthalmology [28].
- Stabilometry is an objective and reproducible method for the recording and evaluation of balance function, in particular following neurologic impairment [29]. Of note, the statokinesigram area is chosen as it is a parameter that might evolve with concussion evolution [30] while the left/right distribution is added as an exploratory parameter.
- The TMT A&B is a recognized test to evaluate executive function [31]. Of note, in the pilot clinical investigation on RGn530 in AD, the TMT B completion time decreased from baseline to W8 in RGn530 group while it increased in the sham group.

- The SCAT5 is a standardized tool for evaluating concussions designed for use by physicians and licensed healthcare professionals [32].
- Anti-inflammatory cytokines, whose major ones are IL-1, IL-4, IL-6, IL-10, IL-11 and IL-13 [33], are released as part of the neuroimmune response to concussion [34].
- S100B, GFAP and UCH-L1 are regarded as biomarkers of acute brain injury [35].

9.5.5. Description of Visits, Procedures and Data to Collect

Data will be collected at D0, D7, D14 and D52.

The principal investigator will perform the informed consent process, apply treatment and conduct all evaluations apart from the oculomotor/oculopostural and stabilometric tests that will be conducted by the coinvestigator.

9.5.5.1. Inclusion, Randomization and First Treatment Session Visit (D0)

During this visit, the principal investigator will **offer patients who meets eligibility criteria to participate in the investigation**. In particular, to be included, patients must have a diagnosis of concussion confirmed via the HIA3 tool. This tool is the third, and last, stage of the head injury assessment protocol. It is to be performed after two night's rest (36-48 hours post-head impact event) to further assess clinical progress and identify a late diagnosis of concussion [36]. The French version of this tool, presented in Appendix 12.1 [36], will be used during this investigation.

Of note, women of childbearing potential will undergo a **pregnancy test** to ensure they are not pregnant and thereby meet the corresponding eligibility criteria.

The principal investigator will thus **inform the patients and obtain their consent** as described in section 9.12.

The investigators will then **collect the following data**:

- **Eligibility criteria**
- **Demographic and clinical data**
  Data such as gender, age, sport practiced, concussion history and concomitant treatments will be collected, along with parameters that are known to influence oculomotor/oculopostural or stabilometric tests such as:
  - For oculomotor/oculopostural tests:
    - Regular orthoptic rehabilitation sessions
  - For stabilometric test:
    - Surgery of the lower limbs within 6 months prior to inclusion.

The investigators will also **perform the following tests**:

- **NPC**
  The NPC is the closest point in space where the patient's eyes can converge [7, 26].
  An objective measurement of the NPC will be performed in line with previous literature. The measurement will be conducted with a fixation stick placed at 30-40 cm of the patient's eye within the median plan. The patient will keep its glasses on in case he/she has glasses. The patient will be asked to "focus on the object with both eyes". The object will then be moved by the investigator closer to the patient's eyes until the patient sees two distinct images or until the investigator observes an outward deviation of one eye. The distance from this point to the lateral canthus will then be measured using a ruler [26].

The measure will be performed three consecutive times and the mean of these three measurements will be calculated.
In accordance with previous literature, a NPC ≤5 cm will be considered normal while a NPC >5 cm will be considered abnormal [37].

- **Cover test**
  There are different variants of the cover test. The unilateral cover test will be used, which consists into covering one eye, horizontally moving a target 5 cm in front of the non-covered eye, and then uncovering the covered eye and observing its movements. If it moves to regain fixation, the patient exhibits deviation. If the covered eye moves to recover fixation (restitution movement), the test is positive. The patient will keep its glasses on in case he/she has glasses.
  The result will be measured qualitatively by the co-investigator using the following four categories:
    - Normal fixation = 0
    - Light restitution movement = 1
    - Important restitution movement = 2
    - Deviated eye without restitution movement = 3.

  The test will then be repeated on the other eye.

- **Maddox Rod test**
  This test will be performed with a pen torch and a red Maddox rod consisting of 17 biconvex cylinders that have enough convergence to transform the image of a white light point into a red line perpendicular to the cylinder axis [28]. During this test, the patient will keep its glasses on in case he/she has glasses.
  The Maddox rod will be placed in front of one eye with the cylinders first oriented horizontally. The fixed light point will be placed at least 3 meters from the patient, at the height of his/her eyes, and will be focused on the midline of the patient's face. The patient will indicate where the vertical red line is positioned relative to the white point. If the white light and vertical red line are not overlapping, there is a horizontal deviation (see Figure 8). In case a deviation is identified, prisms will be held in front of the Maddox rod until the line is centered on the light. The value of the prism will quantify the deviation [38]. The horizontal deviation will be measured on one eye only.
  Then, the Maddox rod will be placed in front of the same eye with the cylinders oriented vertically. If the white light and vertical red streak are not overlapping, there is a vertical deviation (see Figure 9). Similarly, in case of deviation, prisms will be used to quantify it [38]. The test will then be repeated on the other eye to measure the vertical deviation of the other eye.

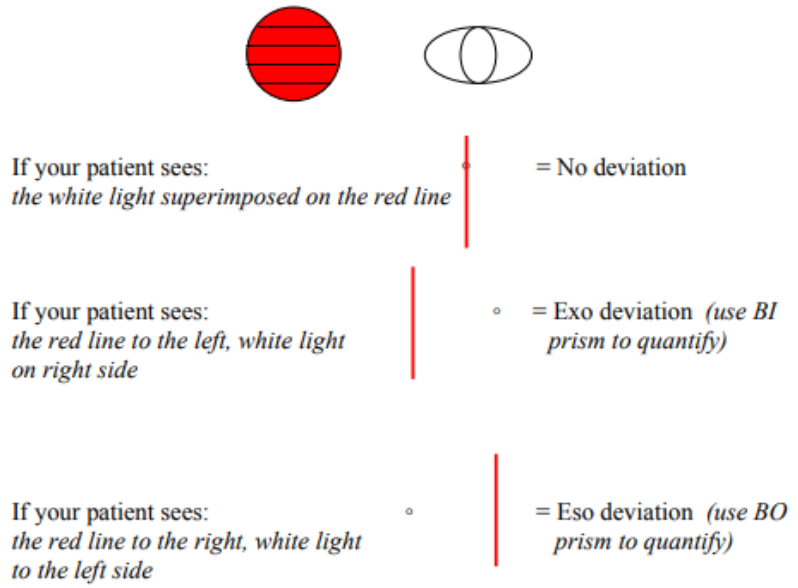

Figure 8: Horizontal orientation of the Maddox rod to identify horizontal deviation (BI: Base In, BO: Base Out) **[38]**

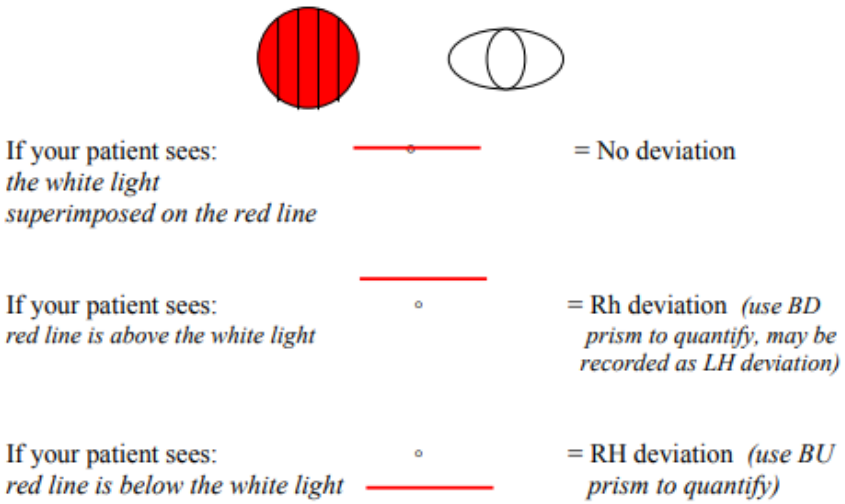

Figure 9: Vertical orientation of the Maddox rod to identify vertical deviation (BD: Base Down, BU: Base Up, LH: Left Hyperphoria, Rh: Right hypophoria, RH: Right Hyperphoria) **[38]**

- **Static stabilometric test**
  Static stabilometric parameters are measured with the use of a stabilometric platform equipped with sensors that monitor the evolution in time of the patient's center of pressure and its movements relative to the center of the platform. The signal is digitalized, evaluated by special computer program and results are visualized on the monitor and recorded [29].
  The patient will be asked to stand on KFORCE Plates (a stabilometric platform manufactured by KINVENT HELLAS, see Figure 10) either barefoot or with his/her shoes and orthopedic inserts in case the patient has inserts. A 30 s-record will be performed, two times consecutively: one time with the patient's eyes open and one time with the patients' eyes closed.
  Following these two records, the two values of the following parameters will be collected, and their mean will be calculated:
  - The statokinesigram area

The statokinesigram is the projection onto a 2-dimensional space of the trajectory of the patient's center of pressure [39]. Its area is measured in mm^2. The larger the area is, the higher the patient's imbalance is.

- The left/right distribution
  The left/right distribution comprises two percentages representing the patient's body weight distribution on his/her left versus right foot. If 50% is obtained for each foot, the patient is stable.

Figure 10: Picture of KFORCE Plates

- **TMT A&B**
  The TMT is an executive function test reflecting various cognitive processes such as selective attention, motor activity and flexibility. In Part A, the subject is instructed to trace a line that connects circled numbers in consecutive order (see Appendix 12.2.1). In Part B, the subject is asked to trace a line that connects circled numbers and circled letters in consecutive order while alternating between numbers and letters (see Appendix 12.2.2). The time to perform the task, number of correct moves and number of errors are collected [31].

Following this, the patient will evaluate his/her symptoms using the **SCAT5 symptom evaluation tool**. The patient will rate the intensity of every symptom from 0 (none) to 6 (severe) using a form. This will allow to calculate the total number of symptoms (out of 22) and the symptom severity score (out of 132) (see Appendix 12.3).

A **blood sample** will also be obtained from the patients by a nurse. The blood sample analysis will be performed by Montpellier Neuroscience Institute (*Institut de Neuroscience de Montpellier*) following the institute standard practice.

During the visit, the patients will be **randomized** in a 1:1 ratio to the 5 Hz group or 10 Hz group using the centralized Interactive Web Response System (IWRS) incorporated into the eCRF. A block randomization method will be used. Only patients will be blinded to their assigned treatment.

Depending on their assigned group, the patients will then be **treated** with one of the 5 Hz RGn550 devices or one of the 10 Hz RGn550 devices for 20 min. To perform the treatment, the principal investigator will follow the below instructions:

- Make the patient comfortable.
- Install the helmet on the patient's head, taking care not to bump it with the modules.
- Lightly tighten the soft helmet holding wire and check the positions of the modules. Each module can be moved slightly to adjust its position.
- On the control unit, in the menu on the left, choose the option 'Program' and choose the proposed treatment
- Finally press the red arrow to start the treatment.

A countdown is displayed on the screen indicating the time remaining until the end of the treatment session. At each treatment session, the principal investigator will fulfil a treatment sheet associated with the used device and mention the number of the treated patient, date of treatment, number of

treatment session and duration of treatment. To stop the treatment, the principal investigator will press the red button with a cross inside that is displayed on the screen (a confirmation message will be displayed to avoid any manipulation error).

Following treatment, the investigators will:

- **Perform the following tests** following the methodology described above:
  - NPC
  - Cover test
  - Maddox rod test
  - Static stabilometric test
- **Collect any AEs and DDs** that occurred during the visit.

9.5.5.2. Second Treatment Session Visit (D7)

This visit will occur at D7 and will correspond to the second treatment session.

Before treatment, the investigators will **collect any AEs** that occurred since the last visit.

Following that, they will **check** that:

- Patients did not have a **second concussion** between the first and second treatment sessions, as this could impact the performance evaluations
- Patients did not become **contraindicated** to RGn550 treatment between the first and second treatment sessions

If that's the case, the second treatment session will not be performed nor any of the remaining performance evaluations described below.

If applicable, before treatment:

- The investigators will **perform the following tests** following the methodology described above:
  - NPC
  - Cover test
  - Maddox rod test
  - Static stabilometric test
- The patient will be asked to evaluate the intensity of his/her symptoms using the SCAT5 symptom evaluation tool.

The patients will then be **treated** for 20 min, as per their assigned group and using the same RGn550 device that was used at D0.

Following treatment, the investigators will:

- **Perform the following tests**:
  - NPC
  - Cover test
  - Maddox rod test
  - Static stabilometric test
  - TMT A&B
- **Collect any AEs and DDs** that occurred during the visit.
- Give the patient a **SCAT5 symptom evaluation tool form** for remote completion by the patient at D14.

9.5.5.3. Remote Visit (D14)

Seven days after the second treatment session, the investigators will **call the patients** to remind them to complete the SCAT5 symptom evaluation tool and bring the form with them during their next visit at D52.

9.5.5.4. Follow-up Visit (D52)

During this visit, which will occur 45 days after the second treatment session, no treatment will be performed.

The investigators will:

- Collect the **SCAT5 symptom evaluation tool form** that was completed by the patient at D14
- **Collect any AEs** that occurred since the last visit
- **Check** that, between the first and second treatment sessions, patients did not have a **second concussion**. If that's the case, remaining performance evaluations won't be performed.
- If applicable, **perform the following tests**:
    - NPC
    - Cover test
    - Maddox rod test
    - Static stabilometric test

The patient will be asked to evaluate the intensity of his/her symptoms using the SCAT5 symptom evaluation tool.

Finally, a **blood sample** will be obtained by the nurse.

Once all these evaluations have been conducted and all the required data have been collected, a treatment session may be offered to patients who did not become **contraindicated** to RGn550 treatment after the second treatment session.

Patients who became contraindicated to RGn550 treatment or had a second concussion between the first and second treatment session will not come on site for this visit since no further performance evaluations will be performed for these patients. However, the principal investigator will call them on D52 to collect any AEs that occurred since the last visit.

9.5.5.5. Schedule

Table 2 below summarizes procedures and evaluations to perform at each visit.

Table 2: Schedule of procedures and evaluations

	D0		D7		D14 (remote)	D52
	Before treatment	After treatment	Before treatment	After treatment		
Patient information / Informed consent	X					
Eligibility criteria	X					
Pregnancy test for women of childbearing potential	X					
Randomization	X					
Demographic and clinical data	X					
NPC	X	X	X	X		X
Cover test	X	X	X	X		X
Maddox rod test	X	X	X	X		X
Stabilometric test	X	X	X	X		X
TMT A&B	X			X		
SCAT5 symptom evaluation tool	X		X		X	X
Blood sampling	X					X
20-min treatment session	X		X			
Collection of AEs and DDs that previously occurred		X	X	X		X

9.5.6. Monitoring

Monitoring activities will be performed by [redacted]

During the investigation, [redacted] monitors will perform:

- **Source data verification during on-site monitoring visits** to confirm that data entered into the eCRF by authorized site personnel are complete, accurate, and verifiable based on source documents. During these visits, the monitors will also check that the informed consent process was performed as planned in section 9.12.
- **Source data review during remote monitoring** (through telephone and/or email) to confirm that data entered into the eCRF by authorized site personnel are complete and consistent. These remote monitoring will also allow to check the inclusion progress, data entry progress and collect any missing documents from the site.

The monitors will ensure that the investigation is conducted according to this Clinical Investigation Plan (CIP), the Good Clinical Practice (GCP) and applicable laws and regulations.

Monitoring will be performed according to the process defined in the Clinical Monitoring Plan, which will notably describe the extent and frequency of monitoring.

Source documents are paper or electronic documents in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X rays, patient files, and records kept at pharmacies, laboratories, and medico technical departments involved in a clinical investigation. Source documents will be saved after the end of the investigation during 15 years by the investigators or site.

The investigators and site must provide authorized personnel (monitors, sponsor, regulatory authorities, Ethics Committee) direct access to applicable source documents for investigation-related monitoring, sponsor audits, health authorities inspections and Ethics Committee review.

9.6. Statistical Considerations

9.6.1. Sample Size Justification

For a sample size of 50 patients, the probability of observing at least one ADE will be 0.87 considering a probability of ADE of 0.04. The sample size calculation was performed with SAS® v9.4.

9.6.2. Analysis Population

All analyses will be performed in the **Full Analysis Set (FAS)**, which will comprise all included patients who have been treated at least once with RGn550 device. Patients will be assigned to the treatment group as treated.

9.6.3. Statistical Analysis

Full details related to statistical analysis will be provided in the Statistical Analysis Plan.

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

The global significance level (type I error rate) will be set at $\alpha = 0.05$ (two-sided). Adjustment for multiplicity in not applicable for the primary endpoint and no adjustment for multiplicity is planned for secondary endpoints.

Continuous data will be described by the number of missing data, number of data analyzed, mean, standard deviation, median, Q1, Q3, minimum, maximum.

Categorical data will be described by the number of missing data, frequencies and percentages of patients in each modality. The percentage of patients will be calculated once missing data are excluded from the denominator.

9.6.3.1. Primary Endpoint Analysis

The proportion of subjects with at least one ADE will be calculated along with the 95% exact Clopper-Pearson confidence interval in the FAS, by treatment groups and overall.

Of 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 in the Statistical Analysis Plan.

9.6.3.2. Secondary Endpoints Analysis

ADEs per severity
A descriptive analysis with 95% exact Clopper-Pearson confidence interval of mild, moderate and severe ADEs will be provided in the FAS, by treatment groups and overall.

AEs
All AEs will be described in the FAS, for each System Organ Class (SOC) and Preferred Term (PT) class using MedDRA (Medical Dictionary for Regulatory Activities) terminology, by treatment groups and overall.

DDs
All DDs will be described in the FAS, by treatment groups and overall.

Secondary performance analyses

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

Imputation of missing data will be handled by the mixed model (details will be provided in the Statistical Analysis Plan).

The analyses will be performed as follows:

- For the evolution of the below parameters, 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) and a mixed effect regression model 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 variables will be added in the model as covariates.
    - Automated oculomotor and oculopostural functions:
        - Convergence, evaluated with the Near Point of Convergence (NPC) (>5 cm vs ≤5 cm)
        - Deviation as evaluated with the cover test (normal fixation or light restitution movement or important restitution movement or deviated eye without restitution movement)
        - Horizontal deviation as evaluated with the Maddox rod test (orthophoria or exophoria or esophoria and measure in diopter)
        - Vertical deviation of the right eye as evaluated with the Maddox rod test (orthophoria or hypophoria or hyperphoria and measure in diopter)
        - Vertical deviation of the left eye as evaluated with the Maddox rod test (orthophoria or hypophoria or hyperphoria and measure in diopter)
    - Balance function:
        - Statokinesigram area (m^2)
        - Difference between left distribution and right distribution (%)

- For the evolution of executive function, the following timepoints will be compared: (D0 before treatment – D7 after treatment) and a mixed effect 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 will be added in the model as covariates.
        - TMT A: time (s)
        - TMT A: number of errors
        - TMT B: time (s)
        - TMT B: number of errors
        - TMT B-A: time (s)
        - TMT B-A: number of errors

- For concussion syndrome symptoms (SCAT5): For the analysis at 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 will be added in the model as covariates. This model will be run for:
    - The total number of symptoms (score from 0 to 22)
    - The symptom severity (score from 0 to 132)

- A description analyses of blood markers at each time point and the change from baseline to each time point will be assessed by groups and overall.

Sensitivity analysis:
A sensitivity analysis will be conducted on the secondary performance endpoints 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).

9.6.4. Timing of Analyses

There will be only one final analysis at the end of the investigation.

9.7. Data Management

Data management activities will be performed by [redacted]

The randomization will be managed centrally using an IWRS. It will be handled in a non-blinded manner since only patients will be blinded to their assigned treatment.

Data will be collected by investigators using an electronic Case Report Form (eCRF) that is compliant with Food and Drug Administration 21 CFR Part 11 regulation.

A clinical database will be created specifically for the investigation, tested and validated before any data has been entered into the eCRF.

In accordance with current laws and regulation, data confidentiality will be ensured using appropriate security means:

- Patients will be identified in the eCRF and clinical database by a numeric identifier. Only the site will maintain a confidential list of included patients linking patients' identifier to their identity.
- No nominative data will be collected.
- Data hosting will be managed by a company certified as a health data company and as ISO 27001, ensuring strong security and confidentiality measures, as well as an IT infrastructure designed for Certified Health Data Hosting.

Two types of queries can be issued within the eCRF:

- Automatic queries which are automatic consistency checks set up in the eCRF that relate to data format, missing data, outliers and inter-field inconsistencies. These will guide the investigators during data entry and inform them that corrections might be needed.
- Manual queries which are queries issued by monitors during on-site monitoring visits and remote monitoring or by data managers or the project manager following data review meetings and reconciliations.

Both automatic and manual queries will be visible by the site which will be able to either confirm the entered data if correct or modify them if not.

To ensure data traceability, all data entries and modifications as well as all queries will be tracked in the eCRF audit trail. The following information will appear in the audit trail: date of entry, modification, or query; name of the person who entered or modified the data or issued the query; data in question.

[redacted] will code safety events in accordance with MedDRA terminology and medicinal treatments in accordance with the World Health Organization's (WHO) medicinal product reference list, which uses the "Anatomical Therapeutic Chemical" (ATC) classification system.

A data review meeting will be held at the end of the investigation to ensure that the database is clean. This meeting may rely on specific listings such as the list of pending queries. Decisions on inconsistent data remaining at the end of investigation will be taken at this meeting with REGEnLIFE.

Following regular or final quality control, the principal investigator will be asked to sign off the eCRF forms to attest the accuracy of entered data. The database will then be locked.

All data will be stored until final report or results publication. They will then be archived on informatic support, transmitted to the responsible of treatment for a retention period in accordance with regulation.

A Data Management Plan will be prepared by [redacted] and submitted to REGEnLIFE for approval. This plan will describe all data management tasks to realize during the investigation and how to realize

them (e.g., database cleaning, database lock etc.). The investigation will be conducted in accordance with this Data Management Plan.

9.8. Clinical Investigation Plan Amendments

Any amendments to this CIP will be prepared by [redacted] validated by REGEnLIFE, and submitted for evaluation to the Ethics Committee in accordance with the regulation.

The investigators will be notified by [redacted] or REGEnLIFE of any relevant modifications.

9.9. Clinical Investigation Plan Deviations

The investigators should strictly follow this CIP.

An investigation deviation may occur when the investigators or any other member of the investigation team fails to conduct the investigation in compliance with the CIP, GCP and the applicable regulation. Such deviations may include lack of documentation of patient information and informed consent, deviations in safety reporting as well as deviations in data recording and archiving.

[redacted] will document any deviations that occur at the site. REGEnLIFE will be informed within 72h following the deviation. If needed, reasonable corrective and preventive actions will be undertaken to avoid any subsequent deviations.

9.10. Investigational Medical Device Accountability

As previously mentioned, two RGn550 devices producing a 5Hz frequency and two producing a 10 Hz frequency will be provided by REGEnLIFE to the site. These devices will be returned to REGEnLIFE at the end of the investigation.

REGEnLIFE will keep records of the physical location of all investigational devices from shipment to return.

The site will keep records of receipt and return of devices. These will include:

- Date of receipt
- Identification (reference number)
- Expiry date
- Date of return.

9.11. Statements of Compliance

9.11.1. Regulatory and Ethical Considerations

The investigation will be conducted in accordance with this CIP, applicable laws and regulations (including European Regulation 2017/745) and ISO 14155:2020 as well as with recognized ethical principles described in the declaration of Helsinki, ISO 14155:2020 standard and applicable laws and regulations.

The investigation will only start once the submission dossier is validated by the French National Agency for the Safety of Medicines and health products (*Agence Nationale de Sécurité des Médicaments et produits de santé* (ANSM)) and the Ethics Committee's approval is obtained. Any additional requirements imposed by the Ethics Committee will be followed.

Since patient personal data will be collected and processed during this investigation, compliance to MR001 or authorization from the French authority of data protection (CNIL: *Commission Nationale de l'Informatique et des Libertés*) is required. REGEnLIFE has a declaration of compliance with MR001. In addition, the processing of personal data will comply with the European General Data Protection Regulation (GDPR) 2016/679.

All information and data concerning patients or their participation in this investigation will be considered confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. Data will be collected and retained in a pseudo-anonymized format, with no identifying values that might link the data to an individual participant of the investigation. Patient names will not be communicated to REGEnLIFE.

Since the clinical part of EUDAMED database is not available yet, the investigation will be registered on a publicly available database. Registration on EUDAMED will be made once available (if available during the investigation).

9.11.2. Financing, Contract and Insurance

REGEnLIFE will finance this clinical investigation.

A financial convention will be put in place with the site.

A specific insurance to the investigation has been subscribed by REGEnLIFE.

9.11.3. Roles and Responsibilities

Each member of the investigation team will comply with their respective following roles and responsibilities.

9.11.3.1. Contract Research Organization

[redacted] is the Contract Research Organization that performs the following activities on behalf of REGEnLIFE:

- Investigation preparation, including writing of this CIP
- Regulatory submission
- Project management
- Site management
- Data management

- Statistical analyses
- Writing of Clinical Investigation Report.

9.11.3.2. Principal Investigator

The role of the principal investigator is to implement, oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and wellbeing of the patients involved in the clinical investigation.

Responsibilities of the principal investigator are to:

- Provide an up-to-date signed and dated copy of his/her curriculum vitae describing his/her experience, qualification and training
- Ensure adequate training and qualifications of the investigation site team and maintain oversight of its activities
- Explain the investigation to the patient in local language using non-technical terms to ensure proper understanding and provide the patient with ample time to read and understand the patient information sheet and to consider participation
- Provide the patient with a copy of the signed and dated patient information and informed consent sheet and document the process of patient's informed consent obtention in the patient's medical file
- Ensure that the anonymity of the patients is strictly maintained and that their identity is protected against unauthorized parties
- Conduct the investigation as per this CIP
- Collect and report the necessary data in the eCRF and ensure their quality
- Perform safety reporting, as described in section 9.13
- Report any deviations to this CIP, the applicable laws and regulations to REGEnLIFE
- Permit authorized representatives of the sponsor, regulatory agencies, and Ethics Committee direct access to review the patient's original medical file for verification of investigation-related procedures and data
- Ensure medical care of the patients
- After the end of the investigation, maintain and archive for 15 years the investigation site file, which will contain at a minimum the CIP and any amendments, the favorable opinion from the Ethics Committee, the list of included patients, any relevant correspondence, as well any other appropriate documents.

9.12. Informed Consent Process

All applicable laws, regulations, and Ethics Committee requirements must be followed during the informed consent process.

As previously mentioned, the participating site will offer investigation participation to patients meeting the eligibility criteria.

The principal investigator will explain to the patient:

- The nature, objectives, benefits, implications, risks and inconveniences of the clinical investigation
- The patient's rights and guarantees regarding their protection, in particular their right to refuse to participate in and the right to withdraw from the clinical investigation at any time without any resulting detriment and without having to provide any justification
- The conditions under which the clinical investigations will be conducted, including the expected duration of patient's participation
- The possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical investigation is discontinued.

The patient will be provided with the current patient information sheet and informed consent form to read. The principal investigator will verify that the patient has understood the information and any questions that may arise will be addressed. Moreover, adequate time will be given for the patient to consider their decision to participate in the clinical investigation.

To participate in the investigation, the patient and the principal investigator must sign and date the informed consent form. The principal investigator will provide patients with a copy of their signed informed consent form and retain the original version in the investigation site file.

The informed consent process and patient participation to the investigation will be documented in the patient medical file.

In case of new information available during the investigation or modification in the investigation procedure, the patient will be informed accordingly. An updated patient information sheet will be given to the patient and the informed consent form will be resigned and dated.

9.13. Safety Recording and Reporting

9.13.1. Definitions within the Context of this Investigation

9.13.1.1. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of investigation, whether or not related to the investigational medical devices *(Regulation 2017/745).*

Relevant notes from ISO 14155:2020 standard:

- *This definition includes events related to the procedures involved.*
- *For users or other persons, this definition is restricted to events related to the use of investigational medical devices*.

9.13.1.2. Serious Adverse Event (SAE)

Any AE that led to any to any of the following *(Regulation 2017/745)*:

- Death
- Serious deterioration in the health of the subject resulting in any of the following:
    - Life-threatening illness or injury
    - Permanent impairment of a body structure or a body function
    - Hospitalization or prolongation of patient hospitalization,
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - Chronic disease
- Fetal distress, fetal death, or a congenital physical or mental impairment or birth defect.

Relevant note from ISO 14155:2020 standard: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE.

9.13.1.3. Adverse Device Effect (ADE)

AE related to the use of an investigational medical device *(ISO 14155:2020 standard)*.

Relevant notes from ISO 14155:2020 standard:

- *This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical devices.*
- *This includes any event resulting from use error or from intentional misuse of the investigational medical device.*

9.13.1.4. Serious Adverse Device Effect (SADE)

ADE that has resulted in any of the consequences characteristic of a SAE *(ISO 14155:2020 standard)*.

9.13.1.5. Unanticipated Serious Adverse Device Effect (USADE)

SADE which by its nature, incidence, severity or outcome has not been identified in the current risk assessment *(ISO 14155:2020 standard)*.

Relevant note from ISO 14155:2020 standard: Anticipated SADE (ASADE) is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk assessment.

9.13.1.6. Device Deficiency (DD)

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer (*Regulation 2017/745*).

9.13.2. Definitions within the Context of Materiovigilance

9.13.2.1. Incident

Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect (*Regulation 2017/745*).

9.13.2.2. Serious Incident

Any incident that directly or indirectly led, might have led or might lead to any of the following (*Regulation 2017/745*):

- The death of a patient, user or other person
- The temporary or permanent serious deterioration of a patient's, user's or other person's state of health
- A serious public health threat.

9.13.2.3. Serious Public Health Threat

An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time (*Regulation 2017/745*).

9.13.3. Safety Reporting to Sponsor

Per Article 80 of the European Regulation 2017/745, the following events shall be recorded:

- Any AE of a type identified in the CIP as being critical to the evaluation of the results of that clinical investigation
- Any SAEs
- Any DD that might have led to a SAE if appropriate action had not been taken intervention had not occurred, or circumstances had been less fortunate
- Any new findings in relation to the above events.

The following events that occur in patients included in RGnCON from inclusion to the end of the 52-day follow-up period will thus be recorded:

- All AEs, including SAEs
- All DDs
- Any new findings in relation to AEs and DDs.

AEs will be reported using the Adverse Event form of the eCRF while DDs will be reported using the Device Deficiency form. The date of the event, its severity, causality, treatment and resolution will notably be collected.

These events will be reported immediately to REGEnLIFE and no later than 3 calendar days after the investigator becomes aware of the event.

If needed, the investigations site team or [redacted] can contact REGEnLIFE's materiovigilance department via email (gchampleboux@regenlife.com) or phone (+33 6 49 81 34 54).

9.13.4. Safety Reporting to Authorities

Per Article 80 of the European Regulation 2017/745, the following events shall be reported to authorities:

- Any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
- Any DD that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
- Any new findings in relation to the above events.

The Medical Device Coordination Group 2021-1 guideline states that, since EUDAMED clinical modules are not operational yet, national provisions apply for safety reporting to authorities.

REGEnLIFE will thus report the above-listed events to the ANSM via the following email address: EC.DMCOS@ansm.sante.fr.
Timeframes for safety reporting to the ANSM are described in Table 3 below.

Table 3: Timeframes for safety reporting to authorities

Type of event	Timeframe
• All SAEs or DDs mentioned at the beginning of section 9.13.4 that led to death or a risk of imminent death, serious injury or disease and that require prompt corrective action for patients, users or others • Any new information related to such events	Immediately and no later than 2 calendar days after REGEnLIFE becomes aware of the event or new information related to an already-reported event
• Other SAEs or DDs mentioned at the beginning of section 9.13.4 • Any new information related to such events	Immediately and no later than 7 calendar days after REGEnLIFE becomes aware of the event or new information related to an already-reported event

9.13.5. Anticipated Adverse Device Effects

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

9.13.6. Data Safety Monitoring Board

There is no Data Safety Monitoring Board for this investigation.

9.14. Vulnerable Population

There will not be any vulnerable patients included in this investigation.

9.15. Suspension or Premature Termination of the Clinical Investigation

9.15.1. Suspension or Premature Termination of the Clinical Investigation

REGEnLIFE has the right to suspend or terminate this investigation at any time. Reasons for suspending or terminating the investigation may include but are not limited to the incidence or severity of ADEs or DDs resulting in an unexpected, significant, or unacceptable risk to participants, and unsatisfactory patient enrollment.

In this case, the investigators will be informed, with the reason for investigation suspension or early termination. Notification of suspension or termination will occur no later than five business days after REGEnLIFE's decision. Moreover, REGEnLIFE will send a report outlining the circumstances to the Ethics Committee and all investigators. The investigators should continue to follow their patients as standard of care at their institution, but data collection will be stopped.

A suspended or terminated investigation may not be reinitiated without approval of the reviewing Ethics Committee, where applicable.

9.15.2. Site Close-Out

REGEnLIFE reserves the right to close the site at any stage, upon giving reasonable written notice to the investigators. Reasons for closing the site may include, but are not limited to excessively slow recruitment, major deviations to regulations or to GCP by the site, inaccurate or incomplete data recording and no investigation activity (i.e., all patients have completed the investigation and all obligations have been fulfilled).

A closed site may not be reinitiated without giving reasonable proof to REGEnLIFE that sufficient preventive and corrective actions have been implemented to resolve root causes of the problem.

9.15.3. Investigator Participation Discontinuation

Likewise, the investigators may discontinue participation upon giving reasonable written notice. In this case, the investigators shall return relevant documents to REGEnLIFE.

At the end of the investigation, or at premature site closure, routine close-out activities will be conducted to ensure site records are complete, investigation data are complete and accurate, arrangements are made for record retention, and Ethics Committee is notified.

9.16. Results and Publication Policy

As previously mentioned, since registration on EUDAMED database is not available yet, the investigation will be registered on a publicly available database. Registration on EUDAMED will be performed once available (if available during the investigation).

A Clinical Investigation Report will be written. Results of the investigation will be communicated to the investigators and made available on the publicly available database.

The investigation results will be submitted for publication in an appropriate peer reviewed journal.

If the investigators wish to publish data from this investigation (poster, abstract, article, etc.), they must first seek approval from REGEnLIFE.

9.17. Provisional Timelines

- Regulatory submission: June 2022
- Site initiation: August-September 2022
- Patient recruitment: September 2022 (first patient first visit) - December 2022 (last patient first visit)
- Last visit last patient: February 2023
- Database lock: March-April 2023
- Statistical analysis and clinical investigation report: May-July 2023

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11.DOCUMENT REFERENCES

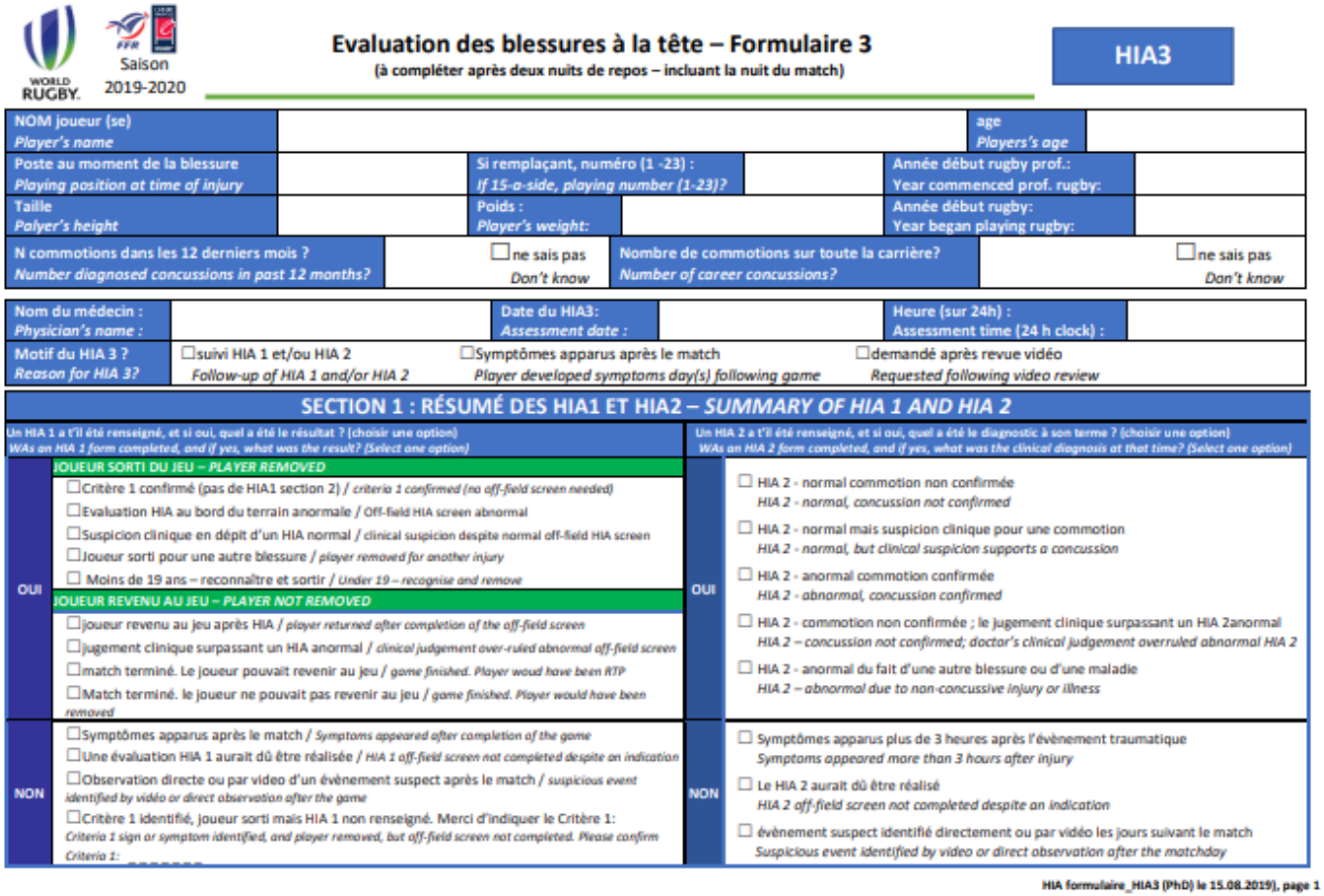
RGn550 IFU: Instructions for Use RGn550 version 1 dated 07 April 2022

RGn550 investigator brochure: RGn550 Brochure Investigateur version 1.0 dated 02 June 2022

12.APPENDICES

All tools provided below are provided in French considering that the investigation will be conducted in France.

12.1. Head Impact Assessment - Form 3



Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

NOM joueur (se) *Player's name*				age *Players's age*	
Poste au moment de la blessure *Playing position at time of injury*		Si remplaçant, numéro (1 -23) : *If 15-a-side, playing number (1-23)?*		Année début rugby prof.: Year commenced prof. rugby:	
Taille *Palyer's height*		Poids : *Player's weight:*		Année début rugby: Year began playing rugby:	
N commotions dans les 12 derniers mois ? *Number diagnosed concussions in past 12 months?*		☐ne sais pas *Don't know*	Nombre de commotions sur toute la carrière? *Number of career concussions?*		☐ne sais pas *Don't know*

Nom du médecin : *Physician's name :*		Date du HIA3: *Assessment date :*		Heure (sur 24h) : Assessment time (24 h clock) :	
Motif du HIA 3 ? *Reason for HIA 3?*	☐suivi HIA 1 et/ou HIA 2 *Follow-up of HIA 1 and/or HIA 2*	☐Symptômes apparus après le match *Player developed symptoms day(s) following game*	☐demandé après revue vidéo *Requested following video review*		

SECTION 1 : RÉSUMÉ DES HIA1 ET HIA2 – *SUMMARY OF HIA 1 AND HIA 2*

Un HIA 1 a t'il été renseigné, et si oui, quel a été le résultat ? (choisir une option) *WAs an HIA 1 form completed, and if yes, what was the result? (Select one option)*		Un HIA 2 a t'il été renseigné, et si oui, quel a été le diagnostic à son terme ? (choisir une option) *WAs an HIA 2 form completed, and if yes, what was the clinical diagnosis at that time? (Select one option)*	
OUI	**JOUEUR SORTI DU JEU – *PLAYER REMOVED*** ☐Critère 1 confirmé (pas de HIA1 section 2) / *criteria 1 confirmed (no off-field screen needed)* ☐Evaluation HIA au bord du terrain anormale / Off-field HIA screen abnormal ☐Suspicion clinique en dépit d'un HIA normal / clinical suspicion despite normal off-field HIA screen ☐Joueur sorti pour une autre blessure / *player removed for another injury* ☐ Moins de 19 ans – reconnaître et sortir / *Under 19 – recognise and remove* **JOUEUR REVENU AU JEU – *PLAYER NOT REMOVED*** ☐joueur revenu au jeu après HIA / *player returned after completion of the off-field screen* ☐jugement clinique surpassant un HIA anormal / *clinical judgement over-ruled abnormal off-field screen* ☐match terminé. Le joueur pouvait revenir au jeu / *game finished. Player would have been RTP* ☐Match terminé. le joueur ne pouvait pas revenir au jeu / *game finished. Player would have been removed*	OUI	☐ HIA 2 - normal commotion non confirmée *HIA 2 - normal, concussion not confirmed* ☐ HIA 2 - normal mais suspicion clinique pour une commotion *HIA 2 - normal, but clinical suspicion supports a concussion* ☐ HIA 2 - anormal commotion confirmée *HIA 2 - abnormal, concussion confirmed* ☐ HIA 2 - commotion non confirmée ; le jugement clinique surpassant un HIA 2anormal *HIA 2 – concussion not confirmed; doctor's clinical judgement overruled abnormal HIA 2* ☐ HIA 2 - anormal du fait d'une autre blessure ou d'une maladie *HIA 2 – abnormal due to non-concussive injury or illness*
NON	☐Symptômes apparus après le match / *Symptoms appeared after completion of the game* ☐Une évaluation HIA 1 aurait dû être réalisée / *HIA 1 off-field screen not completed despite an indication* ☐Observation directe ou par video d'un évènement suspect après le match / *suspicious event identified by video or direct observation after the game* ☐Critère 1 identifié, joueur sorti mais HIA 1 non renseigné. Merci d'indiquer le Critère 1: *Criteria 1 sign or symptom identified, and player removed, but off-field screen not completed. Please confirm Criteria 1:*	NON	☐ Symptômes apparus plus de 3 heures après l'évènement traumatique *Symptoms appeared more than 3 hours after injury* ☐ Le HIA 2 aurait dû être réalisé *HIA 2 off-field screen not completed despite an indication* ☐ évènement suspect identifié directement ou par vidéo les jours suivant le match *Suspicious event identified by video or direct observation after the matchday*

HIA formulaire_HIA3 (PhD) le 15.08.2019), page 1

Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

SECTION 2 : DETAILS DE L'EVENEMENT – INCIDENT DETAILS

Y a-t-il un fait de match ou d'entraînement identifié responsable de la mise en œuvre du processus HIA après le match ou l'entraînement, au stade du HIA2 ou HIA3 ? *Was there a specific game or training incident that cause the player to enter the HIA process after the game or training at the time of HIA 2 or HIA 3?*	☐ OUI ☐ NON ☐ non applicable *not relevant*
S'il s'agit d'un évènement en match, a quel moment est-il survenu ? *If a match injury was responsible in what quarter of the match did this incident occur?*	☐ 1 quart ☐ 2 quart ☐ 3 quart ☐ 4 quart

Incident de jeu - *Game event :*	Collisions avec – *collision with :*	Contact :	Technique du joueur – *Player technique :*
☐ plaqueur Tackling	☐ Adversaire *Opponent*	☐ tête-tête *Head with head*	☐ Technique correcte *Correct technique*
☐ plaqué *Being tackled*	☐ Co-équipier *Co-player*	☐ Tête-épaule *Head with shoulder*	☐ Position de la tête incorrecte *Incorrect head position*
☐ Ruck / Maul	☐ Sol *Ground*	☐ Tête-membre sup. *Head with upper limb*	☐ Autre technique incorrecte *Other Incorrect technique*
☐ Mêlée / Scrum	☐ Inconnu *Unknown*	☐ Tête-hanche/genou *Head with knee or hip*	☐ Inconnu *Unknown*
☐ Collision accidentelle *Accidental collision*	☐ Autre *Other*	☐ Tête-pied/membre inf. *Head with foot/lower leg*	☐ Non applicable *Not applicable*
☐ Inconnu *Unknown*		☐ Tête-sol *Head with ground*	☐ Autre *Other*
☐ Autre *Other*		☐ Transmission indirecte à la tête *Indirect transmission of force to head*	Jeu dangereux *Foul play*
		☐ Inconnu *Unknown*	☐ Plaqueur sanctionné *Sanction given to tackler*
		☐ Autre *Other*	☐ Porteur de balle sanctionné *Sanction given to ball carrier*

SECTION 3 : ÉVALUATION COGNITIVE - *COGNITIVE ASSEESSMENT – Standardized Assessment of Concussion (SAC)*

ORIENTATION (1 point par réponse correcte – *1 point for each correct answer*)	incorrecte	correcte
Quel mois sommes-nous ? *What month is it ?*	☐	☐
Quelle est la date aujourd'hui ? *What is the date today?*	☐	☐
Quel jour de la semaine sommes-nous ? *What is the day of the week?*	☐	☐
En quelle année sommes-nous ? *What year is it ?*	☐	☐
Quelle heure est-il (à une heure près) ? *What time is it right now (within 1 hour)?*	☐	☐
Score d'orientation :	**/ 5**	

Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

SECTION 3 (suite *continued*) : EVALUATION COGNITIVE – Standardized Assessment of Concussion (SAC)

MEMOIRE IMMEDIATE *IMMEDIATE MEMORY*

Choisissez l'une de ces 6 listes de 10 mots. Trois d'entre-elles sont disponibles en anglais. Choisissez l'ordre dans lequel vous allez lire la liste de 10 mots choisie sans le modifier en cours de test

Ordre de lecture choisi	☐ → →	☐ → ←	☐ ← ←	☐ ← →	☐ ↓ ↓	☐ ↑ ↑

Liste	Listes de 10 mots *Alternative 10-word lists*					Test 1	Test 2	Test 3
☐A	**Sorcière** - *Elbow* **Oiseau** - *Candle*	**Chemin** - *Apple* **Leçon** - *Paper*	**Maison** - *Carpet* **Taxi** - *Sugar*	**Objet** - *Saddle* **Odeur** - *Sandwich*	**Prison** - *Bubble* **Police** - *Wagon*			
☐B	**Theatre** - *Baby* **Cheveu** - *Finger*	**Cheval** - *Monkey* **Planete** - *Penny*	**Usine** - *Perfume* **Chateau** - *Blanket*	**Soleil** - *Sunset* **Valise** - *Lemon*	**Image** - *Iron* **Poulet** - *Insect*			
☐C	**Chemise** - *Jacket* **Poisson** - *Dollar*	**Jardin** - *Arrow* **Couleur** - *Honey*	**Chanson** - *Pepper* **Chaussure** - *Mirror*	**Papier** - *Cotton* **Oreille** - *Saddle*	**Montagne** - *Movie* **Enfant** - *Anchor*			
☐D	**Menton** **Lampe**	**Monnaie** **Feuille**	**Rideau** **Sucre**	**Pèche** **Viande**	**Oiseau** **Bateau**			
☐E	**Bebe** **Jambe**	**Poisson** **Pomme**	**Parfum** **Tapis**	**Fumée** **Chaise**	**Ecran** **Balle**			

Score de mémoire immédiate *Immediate memory score* : / 30

Heure à la fin du troisième test *Time that last trial was completed* :

CONCENTRATION : CHIFFRES A L'ENVERS - *DIGITS BACKWARDS* (1 point par série réussie - *1 point for each correct answer*)

série	Test 1		Test 2		Séries alternatives Alternative digit lists		
	Incorrect	correct	Incorrect	correct			
4-9-3 (6-2-9)	☒	☐	☐	☐	**5-2-6** (4-1-5)	**1-4-2** (6-5-8)	**7-8-2** (9-2-6)
3-8-1-4 (3-2-7-9)	☐	☐	☐	☐	**1-7-9-5** (4-9-6-8)	**6-8-3-1** (3-4-8-1)	**4-1-8-3** (9-7-2-3)
6-2-9-7-1 (1-5-2-8-6)	☐	☐	☐	☐	**4-8-5-2-7** (6-1-8-4-3)	**4-9-1-5-3** (6-8-2-5-1)	**1-7-9-2-6** (4-1-7-5-2)
7-1-8-4-6-2 (5-3-9-1-4-8)	☐	☐	☐	☐	**8-3-1-9-6-4** (7-2-4-8-5-6)	**3-7-6-5-1-9** (9-2-6-5-1-4)	**2-6-4-8-1-7** (8-4-1-9-3-5)

CONCENTRATION : MOIS A L'ENVERS – *MONTHS IN REVERSE ORDER* (1 point si séquence réussie – *1 point for entire correct sequence*)

Dec-Nov-Oct-Sep-Aou-Juil-Juin-Mai-Avr-Mar-Fév-Jan	incorrecte	correcte
	☐	☐

Score de concentration – *Concentration score* (Chiffres + mois à l'envers) : / 5

HIA formulaire_HIA3 (PhD) le 15.08.2019), page 3

WORLD RUGBY. Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

SECTION 4 : EVALUATION DES SYMPTOMES - Score de symptomes – *SYMPTOM ASSESSMENT - Symptom Checklist*

A TRANSMETTRE AU JOUEUR POUR LE LIRE – HAND TO PLAYER TO READ

Au joueur : depuis le coup d'envoi jusqu'à maintenant : - *To the player : From kick-off time until now:*

COMBIEN ? *HOW MANY ?*			QUELLE INTENSITE ? *HOW MUCH ?*						QUAND ? *WHEN ?*			COMBIEN DE TEMPS ? *HOW LONG ?*					TOUJOURS PRESENT ? *STILL PRESENT ?*						
Identifiez tous les symptômes inhabituels pour le rugby que vous avez présenté depuis la blessure ou le match *Identify any symptom you have experienced since the injury or following the match which is not usually noted with rugby*			Notez l'intensité maximale de chaque symptôme *Identify the maximum intensity of each symptom*						Notez le moment où chaque symptôme a commencé *Identify when you started to feel each symptom identified*			Notez combien de temps chaque symptôme a duré *Identify how long each of these symptoms lasted*					Notez l'intensité de chaque symptôme inhabituel qui est toujours présent *Confirm the intensity of any unusual symptom that is still present*						
			minime		modéré		sévère											minime		modéré		sévère		
	NON	OUI	1	2	3	4	5	6	A*	B**	C***	0-15 min	15 min – 1 heure	1 heure – 1ère nuit	1ère nuit – 2ème nuit	Après la 2ème nuit	0	1	2	3	4	5	6
Mal à la tête (P) *Headaches*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tête lourde b(P) *Pressure in head*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mal au cou (P) Neck pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausées, vomissements (P) *Nausea or vomiting*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fatigue, faible énergie (P) *Fatigue, low energy*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vertiges (V-O) *dizziness*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Troubles de la vue (V-O) *blurred vision*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Troubles de l'équilibre (V-O) *balance problems*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Gêné(e) par la lumière (V-O) *sensitivity to light*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Gêné(e) par le bruit (V-O) *sensitivity to noise*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sensation d'être ralenti (C) *feeling slowed down*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dans le brouillard (C) *feeling like in a fog*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

HIA formulaire_HIA3 (PhD) le 15.08.2019), page 4

Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

COMBIEN ? *HOW MANY ?*			QUELLE INTENSITE ? *HOW MUCH ?*						QUAND ? *WHEN ?*			COMBIEN DE TEMPS ? *HOW LONG ?*					TOUJOURS PRESENT ? *STILL PRESENT ?*						
Identifiez tous les symptômes inhabituels pour le rugby que vous avez présenté depuis la blessure ou le match *Identify any symptom you have experienced since the injury or following the match which is not usually noted with rugby*			**Notez l'intensité maximale de chaque symptôme** *Identify the maximum intensity of each symptom*						**Notez le moment où chaque symptôme a commencé** *Identify when you started to feel each symptom identified*			**Notez combien de temps chaque symptôme a duré** *Identify how long each of these symptoms lasted*					**Notez l'intensité de chaque symptôme inhabituel qui est toujours présent** *Confirm the intensity of any unusual symptom that is still present*						
			minime		modéré		sévère					0-15 min	15 min – 1 heure	1 heure – 1ère nuit	1ère nuit – 2ème nuit	Après la 2ème nuit		minime		modéré		sévère	
	NON	OUI	1	2	3	4	5	6	A*	B**	C***						0	1	2	3	4	5	6
Je ne me sens pas bien (C) *don't feel right*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Du mal à me concentrer (C) *difficulty concentrating*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Du mal à me souvenir (C) *difficulty remembering*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confus(e) (C) *confusion*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Somnolent(e) (C) *drowsiness*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Du mal à m'endormir (Psy) *difficulty falling asleep*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Plus émotif(ve) (Psy) *more emotional*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Irritabilité (Psy) *irritability*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tristesse (Psy) *sadness*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nerveux(se), anxieux(e) (Psy) *nervous or anxious*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Groupes symptomatiques : P :Physique – V-O : Oculo-vestibulaire – C :cognitif – Psy : Psychologique

A* : sur le terrain - *On the pitch*
B**: post-match le même jour – *Post-match, same day*
C***: post-match, jours suivants – Post-match, days after

AMNESIE ANTEROGRADE ?
(amnésie après la blessure – *amnesia after the injury*)
☐NON ☐OUI Durée : min

AMNESIE RETROGRADE ?
(amnésie avant la blessure - *amnesia before the injury*)
☐NON ☐OUI Durée : min

HIA formulaire_HIA3 (PhD) le 15.08.2019), page 5

Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

SECTION 5 : EQUILIBRE, COORDINATION ET MARCHE – *BALANCE, COORDINATION AND GAIT ASSESSMENT*			
EQUILIBRE – BALANCE EXAMINATION			
MARCHE EN TANDEM		**MBESS**	
	Temps		**N erreur**
Essai 1		**Appui bipodal**	
Essai 2		**Appui tandem**	
Essai 3		**Appui monopodal**	

Résultat diagnostique anormal :
plus d'erreurs qu'en présaison ou s'il n'y a pas de test présaisons disponible, un score d'erreur en bipodal >1, en tandem >3 et en monopodal >5 ; marche en tandem >13 sec – *More errrors than baseline OR if no baseline a score in double leg stance 1 or more errors, tandem stance 4 or more errors, single leg stance 6 or more errors*

EXAMEN NEUROLOGIQUE – NEUROLOGICAL SCREEN	non	oui
Le joueur peut-il lire à voix haute (par ex la liste des symptômes) et suivre les instructions sans difficulté ? *Can the player read aloud (e;g; symptom checklist) and follow instructions without difficulty?*	☐	☐
La mobilisation cervicale passive est-elle sans limitation et indolore ? *Does the player have a full and pain-free PASSIVE cervical spine movement?*	☐	☐
Sans bouger la tête ni le cou, la poursuite horizontale et verticale peut-elle être réalisée sans diplopie ? *Without moving their head or neck, can the player look side-to-side and up-and-down without diplopia?*	☐	☐
Le joueur exécute-t-il la manœuvre doigt-nez normalement ? *Can the player perform the finger-nose coordination test normally ?*	☐	☐
Le joueur réalise-t-il l'épreuve de la marche en tandem normalement ? *Can the player perform tandem gait normally?*	☐	☐

SAC – MEMOIRE DIFFEREE – *DELAYED RECALL* (à réaliser au moins 5 minutes après le test de mémoire immédiate – *Must be asked at lezast 5 minutes after Immediate Memory test*)		
heure :	Nombre de mots retenus (liste de 10 mots) du test de mémoire immédiate : *Number of words from immediate memory test remembered (10 words list)*	/ 10

Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

SECTION 6 : RESULTATS - *MODE RESULTS*	
Nombre de symptômes présents – *symptoms present*	/22
Sévérité des symptômes – *symptoms severity*	/132
Orientation	/5
Mémoire immédiate – *immediate memory 10-words list*	/30
Concentration (chifffres et mois à l'envers – *Digits backwards & months reverse order*)	/5
Appui bipodal – *double leg stance errors*	
Appui tandem – *tandem stance errors*	
Appui monopodal – *single leg stance errors*	
Mémoire différée -*delayed recall 10-words list*	/10
Examen neurologique	☐ Normal ☐ Anormal

DONNEES NORMATIVES – *NORMATIVE DATA*

Les joueurs doivent être évalués en comparaison de leurs données présaisons. Si les données présaisons ne sont pas disponibles, les résultats suivants sont indicatifs d'une commotion cérébrale – *Players with baseline SCAT should be assessed against their own baseline. For players where no baseline is available the following results are indicative of a concussion*

1. Orientation: score < 4
2. Mémoire immediate – *immediate memory*: score < 16
3. Concentration (chiffres et mois à l'envers – *digits backwards and months reverse order*) : score < 3
4. Mémoire différée - delayed results : score < 4
5. Tests d'équilibre – *balance testing*
   - Double appui – *double leg stance* : 1 erreur ou plus – *1 or more errors*
   - *Appui en tandem – tandem stance : 4 erreurs ou plus – 4 or more errors*
   - *Simple appui – single leg stance : 6 erreurs ou plus – 6 or more errors*

Note : la présence d'au moins un symptôme sur le score de symptômes qui n'est pas habituel après un match ou un entraînement de rugby est très évocatrice du diagnostic de commotion cérébrale – *The presence of any syptom in the symptom list which is not usually experienced following a rugby match or training is a strong indicator of concussion*

SECTION 7 : EVALUATION COGNITIVE COMPLEMENTAIRE - *ADDITIONNAL COGNITIVE ASSESSMENT* (si réalisée - *if used*)						
Evaluation cognitive informatisée réalisée : *Computer neurocognitive system used*	☐ Cogsport	☐ Headminder	☐ Impact	☐ autre - *Other* :		
Quel est le résultat de cette évaluation cognitive informatisée ? *What was the result of this computer neurocognitive test ?*	☐ normal	☐ anormal	☐ non utilisée – *not used*			
TMT & CODE	☐ TMT normal	☐ TMT anormal	☐ TMT non réalisé	☐ CODE normal	☐ CODE anormal	☐ CODE non réalisé

Saison 2019-2020

Evaluation des blessures à la tête – Formulaire 3

(à compléter après deux nuits de repos – incluant la nuit du match)

HIA3

SECTION 8 : RÉSULTAT DU HIA 3 – *RESULT OF HIA 3*

HIA 3 Result:

- ☐ HIA 3 - normal
- ☐ HIA 3 - normal mais suspicion clinique pour une commotion
  HIA 3 - normal, but clinical suspicion supports a concussion
- ☐ HIA 3 - anormal commotion confirmée
  HIA 3 - abnormal, concussion confirmed
- ☐ HIA 3 - commotion non confirmée ; le jugement clinique surpassant un HIA 3 anormal
  HIA 3 – concussion not confirmed; doctor's clinical judgement overruled abnormal HIA 3
- ☐ HIA 3 - anormal du fait d'une autre blessure ou d'une maladie
  HIA 3 – abnormal due to non-concussive injury or illness

Un HIA 3 ANORMAL est identifié par un score de symptômes anormal, une évaluation cognitive (SAC et/ou évaluation cognitive complémentaire) anormale, une évaluation de l'équilibre anormale OU une évaluation neurologique anormale

An ABNORMAL HIA 2 is identified by abnormal symptoms, abnormal cognitive assessment (SAC and/or computer assessment), an abnormal balance assessment OR an abnormal neurological screen

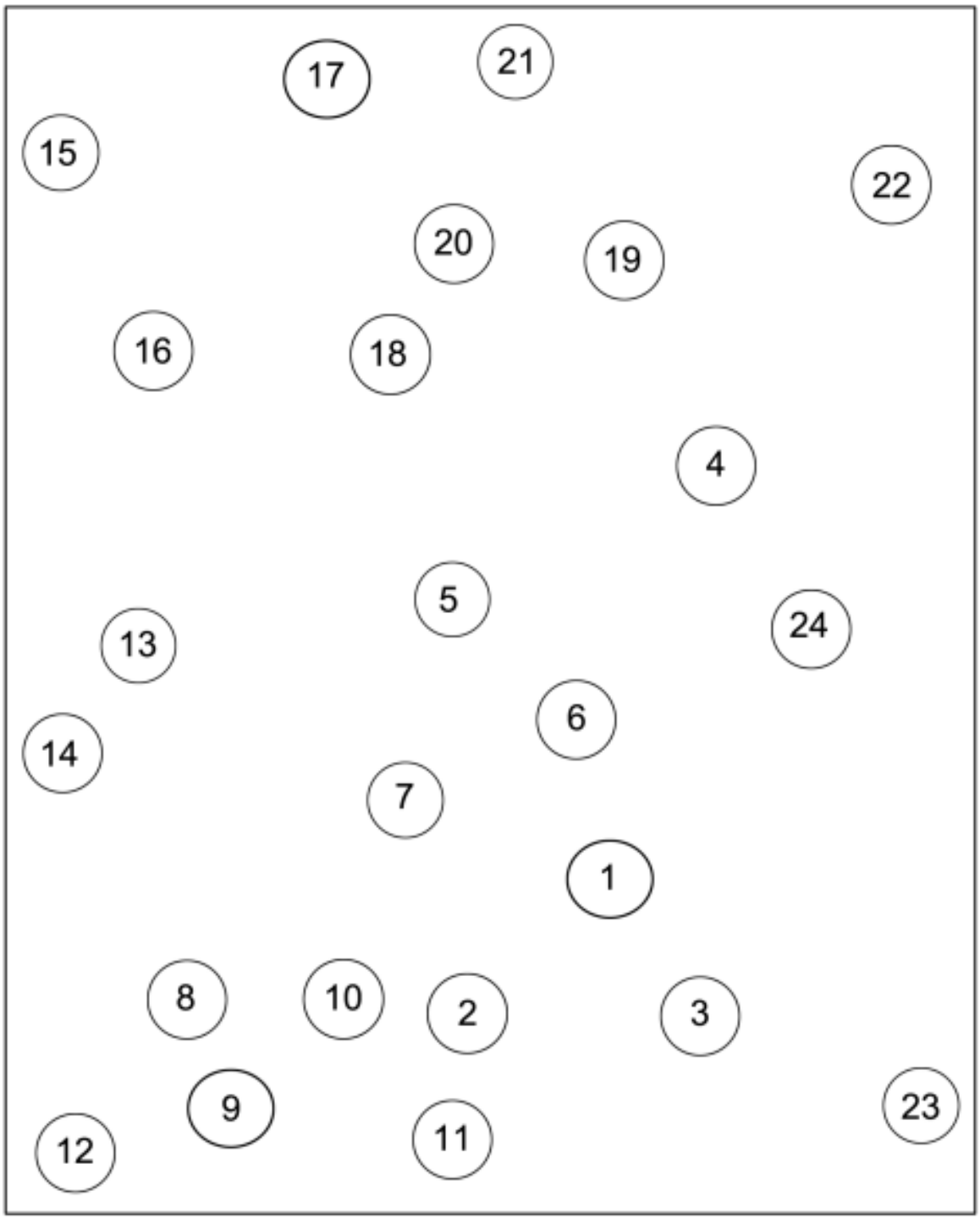
SECTION 9 : SYNTHESE DES RESULTATS – *OVERALL RESULT*

Une commotion a-t-elle été identifiée à l'une des étapes du processus HIA ? - *Was a concussion identified at any stage during the HIA Process?*

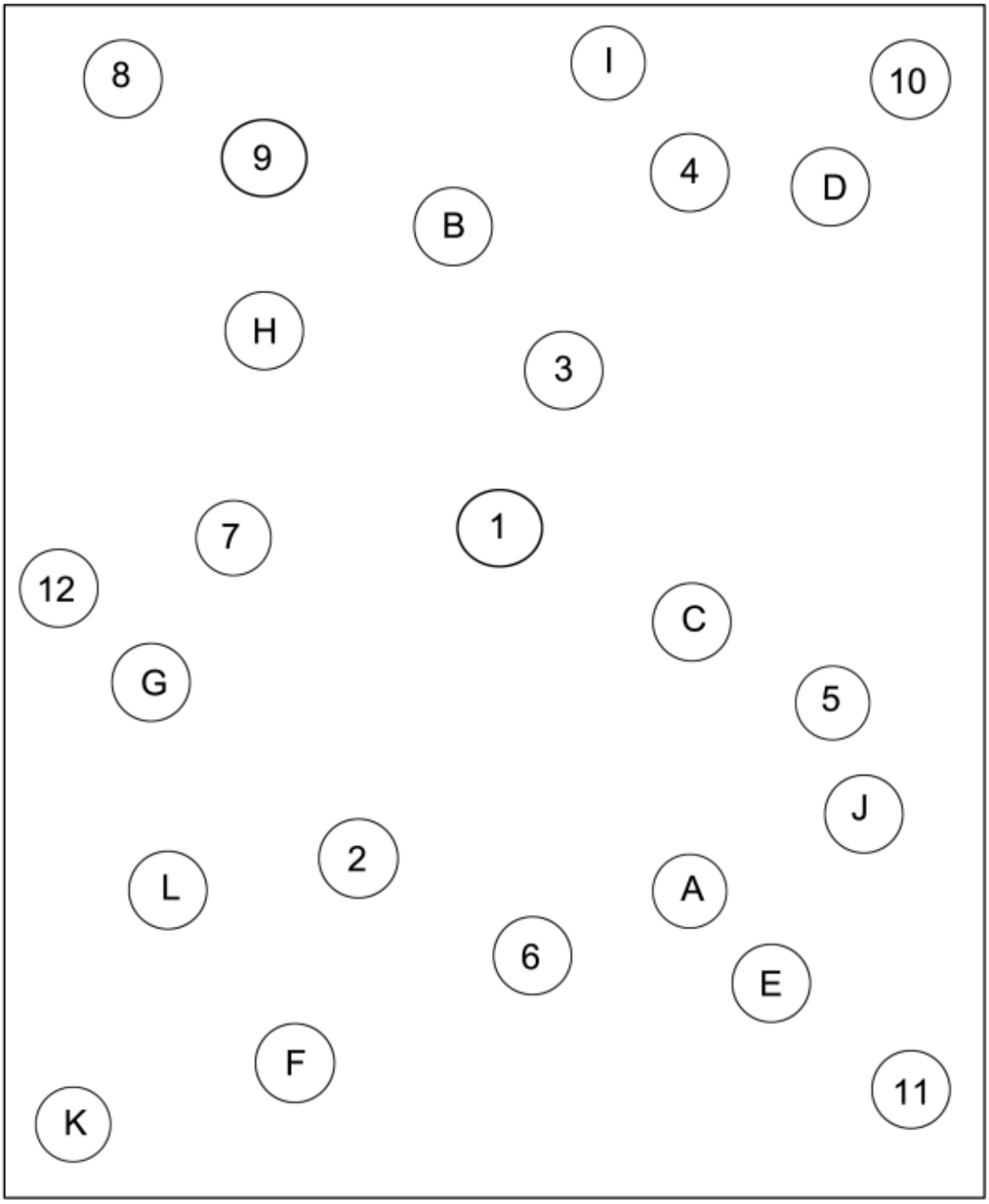
NON	**Raison**	☐ pas de critère 1, HIA 2 normal et HIA 3 normal *Player had no evidence of a criteria 1, a normal HIA 2 and a normal HIA 3*
OUI	**Raison** Plusieurs options possibles *More than one option can be selected*	☐ Critère 1 identifié – *Criteria 1 identified*
		☐ HIA 2 anormal – *HIA 2 abnormal*
		☐ HIA 3 anormal - *HIA 3 abnormal*
		☐ Suspicion clinique à l'une des étapes en dépit de HIA 1, 2 et 3 normaux *Clinical suspicion at any stage despite normal HIA1, 2 and 3*

12.2. Trail Making Test

12.2.1. Part A



12.2.2. Part B



12.3. SCAT5 Symptom Evaluation Tool

ÉTAPE 2: ÉVALUATION DES SYMPTÔMES

Vous devez donner le formulaire des symptômes à l'athlète et lui demander de lire ce paragraphe d'instructions à voix haute avant de remplir l'échelle. Pour l'évaluation de base, l'athlète doit donner une note à ses symptômes selon son ressenti habituel. Pour l'évaluation post-traumatisme, l'athlète doit donner une note à ses symptômes actuels.

Cochez la case correspondante: ☐ **Base** ☐ **Post-traumatisme**

Donnez le formulaire à l'athlète

	RAS	Léger		Modéré		Important	
Maux de têtes	0	1	2	3	4	5	6
«Pression dans le crâne»	0	1	2	3	4	5	6
Douleur dans le cou	0	1	2	3	4	5	6
Nausée ou vomissement	0	1	2	3	4	5	6
Vertiges	0	1	2	3	4	5	6
Vision trouble	0	1	2	3	4	5	6
Problèmes d'équilibre	0	1	2	3	4	5	6
Sensibilité à la lumière	0	1	2	3	4	5	6
Sensibilité au bruit	0	1	2	3	4	5	6
Sensation d'être ralenti.e	0	1	2	3	4	5	6
Sensation d'être «dans le brouillard»	0	1	2	3	4	5	6
«Ne pas se sentir normal.e»	0	1	2	3	4	5	6
Problèmes de concentration	0	1	2	3	4	5	6
Problèmes de mémoire	0	1	2	3	4	5	6
Fatigue ou manque d'énergie	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Somnolence	0	1	2	3	4	5	6
Sensibilité	0	1	2	3	4	5	6
Irritabilité	0	1	2	3	4	5	6
Tristesse	0	1	2	3	4	5	6
Nervosité ou anxiété	0	1	2	3	4	5	6
Difficultés à s'endormir (si applicable)	0	1	2	3	4	5	6
Nombre total de symptômes:							sur 22
Degré de sévérité des symptômes:							sur 132
Vos symptômes s'aggravent-ils pendant une activité physique?					O	N	
Vos symptômes s'aggravent-ils pendant une activité mentale?					O	N	
Si 100 % correspond à une sensation normale, à combien de pour cent vous sentez-vous normal.e?							

Si la réponse n'est pas 100%, pourquoi?

_____

_____

_____

Rendez le formulaire à l'examinateur.trice