PREV-HAP Study - Final Safety Analysis

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Contents

I. General information

1. Safety Population

The **safety population** includes all subjects randomized into the study who received the study drug, even those who have withdrawn their consent.

2. Reporting period

All AE/AR/SAE/SAR must be reported to the sponsor if it happens for a research participant:

- Since the consent signature date,
- During all the participant follow up period scheduled by the study up to the collection of the primary outcome (day 28)

After the end of the patient follow-up and without any time limit if the investigator becomes aware of a SADR possibly linked to one of IMP, including Placebo

3. Exclusion from reporting/notification

Regarding the specificity of the study, some adverse events have not to be collected in safety section of the eCRF: AEs related to the ICU management or related to the medical history (notably the normal course of cause of ICU admission) and which are those classically observed in this context will not be collected as part of this protocol, with the exception of those related to the medicinal products under study or its comparators and placebo, which will be properly collected and notified if necessary

4. Recording rules

According to the protocol:

- The early pneumoniae (<48h after inclusion) are not collected in the primary endpoint page, but are collected in the AE section
- Pneumoniae that occured after the ICU discharge are not collected in the primary endpoint page, but only collected on AE section
- Deaths of patients after D28 are not collected in the AE section but are reported in the end of study page
- All acute respiratory distress syndrome (ARDS) developed after the first IMP administration related or not to an IMP are recorded and notifed as Adverse Event of Special Interest (AESI)
- Seizure related or not to an IMP are recorded and notifed as AESI

5. Adverses events coding

All adverse events are classified in grades from mild (grade 1) to death (grade 5) following the CTC AE version 5.0.

All adverse events are coding with MedDRA dictionnary version 25.0

6. Data export and reference information

This report is based on data extracted from the eVe Report vigilance database, as well as those from eCRF, Ennov Clinical; data were exported on July 22, 2022, after frozen of the database and unblinding:

- Group A = rHuIFN-g
- Group B = Placebo

The export concerns all the patients included in the PREV-HAP Study.

No changes to the RSI, version 1.1 for rHuIFN-g and SmPC (section 4.8), version 02-Jan-2018 for placebo, remained the current version for the duration of the study and served as the reference information for determination of "expectedness" for all adverse reactions; assessment was defined using the standardized approach (EVCTM).

7. Softwares

This report was compiled with R software, version 4.1.2 and Rstudio.

II. Summary information

1. Patients exposure

109 patients were randomized:

- In group rHuIFN-g: [1] 55
- In group Placebo: [1] 54

Table 1: Description of the safety population (Age)

Group of Inclusion	Mean of Age	Median of Age	Min of Age	Max of Age
A	53.12727	57.0	18	76
B	53.53704	57.5	18	78

2. Overview

- 377 adverse events/reactions (including SAE/SAR) were entered in eCRF
- 63 SAE/SAR Reports were received
- Including 7 SUSAR (3 more have been suspected SADR for which unblinding was necessary: patients received placebo)
- 3 AESI (only one met the criteria of AESI defined by the protocol)
- 3 Special Situation reported

The serious adverse reaction are presented as narratives in section III.

3. Drop Out of the Study

- In group rHuIFN-g:

Table 2: Drop out of the study, Groupe A (rHuIFN-g)

Inclusion number	Groupe of inclusion	Patient Sex	Patient Age	Date of Randomisation	ICU admission date	IMP Injection date	Study End date	Resaon for early study end
P-01-013	A	Male	60	09/08/2021	08/08/2021	09/08/2021	11/10/2021	Death
P-01-018	A	Female	71	08/09/2021	06/09/2021	08/09/2021	01/11/2021	Death
P-01-025	A	Male	36	08/10/2021	08/10/2021	08/10/2021	12/10/2021	Death
P-02-001	A	Female	54	06/09/2021	04/09/2021	06/09/2021	12/10/2021	Death
P-03-004	A	Male	56	28/07/2021	27/07/2021	28/07/2021	03/08/2021	Death
P-03-011	A	Male	53	03/09/2021	01/09/2021	03/09/2021	28/09/2021	Death
P-03-013	A	Male	48	17/09/2021	15/09/2021	17/09/2021	06/10/2021	Death
P-03-015	A	Male	41	12/10/2021	10/10/2021	12/10/2021	10/11/2021	Death
P-04-005	A	Male	34	21/09/2021	19/09/2021	21/09/2021	28/09/2021	Death
P-05-002	A	Male	55	21/09/2021	20/09/2021	21/09/2021	20/11/2021	Death
P-06-002	A	Female	71	17/04/2021	17/04/2021	17/04/2021	24/06/2021	Death
P-06-010	A	Female	61	16/05/2021	14/05/2021	16/05/2021	28/05/2021	Death
P-06-029	A	Male	69	01/08/2021	30/07/2021	01/08/2021	10/08/2021	Death

- In group Placebo:

Table 3: Drop out of the study, Groupe B (placebo)

Inclusion number	Groupe of inclusion	Patient Sex	Patient Age	Date of Randomisation	ICU admission date	IMP Injection date	Study End date	Resaon for early study end
P-01-002	B	Male	78	30/04/2021	29/04/2021	30/04/2021	07/06/2021	Withdrawal of patient consent
P-01-012	B	Male	56	28/07/2021	27/07/2021	28/07/2021	24/09/2021	Death
P-01-014	B	Male	59	24/08/2021	24/08/2021	24/08/2021	10/10/2021	Death
P-01-020	B	Male	58	20/09/2021	19/09/2021	20/09/2021	28/09/2021	Death
P-03-003	B	Female	78	26/07/2021	25/07/2021	26/07/2021	10/08/2021	Death
P-03-008	B	Male	71	13/08/2021	11/08/2021	13/08/2021	25/08/2021	Death
P-03-009	B	Male	64	16/08/2021	14/08/2021	16/08/2021	22/08/2021	Death
P-03-014	B	Male	71	21/09/2021	20/09/2021	21/09/2021	24/09/2021	Refusal of the relative for the patient's participation
P-05-004	B	Male	44	08/10/2021	07/10/2021	08/10/2021	16/10/2021	Death
P-06-020	B	Male	65	02/07/2021	01/07/2021	02/07/2021	20/07/2021	Death
P-06-023	B	Male	51	16/07/2021	14/07/2021	16/07/2021	24/09/2021	Death
P-06-032	B	Female	75	03/08/2021	02/08/2021	03/08/2021	31/08/2021	Death
P-06-046	B	Female	35	08/09/2021	06/09/2021	08/09/2021	15/09/2021	Death
P-06-051	B	Female	70	25/09/2021	25/09/2021	25/09/2021	12/10/2021	Death
P-07-001	B	Male	53	23/08/2021	22/08/2021	23/08/2021	24/09/2021	Death

4. Cause of death according to AE section

Table 4: Cause of Death, according the AE section

Inclusion number	Groupe of inclusion	Patient Sex	Patient Age	IMP date (1st injection	AE PT MedDRA	AE Start date	AE End date	Causality for IMP
P-01-020	B	Male	58	20/09/2021	Intracranial pressure increased	24/09/2021	28/09/2021	No
P-01-025	A	Male	36	08/10/2021	Intracranial pressure increased	09/10/2021	12/10/2021	No
P-02-001	A	Female	54	06/09/2021	Coma	06/10/2021	12/10/2021	No
P-03-003	B	Female	78	26/07/2021	Altered state of consciousness	06/08/2021	10/08/2021	No
P-03-004	A	Male	56	28/07/2021	Intracranial pressure increased	30/07/2021	03/08/2021	No
P-03-008	B	Male	71	13/08/2021	Ischaemic stroke	16/08/2021	25/08/2021	Yes
P-03-009	B	Male	64	16/08/2021	Brain oedema	20/08/2021	22/08/2021	Yes
P-03-011	A	Male	53	03/09/2021	Altered state of consciousness	17/09/2021	28/09/2021	No
P-03-013	A	Male	48	17/09/2021	Altered state of consciousness	04/10/2021	06/10/2021	No
P-03-015	A	Male	41	12/10/2021	Altered state of consciousness	05/11/2021	10/11/2021	No
P-04-005	A	Male	34	21/09/2021	Intracranial pressure increased	21/09/2021	28/09/2021	No
P-05-002	A	Male	55	21/09/2021	Acute respiratory distress syndrome	20/11/2021	20/11/2021	No
P-05-004	B	Male	44	08/10/2021	Septic shock	15/10/2021	16/10/2021	No
P-05-004	B	Male	44	08/10/2021	Pulmonary embolism	16/10/2021	16/10/2021	No
P-06-010	A	Female	61	16/05/2021	Stroke in evolution	19/05/2021	28/05/2021	No
P-06-020	B	Male	65	02/07/2021	Coma	20/07/2021	20/07/2021	No
P-06-029	A	Male	69	01/08/2021	Coma	09/08/2021	10/08/2021	No
P-06-046	B	Female	35	08/09/2021	Brain oedema	08/09/2021	15/09/2021	No
P-06-051	B	Female	70	25/09/2021	Chronic obstructive pulmonary disease	25/09/2021	12/10/2021	No
P-07-001	B	Male	53	23/08/2021	Septic shock	22/09/2021	24/09/2021	No

III. Serious Adverse Reactions (SARs) during the Study

Relevant safety data are presented using interval line listings and cumulative summary tabulations in Appendices.

The 7 Serious Adverse Reactions reported during the study are presented here as narratives.

- **FR-CHUNT-202100142**

01-001, a 20 years old Male patient with medical history of Road traffic accident on 27-Mar-2021 with Head injury (cranial trauma), Traumatic chest injury NOS (chest trauma) and Pleural effusion (Abdominal trauma: pleural effusion), had been included in the PREV-HAP study on 29-Mar-2021 in Blinded arm. Because of the events, the randomization arm was unblinded on 11-May-2021.

He had been treated with rHuIFN-g (INTERFERON GAMMA-1B) 100 microgram (Day 1 to day 9 (each to 2 days)) from 29-Mar-2021 to 06-Apr-2021.

On 09-Apr-2021, he experienced Hepatic cytolysis and Anicteric cholestasis (SGPT increased, SGOT increased, GGT increased, Alkaline phosphatase increased and Bilirubin increased (total and direct bilirubin)); grade 3 (Severe), and seriousness criteria reported was Other medically important condition.

On 09-Apr-2021, SGPT was at 206.1 international unit per litre (grade 2),on 11-Apr-2021, at 339.2 international unit per litre (grade 3), and on 12-Apr-2021 at 561.5 international unit per litre (garde 3); on 09-Apr-2021, SGOT was at 215.8 international unit per litre (grade 2), on 11-Apr-2021, at 272.9 international unit per litre (grade 3), and on 12-Apr-2021 at 365.9 international unit per litre (garde 3); on 09-Apr-2021, GGT was at 407 international unit per litre (grade 2), on 11-Apr-2021 at 442 international unit per litre (grade 3), and on 12-Apr-2021, at 485 international unit per litre; on 09-Apr-2021, Alkaline phosphatase was at 147.3 international unit per litre (grade 2), on 11-Apr-2021, at 164.3 international unit per litre (grade 2),and on 12-Apr-2021 at 197 international unit per litre; on 09-Apr-2021, total bilirubin was at 8 umol/l and on 11-Apr-2021 at 7 umol/l. According to the eCRF, liver enzymes were also within normal limits at baseline.

Because of its hepatotoxicity, treatment with paracetamol was stopped on 09-Apr-2021 (administered from 31-Mar-2021); He received Hidonac (Acétylcystéine), 5g as curative treatment (paracetamol intoxication) from 15-Apr-2021 to 16-Apr-2021. There is no acetaminophen dosage to explore paracetamol intoxication.

No alcohol intoxication is documented (chronic nor acute).

The patient had recovered from Hepatic cytolysis and Anicteric cholestasis on 11-Jun-2021.

According to the SmPC, Hepatic cytolysis and Anicteric cholestasis are expected for rHuIFN-g, but unexpected according to the RSI for the study (RSI_V1.1).

The sponsor and the investigator have considered there was a reasonable possibility that the events, Hepatic cytolysis and Anicteric cholestasis, were related to rHuIFN-g.

- **FR-CHUNT-202100292**

03-005, a 75 years old Female patient with medical history of Arterial hypertension, Chronic alcoholism and Traumatic brain injury from 31-Jul-2021 had been included in the PREV-HAP studyon 02-Aug-2021 in Blinded arm. Because of the events, the randomization arm was unblinded on 06-Aug-2021.

She had been treated with rHuIFN-g (INTERFERON GAMMA-1B), 100 microgram every 2 days from 02-Aug-2021 to 08-Aug-2021. She also received, as concomitant drugs, PANTOPRAZOLE 40 mg from 01-Aug-2021, ENOXAPARINE 4000 UI from 03-Aug-2021 and URAPIDIL 10mg/h from 04-Aug-2021.

She presented severe brain trauma, with no surgical management, only intracranial pressure measure placed, sedation were removed on 02 Aug, with progressive awake, patient extubated on 04-Aug-2021, replaced by high flow oxygene therapy up to 06-Aug-2021, with now only nasal device.

On 04-Aug-2021, in the afternoon, she experienced Seizure, grade 3 (Severe), seriousness criteria reported: Other medically important condition, with first partial comitial crisis and generalized; partial and then, generalized seizure on 04-Aug-2021, spontaneously resolving and then, requiring CLONAZEPAM 1mg and LEVETIRACETAM 500 mg x2. On TDM on 04-Aug-2021, there was a stability in size and number of sub dural and subachnoid hemorrhagic areas, especially in sylvian area, as well as contusive hemorrhagic lesion in temporo frontal area with increased peri-contusive oedema, mainly in the left fronto temporal region; mass effect on left ventricle and increased deviation of the brain midline to the right. On 05-Aug, EEG recorded a temporary left temporal seizure, associated with a deviation of the head to the right and blinking of the eyelids.

The patient was out of treatment under study on 08-Aug-2021; Enoxaparine was stopped on 31-Aug-2021 and Urapdil on 09-Aug-2021. The patient had recovered from Seizure on 05-Aug-2021.

The investigator can't rule out the relatedness of IMP, however the treatment remained ongoing, and so has considered there was a reasonable possibility that Seizure is related to rHuIFN-g or to Placebo (CHLORURE DE SODIUM SOLUTION 0,9 %) Despite the sponsor considered the event was probably consecutive to brain lesion, he agreed that IMP can't be rule out blind was removal.

• **FR-CHUNT-202100307**

03-010, a 41 years old Male patient with medical history of Polytraumatism (Fall from a bridge with landing in the water), had been included in the PREV-HAP study on 23-Aug-2021 in Blinded arm. Because of the events, the randomization arm was unblinded on 30-Aug-2021.

He had been treated with rHuIFN-g (INTERFERON GAMMA-1B), 0.5 millilitre (1 dose every 2 days) from 23-Aug-2021 to 27-Aug-2021. He also received as concomitant drugs: ROCURONIUM, solution injectable (BROMURE DE ROCURONIUM), 80 milligram, on 24-Aug-2021; ETOMIDATE, émulsion injectable (ÉTOMIDATE), 20 milligram, on 24-Aug-2021, for Anesthetic induction; SUFENTANIL, solution injectable (SUFENTANIL, CITRATE DE SUFENTANIL), 40 microgram, 1 every Hour from 23-Aug-2021 (ongoing); PROPOFOL, émulsion injectable (PROPOFOL), 250 milligram, 1 every Hour from 23-Aug-2021 (ongoing); MIDAZOLAM, solution injectable (MIDAZOLAM), 20 milligram, 1 every Hour from 21-Aug-2021 to 23-Aug-2021; Dexmedetomidine, solution injectable (DEXMEDETOMIDINE HYDROCHLORIDE), 0.7 microgram per kilogram, 1 every Hour from 23-Aug-2021 (ongoing), for sedation; NORADRENALINE, solution à diluer pour perfusion (TARTRATE DE NORADRÉNALINE), 1.4 milligram, 1 every Hour from 21-Aug-2021 to 25-Aug-2021, for hypotenson; Alprazolam (ALPRAZOLAM), 1 milligram, 1 every Day from 23-Aug-2021 (ongoing), as patient's usual treatment; Pantoprazole (PANTOPRAZOLE), 40 milligram, 1 every Day, from 22-Aug-2021 to 24-Aug-2021, Gastric ulcer prophylaxis.

The patient presented with a fall from a bridge with landing in the water. He was hospitalized on 21-Aug-2021 for polytrauma.

On 24-Aug-2021, the patient experienced Pancytopenia, grade 3 (Severe), seriousness criteria reported: Hospitalisation or prolongation of existing Hospitalisation).

On 23-Aug-2021, White blood cell count was 5.3 international unit per litre; Hemoglobin was 7.5 gram per litre; Platelet count was 131 international unit per litre. On 24-Aug-2021, White blood cell count was 2.7 international unit per litre; Hemoglobin was 6.7 gram per litre; Platelet count was 122 international unit per litre. On 25-Aug-2021, White blood cell count was 2.4 international unit per litre; Hemoglobin was 6.4 gram per litre; Platelet count was 118 international unit per litre. On 27-Aug-2021, White blood cell count was 2.6 international unit per litre; Hemoglobin was 7.4 gram per litre; Platelet count was 250 international unit per litre. On 06-Sep-2021, White blood cell count was 6.86 international unit per litre; Hemoglobin was 9 gram per litre; Platelet count was 764 international unit per litre. On 18-Sep-2021, White blood cell count was 4.59 international unit per litre; Hemoglobin was 10.5 gram per litre; Platelet count was 323 international unit per litre.

He has been transfused with one packed red blood cell per day since 24-Aug-2021.

Due to event, the study treatment was stopped on 27-Aug-2021.

The patient had recovered from Pancytopenia on 18-Sept-2021; the investigator has considered there is a baseline return on 18-Sep-2021.

According to the RSI for the study (RSI_V1.1) Pancytopenia is unexpected for rHuIFN-g.

The investigator and the sponsor have considered there was a reasonable possibility that the event, Pancytopenia, is related to rHuIFN-g. They also considered there is a reasonable possibility that the event was related to concomitant drug, Pantoprazole.

- **FR-CHUNT-202100314**

01-016, a 35 years old Male patient with medical history of Polytraumatism, Hemorrhagic shock and Fracture of pelvis, had been included in the PREV-HAP study on 27-Aug-2021 in Blinded arm. Because of the events, the randomization arm was unblinded on 06-Sep-2021.

He had been treated with rHuIFN-g (INTERFERON GAMMA-1B), 0.1 milligram (1 dose every 2 days) from 27-Aug-2021 to 02-Sep-2021. He received also propofol 25ml/h from 27-Aug-2021, midazolam 30mg/h from 30-Aug and cisatracurium 20 mg/h from 30-Aug-2021 and amoxiciline and clavulanic acid 3g from 27-Aug-2021 to 28-Aug-2021.

The patient was admitted in ICU following a polytraumatism with hemorrhagic shock.

On 01-Sep-2021, the patient experienced Pancreatitis, grade 3 (Severe), seriousness criteria reported: Life Threatening; on 01-Sep-2021 lipase was increased at 614 international unit per litre, so a CT scan was performed, and showed Pancreatitis. On 02-Sept-2021, lipase was at 1006 international unit per litre.

Because of event, the fourth injection of the treatment under study was not administered (IMP was stopped).

On 13-Sept-2021, Lipase was 292.6 international unit per litre, SGOT was 47.6 international unit per litre, SGPT was 47.6 international unit per litre.

The patient had recovered from Pancreatitis on 26-Sep-2021.

According to the RSI for the study (RSI_V1.1) Pancratitis is unexpected for rHuIFN-g; Pancreatitis event is expected in SmPC, including with fatal outcome.

The investigator and the sponsor have considered there was a reasonable possibility that the event, Pancratitis, is related to rHuIFN-g.

- **FR-CHUNT-202100324**

03-002, a 41 years old Male patient with medical history of Polytraumatism (on a bull load), Arterial hypertension, Obesity and Sleep apnoea syndrome had been included in the PREV-HAP study on 23-Jul-2021 in Blinded arm. Because of the events and the suspicion of SADR, the treatment arm was unblinded on 16-Sep-2021.

Firstly, the patient was admitted on 22-Jul-2021 in ICU due to an abdominal and thoracic trauma after being charged by a cow in the course of his work.

He had been treated with rHuIFN-g (INTERFERON GAMMA-1B), 0.5 millilitre (one dose every two days) from 23-Jul-2021 to 31-Jul-2021. He also received, as concomitant's drugs, Sufentanyl 20µg/h from 20-Jul-2021 to 06-Aug-2021, Propofol 200mg/h from 23Jul-2021 to 03-Aug-2021, Acide tranexamique 1g from 22-Jul-2021 to 23-Jul-2021, Noradrenaline 0.8 mg/h from 22-Jul-2021 to 24-Jul-2021, Cisatracurium 15mg/h from 24-Jul-2021 to 25-Jul-2021, Amoxicillin+clavulanic acid 6g from 23-Jul-2021 to 27-Jul-2021.

On 24-Jul-2021, the patient experienced Embolism pulmonary, grade 3 (Severe), and Deep vein thrombosis, grade 3 (Severe) seriousness criteria reported: Hospitalisation or prolongation of existing Hospitalisation; Pulmonary embolism was discorvered "accidentally" on a CT scan; an echodoppler of the lower limbs found a Deep vein thrombosis proximal femoral and left popliteal. The patient had a liver laceration and could not be put on an anticoagulant. Therefore, a vena cava filter was placed on 24 July 2021.

The patient has also presented with a left pneumothorax (non serious event, not specifically reported) and was drained and a pneumopathy acquired under mechanical ventilation (non serious event, not specifically reported) and was treated with CEFEPIME for 7 days.

The pulmonary embolism was treated with Heparin then Arganova from 02-Aug-2021 to 13-Aug-2021 then with Xarelto since 13-Aug-2021, 15 mg twice a day, relayed from 13-Sept-2021 by 20 mg in the morning.

The evolution was favorable on the respiratory level, and the left thoracic drain was removed on 01-Aug-2021.

The patient had recovered from Deep vein thrombosis on 22-Apr-2022. Because of the absence of new hospitalization, the absence of clinical respiratory signs, the time elapsed since the event, the organization of the examinations for the removal of the vena cava filter can allow us to consider that the pulmonary embolism is resolved The investigator has considered the event Embolism pulmonary, was recovered on 20-Jun-2022.

According to the RSI for the study (RSI_V1.1) Embolism pulmonary and Deep vein thrombosis are unexpected for rHuIFN-g; hovewer these events are expected in SmPC.

The investigator and the sponsor have considered there was a reasonable possibility that the events, Embolism pulmonary and Deep vein thrombosis, are related to rHuIFN-g. They have also considered that the event may be also due to Deep vein thrombosis, and Deep vein thrombosis due to ICU.

- **FR-CHUNT-202100332**

03-006, a 58 years old Female patient with medical history of Subarachnoid haemorrhage (FISHER 4 WFNS 5, on ruptured aneurysm of the left sylvian bifurcation) had been included in the PREV-HAP study on 05-Aug-2021 in Blinded arm. Because of the events and the suspicion of SADR, the treatment arm was unblinded on 21-Sep-2021.

She had been treated with rHuIFN-g (INTERFERON GAMMA-1B), 0.5 millilitre (one dose every two days) from 05-Aug-2021 to 13-Aug-2021. The patient also received, as concomitant drugs:Sufentanyl 20µg/h from 04-Aug to 10-Aug-2021, Propofol 200mg/h from 05-Aug to 07-Aug-2021, Midazolam 20 mg/h from 04-Aug to 09-Aug-2021, Noradrenaline 3.4mg/h from 05-Aug to 09-Aug-2021, with dosage increased and improved the event, Levetiracetam 1000mg from 05-Aug to 11-Aug-2021,Nimodipine 360 mg from 04-Aug-2021, ongoing, Pantoprazole 40mg from 05-Aug to 16-Aug-2021, and Atracurium 30 mg/h from 05-Aug to 07-Aug-2021.

The patient was admitted on 04-Aug-2021 on emergency room following a Subarachnoid haemorrhage. She was intubated, ventilated and sedated.

On 06-Aug-2021, the patient experienced Septic shock, grade 4 (Life Threatening), seriousness criteria reported: Life Threatening, and an early Ventilator associated bacterial pneumonia, grade 3 (Severe), no seriousness criteria reported (non serious AE).

The patient showed an increase in lactate to 3.03 so, Noradrenaline was increased to 5mg/h. Antibiotic therapy was introduced with amoxicillin and clavulanic acid. The patient also received hydrocortisone hemisuccinate and fludrocortisone.

The patient had recovered from the both events, Septic shock and Ventilator associated bacterial pneumonia, on 09-Aug-2021.

According to the RSI for the study (RSI_V1.1) Septic shock is unexpected for rHuIFN-g.

The investigator has considered there was a reasonable possibility that the events, Septic shock and Ventilator associated bacterial pneumonia were related to rHuIFN-g. The investigator has also considered the event probably due to Hospital Acquired Pneumonia.

The sponsor has considered there was no reasonable possibility that the events, Septic shock and Ventilator associated bacterial pneumonia was related to rHuIFN-g, but more probably due to to Hospital Acquired Pneumonia.

• **FR-CHUNT-202100395**

02-002, a 64 years old Female patient with medical history of Hemorrhage subarachnoid (with intracerebral hemorrhage, midline shift, cerebral herniation, intracranial hypertension) had been included in the PREV-HAP study on 22-Sep-2021 in Blinded arm. Because of the events and the suspicion of SADR, the treatment arm was unblinded on 09-Dec-2021.

She had been treated with rHuIFN-g (INTERFERON GAMMA-1B), 0.1 milligram (One dose every 2 days) from 22-Sep-2021 to 30-Sep-2021. She also received, as concomitant drugs, Ketamine, 20 mg from 23-sept-2021 to 26-sept-2021, Oxycodone, 5 mg from 23-sept-2021 to 27-sept-2021, Hydrocortisone, 200 mg from 20-sept-2021 to 07-oct-2021, Nimotop, 2mg/h from 20-sept-2021 to 12-oct-2021, Noradrenaline from 20-sept-2021 to 09-oct-2021, Insuline, 1ml/h from 21-sept-2021 to 04-oct-2021 and Paracetamol.

The patient was admitted in ICU on 20-Sept-2021.

On 24-Sep-2021, the patient experienced Epilepsy temporal lobe, grade 2 (Moderate), seriousness criteria reported: Hospitalisation or prolongation of existing Hospitalisation), non convulsant (EEG recording). She received Levetiracetan 1000 mg from 24-sept-2021 to 20-oct-2021. The patient was discharge on 20-oct-2021.

The patient had recovered from Epilepsy temporal lobe on 20-Oct-2021.

The investigator has considered there was a reasonable possibility that the event, Epilepsy temporal lobe, was related to rHuIFN-g, as well as the underlying condition (haemorrhage). The sponsor has considered there was no reasonable possibility that the event, Epilepsy temporal lobe, was related to rHuIFN-g, but more probably due to the underlying condition.

Additionaly, 3 more cases have been suspected SADR for which unblinding was necessary (patients received placebo).

• **FR-CHUNT-202100327**

03-008, a 71 years old Male patient with medical history of CVA (with right cerebellar haemorrhage and hydrocephaly) and Diabetes mellitus had been included in the PREV-HAP study on 13-Aug-2021 in Blinded arm. Because of the events and the suspicion of SADR, the treatment arm was unblinded on 17-Sep-2021.

He had been treated with Placebo (CHLORURE DE SODIUM SOLUTION 0,9 %), 0.5 millilitre (one dose every two days) from 13-Aug-2021 to 21-Aug-2021. As concomittant's drugs, he received Propofol 100mg/h on 14-Aug-2021. His usual treatment were Nicardipine, Irbesartan, Pravastatine, Glimepiride, Sitagliptine and Metformine.

The patient was admitted on emergency room on 11-Aug-2021 due to CVA with cerebellar haemorrhage and hydrocephaly.

On 16-Aug-2021, the patient experienced ischemic stroke, grade 4 (Life threatening), then on 25-Aug-2021, grade 5 (Death), seriousness criteria reported: Death. The CT scan showed two ischemic strokes: one cerebellar and one right parietal, with a rapidly unfavorable evolution.

The patient died from ischemic stroke on 25-Aug-2021, due to cardio-respiratory arrest (Cerebral engagement leading to Cardio-respiratory arrest).

The investigator and the sponsor have considered there was a reasonable possibility that the event, Ischemic stroke, is related to rHuIFN-g despite concomitant disease (not specified) may be involved; they have considered there was No reasonable possibility that the event, Ischemic stroke, is related to CHLORURE DE SODIUM 0,9 %. The sponsor has also considered that the patient's history could be involved.

• **FR-CHUNT-202100329**

03-009, a 64 years old Male patient with medical history of Skull trauma (with convulsive seizures) and Chronic alcoholism had been included in the PREV-HAP study on 16-Aug-2021 in Blinded arm. Because of the events and the suspicion of SADR, the treatment arm was unblinded on 17-Sep-2021.

He had been treated with Placebo (CHLORURE DE SODIUM SOLUTION 0,9 %), 0.5 millilitre from 16-Aug-2021 to 20-Aug-2021.

The patient received Urapidil 45mg/h from 18-Aug-2021 stopped on 22-Aug-2021, Levetiracetam 1000mg from 14-Aug-2021 to 21-Aug-2021 and Midazolam 6mg/h from 14-Aug-2021 to 22-Aug-2021.

The patient was admitted in emergency room on 14-Aug-2021, due to a skull trauma, complicated with convulsive seizures. The patient presented with secondary neurological deterioration at day 6 with a Glasgow score at 6, requiring re-intubation.

On 20-Aug-2021, he Oedema cerebral, grade 5 (Death), seriousness criteria reported: Other medically important condition, found on CT scan which showed an increase in peri-injury oedema (not accessible to treatment); palliative comfort care were applied.

The patient died on 22-Aug-2021 from cardiorespiratory arrest in the context of severe intracranial hypertension related to this cerebral oedema.

The sponsor and the investigator have considered there was a reasonable possibility that the event, increased Oedema cerebral, was related to rHuIFN-g, they have considered there was no reasonable possibility that the event, increased Oedema cerebral, is related to CHLORURE DE SODIUM 0,9 %. Concomitant disease may be involved.

- **FR-CHUNT-202100335**

03-014, a 71 years old Male patient with medical history of Adenocarcinoma lung, Lung bilobectomy (lower right) from 02-Sep-2021, Shock haemorrhagic and Haemothorax (right, requiring pleural surgical removal) on 20-Sep-2021, had been included in the PREV-HAP study on 21-Sep-2021 in Blinded arm. Because of the events and the suspicion of SADR, the treatment arm was unblinded on 22-Sep-2021.

He had been treated with Placebo (CHLORURE DE SODIUM SOLUTION 0,9 %), 0.5 millilitre (one dose every two days) on 21-Sep-2021 (treatment stopped).

On 21-Sep-2021, the patient experienced suspected Pulmonary collapse with Shock, grade 4 (Life Threatening), seriousness criteria reported: Life Threatening.
The patient was in shock state with an acute heart pulmonary disease; the investigator has a strong suspicion of severe pulmonary embolism. The patient received curative heparin, and was increased in amine. Firstly, Embolism pulmonary was suspected (and notified to the sponsor), however an angioscanner performed on 21-Sep-2021, has permitted to confirmed the final diagnosis of Pulmonary collapse of the right cavities.

The patient had recovered from Pulmonary collapse with Shock on 24-Sep-2021.

The investigator has considered there was a reasonable possibility that the events, Pulmonary collapse and Shock, were related to rHuIFN-g; he has considered there was No reasonable possibility that the events, Pulmonary collapse and Shock, wad related to CHLORURE DE SODIUM 0,9 %. The investigator has also considered the events probably due to medical history of neoplasia and postoperative condition (patient admitted for haemorragic shock on haemothorax).

The sponsor has considered there was no reasonable possibility that the events, Pulmonary collapse and Shock, were related to rHuIFN-g nor to CHLORURE DE SODIUM 0,9 %; he has considered the events were probably due to medical history of neoplasia and postoperative condition (patient admitted for haemorragic shock on haemothorax).

IV. Summary tabulation

1. All Adverse Events/Reactions (Serious and Non Serious) occured during the study

Table 5: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	224	153
Number of Reactions	41	20
Number of Patient with at least one AE	52	51
Number of Patient with at least one AR	22	13

Table 6: Summary tabulation of All Adverse Events/Reactions (Serious and Not Serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	18	20	14	16
Anaemia	12	13	12	13
Heparin-induced thrombocytopenia	1	1	0	0
Hyperleukocytosis	1	1	0	0
Iron deficiency anaemia	1	1	0	0
Pancytopenia	1	1	0	0
Thrombocytopenia	1	1	2	2
Thrombocytosis	2	2	1	1
CARDIAC DISORDERS	4	6	2	2
Atrial fibrillation	3	3	2	2
Bradycardia	1	1	0	0
Cardiac arrest	1	1	0	0
Sinus bradycardia	1	1	0	0
EYE DISORDERS	0	0	1	1
Keratitis	0	0	1	1
GASTROINTESTINAL DISORDERS	4	6	3	3

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Abdominal discomfort	0	0	1	1
Gastric ulcer	1	1	0	0
Gastritis	1	1	0	0
Haemoperitoneum	1	1	0	0
Ileus	0	0	1	1
Intestinal obstruction	1	1	0	0
Melaena	1	1	0	0
Pancreatic fistula	0	0	1	1
Pancreatitis	1	1	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7	7	4	4
Drug withdrawal syndrome	1	1	0	0
Granuloma	1	1	0	0
Hyperthermia	2	2	0	0
Inflammation	1	1	0	0
Oedema	1	1	1	1
Pyrexia	1	1	3	3
HEPATOBILIARY DISORDERS	14	19	8	12
Cholelithiasis	0	0	1	1
Cholestasis	6	6	3	3
Hepatic cytolysis	13	13	8	8
IMMUNE SYSTEM DISORDERS	1	1	0	0
Anaphylactic reaction	1	1	0	0
INFECTIONS AND INFESTATIONS	44	74	42	63
Abscess	1	1	0	0
Bacteraemia	3	3	3	3
Brain empyema	0	0	2	2
Cns ventriculitis	1	1	0	0
Conjunctivitis bacterial	1	1	0	0
Device related bacteraemia	0	0	2	2
Device related infection	1	1	1	1
Empyema	1	1	0	0
Enterobacter bacteraemia	1	1	0	0
Escherichia bacteraemia	0	0	1	1
Fungal infection	0	0	1	1
Lymphangitis	1	1	0	0

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Meningitis	5	5	1	1
Meningoencephalitis herpetic	1	1	0	0
Oesophageal candidiasis	1	1	0	0
Peritonitis	1	1	0	0
Pleural infection bacterial	1	1	0	0
Pneumonia	9	10	7	7
Pneumonia bacterial	13	16	9	10
Pneumonia staphylococcal	1	1	0	0
Sepsis	1	1	1	1
Septic shock	2	2	2	2
Sinusitis	1	1	0	0
Staphylococcal bacteraemia	0	0	2	2
Streptococcal bacteraemia	1	1	0	0
Tracheobronchitis	9	9	17	17
Urinary tract infection	13	14	12	13
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2	2	2	2
Eschar	1	1	0	0
Weaning failure	1	1	2	2
INVESTIGATIONS	7	11	0	0
Alanine aminotransferase increased	1	1	0	0
Aspartate aminotransferase increased	1	1	0	0
Blood alkaline phosphatase increased	1	1	0	0
Blood phosphorus decreased	1	2	0	0
Gamma-glutamyltransferase increased	4	4	0	0
Klebsiella test positive	1	1	0	0
Red blood cell count decreased	1	1	0	0
METABOLISM AND NUTRITION DISORDERS	14	20	7	9
Cerebral salt-wasting syndrome	3	3	0	0
Hyperlipasaemia	11	11	7	7
Hypokalaemia	1	2	2	2
Hyponatraemia	2	2	0	0
Hypoproteinaemia	1	1	0	0
Metabolic acidosis	1	1	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	2	2
Osteitis	0	0	1	1

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Rhabdomyolysis	0	0	1	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	3	0	0
Malignant melanoma	1	1	0	0
Metastasis	1	2	0	0
NERVOUS SYSTEM DISORDERS	14	15	9	9
Altered state of consciousness	3	3	2	2
Brain oedema	0	0	2	2
Cerebral venous sinus thrombosis	0	0	1	1
Coma	2	2	1	1
Epilepsy	1	1	0	0
Generalised tonic-clonic seizure	1	1	0	0
Hemiparesis	1	1	0	0
Intensive care unit acquired weakness	0	0	1	1
Intracranial pressure increased	4	4	1	1
Ischaemic stroke	0	0	1	1
Seizure	1	1	0	0
Stroke in evolution	1	1	0	0
Temporal lobe epilepsy	1	1	0	0
PSYCHIATRIC DISORDERS	3	3	2	3
Agitation	3	3	2	2
Confusional state	0	0	1	1
RENAL AND URINARY DISORDERS	3	3	3	3
Acute kidney injury	2	2	1	1
Oliguria	1	1	0	0
Polyuria	0	0	1	1
Renal failure	0	0	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	18	20	10	12
Acute respiratory distress syndrome	8	8	2	3
Acute respiratory failure	1	1	0	0
Atelectasis	1	1	0	0
Chronic obstructive pulmonary disease	0	0	1	1
Hypoxia	1	1	0	0
Laryngeal dyspnoea	0	0	1	1
Laryngeal oedema	3	3	1	1

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Lower respiratory tract congestion	1	1	0	0
Pleural effusion	0	0	1	1
Pleurisy	1	1	1	1
Pneumothorax	2	2	2	2
Pulmonary embolism	1	1	1	1
Pulmonary oedema	0	0	1	1
Respiratory tract congestion	1	1	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	2	1	1
Drug eruption	1	1	0	0
Purpura	1	1	0	0
Rash	0	0	1	1
SURGICAL AND MEDICAL PROCEDURES	0	0	1	1
Endotracheal intubation	0	0	1	1
VASCULAR DISORDERS	11	12	10	10
Axillary vein thrombosis	0	0	1	1
Circulatory collapse	1	1	1	1
Deep vein thrombosis	1	1	1	1
Hypertension	4	4	5	5
Hypotension	2	2	0	0
Hypovolaemic shock	0	0	1	1
Superficial vein thrombosis	1	1	1	1
Vasospasm	2	2	0	0
Venous thrombosis	1	1	0	0

2. Serious Adverse Events/Reactions occured during the study

Table 7: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	48	25
Number of Reactions	9	6
Number of Patient with at least one SAE	24	17
Number of Patient with at least one SAR	6	4

Table 8: Summary tabulation of Serious Adverse Events/Reactions

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1	0	0
Pancytopenia	1	1	0	0
CARDIAC DISORDERS	1	1	0	0
Cardiac arrest	1	1	0	0
GASTROINTESTINAL DISORDERS	1	1	1	1
Pancreatic fistula	0	0	1	1
Pancreatitis	1	1	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	2	2
Pyrexia	0	0	2	2
HEPATOBILIARY DISORDERS	1	2	1	2
Cholestasis	1	1	1	1
Hepatic cytolysis	1	1	1	1
IMMUNE SYSTEM DISORDERS	1	1	0	0
Anaphylactic reaction	1	1	0	0
INFECTIONS AND INFESTATIONS	8	13	4	5
Empyema	1	1	0	0
Enterobacter bacteraemia	1	1	0	0
Meningitis	1	1	0	0
Meningoencephalitis herpetic	1	1	0	0
Peritonitis	1	1	0	0

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Pneumonia	1	1	0	0
Pneumonia bacterial	4	5	3	3
Septic shock	2	2	2	2
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	3	0	0
Malignant melanoma	1	1	0	0
Metastasis	1	2	0	0
NERVOUS SYSTEM DISORDERS	11	12	7	7
Altered state of consciousness	3	3	2	2
Brain oedema	0	0	2	2
Coma	2	2	1	1
Intracranial pressure increased	4	4	1	1
Ischaemic stroke	0	0	1	1
Seizure	1	1	0	0
Stroke in evolution	1	1	0	0
Temporal lobe epilepsy	1	1	0	0
PSYCHIATRIC DISORDERS	1	1	0	0
Agitation	1	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9	10	6	7
Acute respiratory distress syndrome	7	7	2	2
Acute respiratory failure	1	1	0	0
Chronic obstructive pulmonary disease	0	0	1	1
Pleural effusion	0	0	1	1
Pleurisy	0	0	1	1
Pneumothorax	0	0	1	1
Pulmonary embolism	1	1	1	1
Respiratory tract congestion	1	1	0	0
VASCULAR DISORDERS	3	3	1	1
Circulatory collapse	1	1	1	1
Deep vein thrombosis	1	1	0	0
Vasospasm	1	1	0	0

3. Grade 3 or higher Adverse Events/Reactions occured during the study

Table 9: Patient with at least one Grade 3 or higher Adverse Events/Reactions

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	104	56
Number of Reactions	28	15
Number of Patient with at least one AE G3 or higher	38	29
Number of Patient with at least one AR G3 or higher	16	11

Table 10: Summary tabulation of Grade 3, or higher, Adverse Events/Reactions

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	13	13	4	4
Anaemia	10	10	3	3
Heparin-induced thrombocytopenia	1	1	0	0
Hyperleukocytosis	1	1	0	0
Pancytopenia	1	1	0	0
Thrombocytosis	0	0	1	1
CARDIAC DISORDERS	1	2	0	0
Cardiac arrest	1	1	0	0
Sinus bradycardia	1	1	0	0
GASTROINTESTINAL DISORDERS	2	2	2	2
Abdominal discomfort	0	0	1	1
Gastric ulcer	1	1	0	0
Ileus	0	0	1	1
Pancreatitis	1	1	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	1	1
Pyrexia	0	0	1	1
HEPATOBILIARY DISORDERS	8	11	8	9
Cholestasis	4	4	2	2
Hepatic cytolysis	7	7	7	7

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
IMMUNE SYSTEM DISORDERS	1	1	0	0
Anaphylactic reaction	1	1	0	0
INFECTIONS AND INFESTATIONS	17	25	14	16
Brain empyema	0	0	2	2
Empyema	1	1	0	0
Enterobacter bacteraemia	1	1	0	0
Meningitis	3	3	1	1
Meningoencephalitis herpetic	1	1	0	0
Oesophageal candidiasis	1	1	0	0
Peritonitis	1	1	0	0
Pneumonia	3	3	1	1
Pneumonia bacterial	9	11	8	9
Sepsis	1	1	0	0
Septic shock	2	2	2	2
Staphylococcal bacteraemia	0	0	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1	1
Weaning failure	0	0	1	1
INVESTIGATIONS	4	5	0	0
Alanine aminotransferase increased	1	1	0	0
Aspartate aminotransferase increased	1	1	0	0
Blood alkaline phosphatase increased	1	1	0	0
Gamma-glutamyltransferase increased	2	2	0	0
METABOLISM AND NUTRITION DISORDERS	8	9	2	2
Hyperlipasaemia	8	8	2	2
Hypoproteinaemia	1	1	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	2	2
Osteitis	0	0	1	1
Rhabdomyolysis	0	0	1	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	3	0	0
Malignant melanoma	1	1	0	0
Metastasis	1	2	0	0
NERVOUS SYSTEM DISORDERS	13	13	7	7
Altered state of consciousness	3	3	2	2
Brain oedema	0	0	2	2

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Coma	2	2	1	1
Epilepsy	1	1	0	0
Generalised tonic-clonic seizure	1	1	0	0
Intracranial pressure increased	4	4	1	1
Ischaemic stroke	0	0	1	1
Seizure	1	1	0	0
Stroke in evolution	1	1	0	0
PSYCHIATRIC DISORDERS	1	1	0	0
Agitation	1	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12	14	7	9
Acute respiratory distress syndrome	8	8	2	3
Acute respiratory failure	1	1	0	0
Chronic obstructive pulmonary disease	0	0	1	1
Laryngeal oedema	0	0	1	1
Lower respiratory tract congestion	1	1	0	0
Pleurisy	1	1	1	1
Pneumothorax	1	1	2	2
Pulmonary embolism	1	1	1	1
Respiratory tract congestion	1	1	0	0
SURGICAL AND MEDICAL PROCEDURES	0	0	1	1
Endotracheal intubation	0	0	1	1
VASCULAR DISORDERS	5	5	2	2
Circulatory collapse	1	1	1	1
Deep vein thrombosis	1	1	0	0
Hypertension	1	1	0	0
Hypovolaemic shock	0	0	1	1
Vasospasm	2	2	0	0

V. Adverse Events/Reactions by System of Class Organ

1. Infectious and Respiratory events

• All Infectious and Respiratory Adverse Events/Reactions reported (Serious and not Serious)

Table 11: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	94	75
Number of Patient with at least one AE	44	45
Number of Patient with at least one AR	10	10

Table 12: Infectious and Respiratory Adverse Events/Reaction (serious and non serious

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
INFECTIONS AND INFESTATIONS	44	74	42	63
Abscess	1	1	0	0
Bacteraemia	3	3	3	3
Brain empyema	0	0	2	2
Cns ventriculitis	1	1	0	0
Conjunctivitis bacterial	1	1	0	0
Device related bacteraemia	0	0	2	2
Device related infection	1	1	1	1
Empyema	1	1	0	0
Enterobacter bacteraemia	1	1	0	0
Escherichia bacteraemia	0	0	1	1
Fungal infection	0	0	1	1
Lymphangitis	1	1	0	0
Meningitis	5	5	1	1
Meningoencephalitis herpetic	1	1	0	0

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Oesophageal candidiasis	1	1	0	0
Peritonitis	1	1	0	0
Pleural infection bacterial	1	1	0	0
Pneumonia	9	10	7	7
Pneumonia bacterial	13	16	9	10
Pneumonia staphylococcal	1	1	0	0
Sepsis	1	1	1	1
Septic shock	2	2	2	2
Sinusitis	1	1	0	0
Staphylococcal bacteraemia	0	0	2	2
Streptococcal bacteraemia	1	1	0	0
Tracheobronchitis	9	9	17	17
Urinary tract infection	13	14	12	13
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	18	20	10	12
Acute respiratory distress syndrome	8	8	2	3
Acute respiratory failure	1	1	0	0
Atelectasis	1	1	0	0
Chronic obstructive pulmonary disease	0	0	1	1
Hypoxia	1	1	0	0
Laryngeal dyspnoea	0	0	1	1
Laryngeal oedema	3	3	1	1
Lower respiratory tract congestion	1	1	0	0
Pleural effusion	0	0	1	1
Pleurisy	1	1	1	1
Pneumothorax	2	2	2	2
Pulmonary embolism	1	1	1	1
Pulmonary oedema	0	0	1	1
Respiratory tract congestion	1	1	0	0

• **Grade3, or higher, Infectious and Respiratory Adverse Events/Reactions (Serious and non Serious)**

Table 13: Grade 3 or higher Infectious and Respiratory Adverse Events/Reaction (serious and non serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
INFECTIONS AND INFESTATIONS	17	25	14	16
Abscess	0	0	0	0
Bacteraemia	0	0	0	0
Brain empyema	0	0	2	2
Cns ventriculitis	0	0	0	0
Conjunctivitis bacterial	0	0	0	0
Device related bacteraemia	0	0	0	0
Device related infection	0	0	0	0
Empyema	1	1	0	0
Enterobacter bacteraemia	1	1	0	0
Escherichia bacteraemia	0	0	0	0
Fungal infection	0	0	0	0
Lymphangitis	0	0	0	0
Meningitis	3	3	1	1
Meningoencephalitis herpetic	1	1	0	0
Oesophageal candidiasis	1	1	0	0
Peritonitis	1	1	0	0
Pleural infection bacterial	0	0	0	0
Pneumonia	3	3	1	1
Pneumonia bacterial	9	11	8	9
Pneumonia staphylococcal	0	0	0	0
Sepsis	1	1	0	0
Septic shock	2	2	2	2
Sinusitis	0	0	0	0
Staphylococcal bacteraemia	0	0	1	1
Streptococcal bacteraemia	0	0	0	0
Tracheobronchitis	0	0	0	0
Urinary tract infection	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12	14	7	9
Acute respiratory distress syndrome	8	8	2	3

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
Acute respiratory failure	1	1	0	0
Atelectasis	0	0	0	0
Chronic obstructive pulmonary disease	0	0	1	1
Hypoxia	0	0	0	0
Laryngeal dyspnoea	0	0	0	0
Laryngeal oedema	0	0	1	1
Lower respiratory tract congestion	1	1	0	0
Pleural effusion	0	0	0	0
Pleurisy	1	1	1	1
Pneumothorax	1	1	2	2
Pulmonary embolism	1	1	1	1
Pulmonary oedema	0	0	0	0
Respiratory tract congestion	1	1	0	0

2. Metabolism and hepatobilary disorders

• All Metabolism and hepatobilary Adverse events/reactions reported (Serious and not Serious)

Table 14: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	39	21
Number of Patient with at least one AE	20	14
Number of Patient with at least one AR	3	3

Table 15: Metabolism and Hepatobilary Adverse events/reactions (serious and non serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
HEPATOBILIARY DISORDERS	14	19	8	12
Cholelithiasis	0	0	1	1
Cholestasis	6	6	3	3
Hepatic cytolysis	13	13	8	8
METABOLISM AND NUTRITION DISORDERS	14	20	7	9
Cerebral salt-wasting syndrome	3	3	0	0
Hyperlipasaemia	11	11	7	7
Hypokalaemia	1	2	2	2
Hyponatraemia	2	2	0	0
Hypoproteinaemia	1	1	0	0
Metabolic acidosis	1	1	0	0

• **Summary tabulation of Grade 3 or higher, Metabolism and hepatobilary Adverse Events/Reactions (Serious and not Serious)**

Table 16: Grade 3 or higher Metabolism and Hepatobilary Adverse events/reactions (serious and non serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
HEPATOBILIARY DISORDERS	14	19	8	12
Cholelithiasis	0	0	1	1
Cholestasis	6	6	3	3
Hepatic cytolysis	13	13	8	8
METABOLISM AND NUTRITION DISORDERS	14	20	7	9
Cerebral salt-wasting syndrome	3	3	0	0
Hyperlipasaemia	11	11	7	7
Hypokalaemia	1	2	2	2
Hyponatraemia	2	2	0	0
Hypoproteinaemia	1	1	0	0
Metabolic acidosis	1	1	0	0

3. Blood disorders

• Summary tabulation of all Blood disorders Adverse Events/Reactions reported (Serious and not Serious)

Table 17: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	21	16
Number of Patient with at least one AE	18	14
Number of Patient with at least one AR	2	3

Table 18: Blood and lymphatic system Adverse events/reactions (serious and non serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	18	20	14	16
Anaemia	12	13	12	13
Heparin-induced thrombocytopenia	1	1	0	0
Hyperleukocytosis	1	1	0	0
Iron deficiency anaemia	1	1	0	0
Pancytopenia	1	1	0	0
Thrombocytopenia	1	1	2	2
Thrombocytosis	2	2	1	1
INVESTIGATIONS	1	1	0	0
Red blood cell count decreased	1	1	0	0

• **Grade 3 or higher, Blood Adverse Events/Reactions (Serious and not Serious)**

Table 19: Grade 3 or higher Blood and lymphatic system Adverse events/reactions (serious and non serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n 1	A (rHuIFN-g); n 2	B (Placebo); n 1	B (Placebo); n 2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	13	13	4	4
Anaemia	10	10	3	3
Heparin-induced thrombocytopenia	1	1	0	0
Hyperleukocytosis	1	1	0	0
Pancytopenia	1	1	0	0
Thrombocytosis	0	0	1	1

4. Cardiac & Vascular events

• Cardiac & Vascular Adverse Events/Reactions (Serious and not Serious)

Table 20: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	18	12
Number of Patient with at least one AE	13	11
Number of Patient with at least one AR	3	2

Table 21: Summary tabulation of Cardiac & Vascular Adverse Events/Reactions (Serious and Non Serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
CARDIAC DISORDERS	4	6	2	2
Atrial fibrillation	3	3	2	2
Bradycardia	1	1	0	0
Cardiac arrest	1	1	0	0
Sinus bradycardia	1	1	0	0
VASCULAR DISORDERS	11	12	10	10
Axillary vein thrombosis	0	0	1	1
Circulatory collapse	1	1	1	1
Deep vein thrombosis	1	1	1	1
Hypertension	4	4	5	5
Hypotension	2	2	0	0
Hypovolaemic shock	0	0	1	1
Superficial vein thrombosis	1	1	1	1
Vasospasm	2	2	0	0
Venous thrombosis	1	1	0	0

• **Grade 3 or higher, Cardiac & Vascular Adverse Events/Reactions (Serious and not Serious)**

Table 22: Grade 3 or higher Cardiac & Vascular Adverse Events/Reactions (Serious and Non Serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
CARDIAC DISORDERS	1	6	0	0
Cardiac arrest	1	1	0	0
Sinus bradycardia	1	1	0	0
VASCULAR DISORDERS	5	18	2	2
Circulatory collapse	1	1	1	1
Deep vein thrombosis	1	1	0	0
Hypertension	1	1	0	0
Hypovolaemic shock	0	0	1	1
Vasospasm	2	2	0	0

5. Nervous disorders

• All Nervous disorders Adverse Events/Reactions reported (Serious and not Serious)

Table 23: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	18	12
Number of Patient with at least one AE	17	11
Number of Patient with at least one AR	3	2

Table 24: Nervous disorders Adverse Events/Reactions reported (Serious and Non Serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
NERVOUS SYSTEM DISORDERS	14	15	9	9
Altered state of consciousness	3	3	2	2
Brain oedema	0	0	2	2
Cerebral venous sinus thrombosis	0	0	1	1
Coma	2	2	1	1
Epilepsy	1	1	0	0
Generalised tonic-clonic seizure	1	1	0	0
Hemiparesis	1	1	0	0
Intensive care unit acquired weakness	0	0	1	1
Intracranial pressure increased	4	4	1	1
Ischaemic stroke	0	0	1	1
Seizure	1	1	0	0
Stroke in evolution	1	1	0	0
Temporal lobe epilepsy	1	1	0	0
PSYCHIATRIC DISORDERS	3	3	2	3
Agitation	3	3	2	2
Confusional state	0	0	1	1

• **Grade 3 or higher, Nervous Adverse Events/Reactions (Serious and not Serious)**

Table 25: Grade 3 or higher Nervous Adverse Events/Reactions (Serious and Non Serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
NERVOUS SYSTEM DISORDERS	14	15	9	9
Altered state of consciousness	3	3	NA	2
Brain oedema	0	0	NA	2
Cerebral venous sinus thrombosis	0	0	NA	1
Coma	2	2	NA	1
Epilepsy	1	1	NA	0
Generalised tonic-clonic seizure	1	1	NA	0
Hemiparesis	1	1	NA	0
Intensive care unit acquired weakness	0	0	NA	1
Intracranial pressure increased	4	4	NA	1
Ischaemic stroke	0	0	NA	1
Seizure	1	1	NA	0
Stroke in evolution	1	1	NA	0
Temporal lobe epilepsy	1	1	NA	0
PSYCHIATRIC DISORDERS	3	3	2	3
Agitation	3	3	NA	2
Confusional state	0	0	NA	1

6. Gastrointestinal disorders

• All Gastrointestinal Adverse Events/Reactions (Serious and not Serious) reported

Table 26: Patient with at least one Adverse Events/Reactions (Serious and Non Serious)

	A (rHuIFN-g)	B (Placebo)
Number of Events/Reactions	6	3
Number of Patient with at least one AE	4	3
Number of Patient with at least one AR	2	2

Table 27: Gastrointestinal Adverse Events/Reactions (Serious and Non Serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
GASTROINTESTINAL DISORDERS	4	6	3	3
Abdominal discomfort	0	0	1	1
Gastric ulcer	1	1	0	0
Gastritis	1	1	0	0
Haemoperitoneum	1	1	0	0
Ileus	0	0	1	1
Intestinal obstruction	1	1	0	0
Melaena	1	1	0	0
Pancreatic fistula	0	0	1	1
Pancreatitis	1	1	0	0

• **Grade 3 or higher, Gastrointestinal Adverse Events/Reactions (Serious and not Serious)**

Table 28: Grade 3 or higher Gastrointestinal Adverse Events/Reactions (Serious and Non Serious)

AE according SOC/PT MedDRA (n1 : number of patients with at least one event/reaction; n2 : number of events/reactions)	A (rHuIFN-g); n1	A (rHuIFN-g); n2	B (Placebo); n1	B (Placebo); n2
GASTROINTESTINAL DISORDERS	4	2	2	2
Abdominal discomfort	0	0	1	1
Gastric ulcer	1	1	0	0
Gastritis	0	0	0	0
Haemoperitoneum	0	0	0	0
Ileus	0	0	1	1
Intestinal obstruction	0	0	0	0
Melaena	0	0	0	0
Pancreatic fistula	0	0	0	0
Pancreatitis	1	1	0	0

VI. Appendix

Additional data from the safety software eVeReport are attached to this report; these data concern line listing.

- Appendix I. Listing of all AE and SAE recorded in AE Section of the eCRF
- Appendix II. Line Listing of SUSAR reported during the study
- Appendix III. Line Listing of death reported during the study
- Appendix IV. Line Listing of SAE (not related) reported during the study
- Appendix V. Line Listing of AESI (even without seriousness criteria) reported during the study
- Appendix VI. Line Listing of Special situation reported during the study

NB: Some of cases presented in line listing can appears in different SOC section, because they contain several events/reactions in different SOC, as for exemple:

- *the case FR-CHUNT-202100324 contains 2 reactions in different SOC and appears in "Vascular disorders" and "Respiratory, thoracic and mediastinal disorders"*
- *the case FR-CHUNT-202100370 contains 3 reactions in different SOC and appears in SOC "Infections and infestations" and "Respiratory, thoracic and mediastinal disorders"*
- *the FR-CHUNT-202100374 contains 2 reactions in different SOC and appears in SOC "Infections and infestations" and "Respiratory, thoracic and mediastinal disorders"*