FINAL STUDY REPORT

Full title of the trial:	COVID-19: Immune response in patients with cancer undergoing mRNA vaccination against SARS-CoV-2
Short title of the trial:	I-SPARC
EudraCT number:	2021-003710-39
Sponsor protocol number:	IJB-COVID-001
ClinicalTrials.gov Number:	NCT05075538
Sponsor	Institut Jules Bordet Rue Meylemeersch 90, 1070 Anderlecht Belgique/België
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Report date	20 Dec 2024

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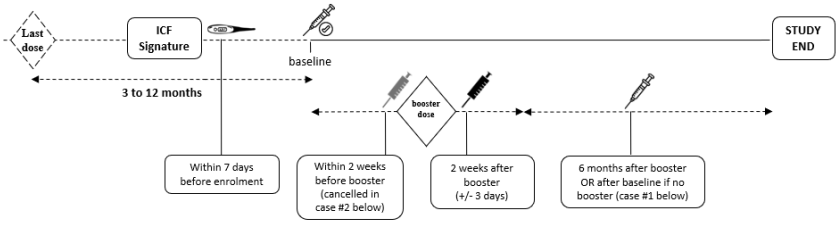
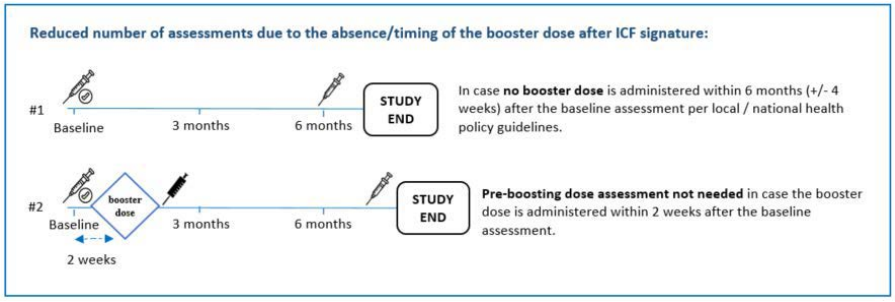
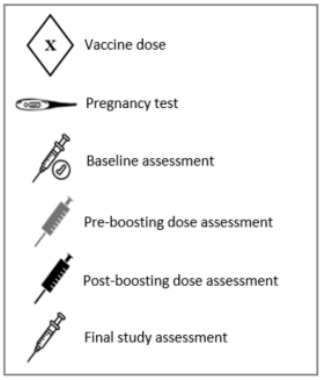
TABLE OF CONTENTS

1 TRIAL INFORMATION

PHASE	Phase IV
TRIAL DESIGN	Multi-centre, open-label, single-arm, multi-cohort, clinical trial, which will focus on subjects with diagnosis of cancer (invasive solid tumour or haematological malignancy), who received at least two doses of one mRNA anti-SARS-CoV-2 vaccine authorized by the EMA, according to the national plans for COVID-19 vaccination, and were undergoing systemic treatment or in complete remission without active cancer treatment for the last 12 months at the time of the last dose before ICF signature.    The last dose is defined as either the 2nd dose or any subsequent dose of an mRNA anti-SARS-CoV-2 vaccine administered before ICF signature. A booster dose is defined as the 3rd dose or any subsequent dose of an mRNA anti-SARS-CoV-2 vaccine authorised by the local guidelines administered after ICF signature until 6 months (+/- 4 weeks) after the baseline assessment. An exploratory sub-study will be performed to assess the adaptive immune response of 20 subjects of the Institut Jules Bordet (IJB).

SCIENTIFIC BACKGROUND	The pandemic of coronavirus disease 19 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the cause of more than 6.9 million deaths worldwide as of 25 September 2023 (1). To prevent the spread of disease and control the pandemic, according to the World Health Organization (WHO), there were 183 COVID-19 vaccines in clinical development and 199 vaccine candidates in pre-clinical development as of 25 September 2023 (2). As of 19 August 2021, 24 vaccines were registered in the WHO Emergency Use Listing Procedure, either approved or under evaluation process by different agencies across the globe. By September 2023, the European Medicines Agency (EMA) has authorised eight vaccines for preventing SARS-CoV-2. SARS-CoV-2 has a characteristic spike (S) glycoprotein which induces humoral and cellular immune responses against SARS-CoV-2, making it a potent target for vaccine development (3). Most of the vaccines aim to generate an immune response against this S glycoprotein and are based on different platforms such as mRNA, DNA, viral vector, protein subunit, inactivated virus, and live attenuated virus (2,4). The first available vaccines are based on the SARS-CoV-2 S glycoprotein antigen encoded by mRNA and formulated in lipid nanoparticles known as Comirnaty (Pfizer/BioNTech) and Spikevax (Moderna). Preliminary data suggest high vaccine efficacy in preventing COVID-19 following receipt of two doses of mRNA COVID-19 vaccine: Comirnaty is 95.0% [95% CI: 90.3%, 97.6%] after 2 months (5), and Spikevax is 94.1% [95% CI: 89.3%, 96.8%]) after 3 months (6). Vaccination is crucial to prevent severe COVID-19 infection in vulnerable patients like those with solid or hematologic malignancies and to avoid any delay of their oncological treatment which may have an impact on the prognosis. A systematic review and pooled analysis of 18,650 patients with both COVID-19 and cancer showed that their probability of death was 25.6% (95% CI 22-29.5) (7). Patients with lung cancer and hematologic malignancies are at highest risk (8). The exclusion of cancer patients from the initial registration trials of COVID-19 vaccines raises questions about the efficacy and safety of SARS-CoV-2 vaccination in this patient population, particularly those receiving systemic anti-cancer therapies. Currently there is limited data available to assess vaccine efficacy in cancer patients. Only 1 of 704 patients with malignancy developed severe COVID-19 infection after vaccination with Comirnaty compared to 4 of 681 patients receiving placebo, demonstrating a 75.7 % (-145.8, 99.5) vaccine efficacy after the 2nd dose (9). Data from elderly cancer patients vaccinated in United Kingdom with Comirnaty, in the UK SARS-CoV-2 fOr cAncer Patients (SOAP) study, demonstrate that delayed boosting with the second dose potentially leaves most solid and haematological cancer patients wholly or partially unprotected. Anti-S protein immunoglobulin levels 21 days following the first dose of the Comirnaty showed that only 39% (21/54) of patients with solid cancer, and 13% (5/39) of patients with haematological cancer had developed adequate level of immune protection.

	However, prompt boosting of solid cancer patients quickly overcomes the poor efficacy of the primary inoculum in solid cancer patients, reaching 95% within 2 weeks after the boost with the second dose (10). A report from France, using Elecsys® Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, France) to assess immunogenicity of Comirnaty in 122 cancer patients, reported consistent findings. During the first serological analysis at the time of the boost with second dose, 47.5% (CI95 38.4-56.8) of patients had anti-S seroconversion, while after the boost 95.2% (CI95 83.8-99.4) patients presented anti-S seroconversion. All the healthy volunteers experienced anti-S seroconversion at the two time points (11). Ultimately, Heudel et al, demonstrated in a cohort of 1503 cancer subjects, that a second dose confer higher protection against documented COVID-19 (12). Three other clinical studies demonstrated weak humoral response to anti-SARS-CoV-2 vaccination in hematologic cancer subjects, specifically in multiple myeloma and chronic lymphocytic leukaemia subjects (13–15). More recently, B-VOICE study, demonstrated similar findings at 28 days post-boost with second dose of Comirnaty in 197 cancer subjects, showing lower humoral response in the hematologic and in the chemotherapy cohorts (16). The reduced humoral response to anti-SARS-CoV-2 vaccination related with systemic treatments, does not seem to be exclusive of chemotherapy, as shown by Terpos et al. The authors also found low titers of SARS-CoV-2 neutralizing antibodies after vaccination in cancer patients receiving immune checkpoint inhibitors (ICI) (17). These reports, also present reassuring safety data of mRNA vaccination in cancer patients (10,18). However, there is no robust data about the duration of the humoral and adaptive immune response to the anti-SARS-CoV-2 vaccination beyond the first months post-boosting. Few data is also available for the subgroup of individuals with prior history of cancer in complete remission that may also have some degree of immune system compromise derived from previous received treatment. This gap of knowledge gains particular importance now that booster doses of mRNA anti-SARS-CoV-2 vaccination are being administered. On August 13th 2021, CDC (19) and FDA (20) endorsed the administration of a third dose of mRNA-based vaccines for immunocompromised subjects, such as cancer patients under treatment. In most European countries, a boost with third dose of Comirnaty or Spikevax was also approved by the EMA since early October 2021 (21). Moreover, in October 2022 four other vaccines against SARS-CoV-2 were given a conditional marketing authorisation by EMA: Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5, Spikevax bivalent Original/Omicron BA.1 and Spikevax bivalent Original/Omicron BA.4-5. These are bivalent vaccines, developed for preventing Omicron BA.1 and BA.4-5 subvariants of SARS-CoV-2. The safety profile was similar to the one reported for Comirnaty and Spikevax. By September 2023, two additional vaccines were authorised by EMA: Comirnaty Omicron XBB.1.5 and Spikevax XBB.1.5, monovalent vaccines, preventing Omicron XBB.1.5 subvariant, with safety profile comparable to the previous ones. Overall mRNA-based vaccines have shown >90% protection from COVID-19 disease with good tolerance (5,6), whereas non-replicating adenoviral

	vector-based vaccines have shown protection rates of 62%-90% conferred by different dosing regimens (22). Therefore, this study will focus on m-RNA based vaccines.
RATIONALE	After symptomatic SARS-CoV-2 infection, most patients develop a specific antibody response in the acute phase (14-28 days). Antibody responses after infection are generally detected against the nucleocapsid (N), spike (S) proteins (23) or Receptor Binding Domain (24), among others, while only by anti-spike protein antibodies occur after vaccination with mRNA vaccines. Virus-specific immunoglobulin (Ig) M rise during the acute phase to a peak around 2 to 5 weeks following disease onset (25) and then decline over a further 3-5 week period before becoming undetectable (26). The IgG peak occurs later, at 3 to 7 weeks following disease onset and then plateau, to persist for at least 3 to 4 months (27–29). However, IgG titers began decreasing by 8 weeks post symptom onset (25) but remained above the detection threshold, as reported by a study testing plasma of infected patients for SARS-Cov-2 IgM and IgG antibodies by ELISA and using nine different commercially available lateral flow immunoassay devices (30). Neutralizing antibody titers remain stable for a period ranging from 75 days to 6 months in COVID-19 convalescent individuals with a broad spectrum of disease severity (31,32) are observed in 70% of patients (32). Memory B cell responses continue to evolve in recovered individuals for at least 6 months after infection (33). Decreasing antibody titers do not necessarily imply waning or defective immunity. In fact, antibody titers are expected to decrease following the resolution of an acute infection as a natural consequence of the depletion of short-lived plasma cells when immediate and sustained immune responses are no longer necessary (34,35). It is unclear whether differences exist on the effectiveness and duration between immunity procured by a natural SARS-CoV-2 infection and vaccine-mediated immunity. It is challenging to evaluate the acquired immunity against COVID-19 infection, its duration, and the protection from reinfections in vaccinated patients with cancer, particularly with active disease undergoing systemic cancer treatments, high-risk population with potentially compromised efficacy of the vaccination against SARS-CoV-2. Viral load appears to be significantly reduced in cases of COVID-19 infection after vaccination (36). This can make vaccinated people less infectious, given that viral load appears to be a leading indicator of SARS-CoV-2 transmission (37). Equally important to track in SARS-CoV-2 breakthrough infections after vaccination, the identification of mutant viral strains might unravel SARS-CoV-2 variants of concern for which there might be less vaccine efficacy (38). It is also unknown the impact of other baseline determinants on the immune response to vaccination in this specific population, such as age at vaccination (39), race (40), smoking status, comorbidities or body mass index (41). These determinants are essential to characterise the need for priority of this population regarding vaccination campaigns, and the need for the booster doses of the anti-SARS-CoV-2 vaccine.

	This trial aims to measure the long-term humoral and adaptive immune response in patients with cancer diagnosis undergoing mRNA vaccination against SARS-CoV-2 and assess its efficacy in preventing COVID-19.
OBJECTIVES	**Primary objective**: • To evaluate the long-term humoral immune response against SARS-CoV-2 between 3 and 12 months after the last dose (before ICF signature) of an mRNA anti-SARS-CoV-2 vaccine (baseline assessment). **Secondary objectives**: • To evaluate the duration of the humoral immune response against SARS-CoV-2 based on the final study assessment, namely at 6 months (+ /- 4 weeks) after the baseline assessment or at 6 months (+ 4 weeks/- 8 weeks) after the first booster dose after ICF signature, if a booster dose of the vaccine is administered during the study per local / national health policy guidelines. • To evaluate the humoral immune response after vaccination against SARS-CoV-2, by cohort: i) between 3 and 12 months after the last dose before ICF signature; and ii) At the final study assessment timepoint, namely at 6 months (+/- 4 weeks) after baseline assessment or 6 months (+4 weeks/- 8 weeks) after the first booster dose after ICF signature, if a booster dose of the vaccine is administered during the study per local / national health policy guidelines. • To assess the clinical efficacy of the vaccination against SARS-CoV-2. • To evaluate safety of booster dose(s) of mRNA anti-SARS-CoV-2 vaccine received after ICF signature, if booster dose(s) of the vaccine are administered during the study per local / national health policy guidelines.
INCLUSION CRITERIA	1. Age ≥ 18 years old 2. ECOG performance status ≤ 2 3. Subjects with histologically or cytologically confirmed cancer diagnosis (invasive solid tumour or haematological malignancy) - undergoing active systemic cancer treatment at the time of the last dose (before ICF signature) of the anti-SARS-CoV-2 mRNA vaccine (such as chemotherapy, immunotherapy, targeted agents, endocrine therapy) in o non-metastatic/curative setting **or** o metastatic/palliative setting • or undergoing follow-up after confirmed cancer complete remission without active cancer treatment for the last 12 months

	at the time of the last dose (before ICF signature) of the anti-SARS-CoV-2 mRNA vaccine. 4. Life expectancy > 6 months 5. Subjects who received at least 2 doses of mRNA platform vaccination against SARS-CoV-2 as per local guidelines, with the last dose being given between 3 and 12 months prior to baseline assessment. 6. Urine/serum pregnancy test negative for all female subjects of childbearing potential within 7 days prior to subject enrolment. 7. Signed Informed Consent form (ICF) obtained prior to any study related procedure. 8. Subjects willing and able to comply with the protocol for the duration of the study including treatment and scheduled visits and examinations.
EXCLUSION CRITERIA	1. Known pregnant and/or lactating women 2. Subject with a known significant medical, neuro-psychiatric, or surgical condition, currently uncontrolled by treatment, which, in the principal investigator's opinion, may interfere with completion of the study. 3. Subjects with active diagnosis of acute leukaemia. 4. Subjects treated with bone marrow transplant < 90 days before the last dose of vaccination against SARS-CoV-2 received before ICF signature. 5. Subjects with a known history of HIV infection. 6. COVID-19 infection in the last 28 days prior to subject enrolment. 7. Subjects receiving prolonged and/or high doses of systemic immunosuppressive therapies including corticosteroids during the last 28 days before receiving first dose of vaccination against SARS-CoV-2 and up to subject enrolment. 8. Subjects who, for any reason, did not receive the 2nd dose of the anti-SARS-CoV-2 mRNA vaccine. 9. Subjects that received the 3rd dose of anti-SARS-CoV-2 mRNA vaccine prior to study entry. Exclusion criterion number 9 is only applicable for previous versions of the protocol and is not applicable for protocol version 3.0 and subsequent versions. 10. Subject that received any dose of non-mRNA anti-SARS-CoV-2 vaccine platform. 11. Subjects with a known or suspected history of severe adverse reactions associated with a vaccine and/or with severe allergic reaction to vaccine components or anaphylaxis in the past. 12. Subjects who planned to receive any other licensed vaccines for other indications within 28 days prior to the first booster dose after ICF signature, or who are planning to receive any other vaccine up to 14 days after the first booster dose of the mRNA anti-SARS-CoV-2 vaccine after ICF signature (28 days for live attenuated vaccines). For influenza

	vaccination, a shorter interval or simultaneous administration is acceptable. 13. Subjects who have planned to receive a booster dose after ICF signature but before the baseline assessment. 14. Subjects who received COVID-19 pre-exposure prophylactic monoclonal antibodies or who have been treated with anti-SARS-CoV-2 monoclonal antibodies or COVID-19 convalescent plasma during the last 6 months before ICF signature.
INVESTIGATIONAL MEDICINAL PRODUCTS	All subjects have received at least two doses of one of the mRNA anti-SARS-CoV-2 vaccines **authorized by the European Medicine Agency,** and according to the national plan for COVID-19 vaccination. All subjects will potentially receive a booster dose during the study, as per the national guidelines for vaccination and respecting other local/national recommendations about the ideal timing for vaccination.
INDICATION OF USE	Immune response against SARS-CoV-2 after mRNA vaccine in adult cancer patients
TARGETED POPULATION	Adult (18 years of age and older) men and women with diagnosis of cancer (invasive solid tumour or haematological malignancy) undergoing systemic treatment OR in remission without active cancer treatment for the last 12 months, that received at least two doses of anti-SARS-CoV-2 mRNA vaccine authorized by the European Medicine Agency, and according to the national plans for COVID-19 vaccination. 4 cohorts: - **Cohort A.1+ A.2:** Subjects with active solid malignancies undergoing immunotherapy, endocrine therapy, or targeted agents (alone or in combination, except if with cytotoxic chemotherapy): 100 evaluable subjects - **Cohort A.3:** Subjects with active solid malignancies undergoing cytotoxic chemotherapy +/- any other treatment modality in combination: 100 evaluable subjects - **Cohort B:** Subjects with active haematological cancers undergoing systemic treatment: 100 evaluable subjects - **Cohort C:** Subjects with malignancy in complete remission, without active cancer treatment for the last year: 100 evaluable subjects **Evaluable subjects:** all subjects who received at least two doses of an mRNA anti-SARS-CoV-2 vaccine and from which peripheral blood sample was collected during study In each cohort, 100 evaluable subjects were needed, i.e. 400 evaluable subjects in total.

PARTICIPATING COUNTRY/-IES	Belgium
START DATE OF THE TRIAL	08/11/2021
PARTICIPATING SITES NUMBER	2
LENGTH OF THE STUDY	• Actual start date of recruitment to the protocol: 01/12/2021 • Actual date stop date of recruitment to the protocol: 26/10/2023 • Long term follow-up planned? No
INDEPENDENT DATA MONITORING COMMITTEE	No
PAEDIATRIC REGULATORY DETAILS	• Is trial part of an agreed paediatric investigation plan (PIP)? No • Does Article 45 of REGULATION (EC) No 1901/2006 apply to this trial? No • Does Article 46 of REGULATION (EC) No 1901/2006 apply to this trial? No
PROTECTION OF TRIAL SUBJECTS	The protection of subject data and the related rights are guaranteed by the General Data Protection Regulation (European Regulation 2016/679), by the law of 22 August 2002 concerning subject rights in Belgium as well as any new applicable legislation in the participating countries.
STATISTICAL METHODS USED	The 95% CI for the immune response rates were calculated using the exact method. For the explanatory analyses: Differences in continuous variables were assessed using the Kruskal-Wallis test or Wilcoxon test. Differences in categorical variables were assessed using Fisher Exact test. Multivariate regression was performed using robust MM regression.
RESULT ANALYSIS STAGE	Final Date of final analysis: 01/10/2024
PRIMARY COMPLETION DATA	• Is this the analysis of the primary completion data? Yes • Primary completion date: 31/10/2023
GLOBAL END OF TRIAL DATE	• Global end of trial reached? Yes • Global end of trial date: 08/01/2024

PREMATURE END OF TRIAL	Yes, premature end of trial due to slow subjects' accrual

2 POPULATION OF TRIAL SUBJECTS

The actual number of subjects enrolled in the I-SPARC trial per country is

	Number of subjects				
Country	Total	**A1 + A2**	**A3**	**B**	**C**
Belgium	152	73	39	11	29

The number of subjects enrolled per age group is displayed in the below table.

Age of subjects	**Number of subjects**
In utero	-
Preterm newborn - gestational age <37 wk	-
Newborns (0-27 days)	-
Infants and toddlers (28 days - 23 months)	-
Children (2-11 years)	-
Adolescents (12-17 years)	-
Adults (between 18 and 64 years)	90
From 65 to 84 years	61
85 years and over	1

3 SUBJECT DISPOSITION

3.1 Recruitment

Recruitment details	Between 01/12/2023 and 26/10/2023 subjects with histologically or cytologically confirmed cancer diagnosis were recruited in 1 country (Belgium).
Screening details	Eligibility criteria were: A. Subjects undergoing active systemic cancer treatment at the time of the last dose (before ICF signature) of the anti-SARS-CoV-2 mRNA vaccine (such as chemotherapy, immunotherapy, targeted agents, endocrine therapy) in non-metastatic/curative setting or metastatic/palliative setting B. or subjects undergoing follow-up after confirmed cancer complete remission without active cancer treatment for the last 12 months at the time of the last dose (before ICF signature) of the anti-SARS-CoV-2 mRNA vaccine

3.2 Pre-assignment period

Not applicable.

3.3 Post assignment period(s)

Period title:	Overall trial
Baseline period:	Yes
Allocation method:	Not applicable
Blinding used:	Not blinded
Roles blinded:	Not applicable
Blinding implementation details:	Not applicable
Arms	Single arm study
Arm title: mRNA vaccination against SARS-CoV-2	
Arm description:	anti-SARS-CoV-2 booster dose during the study, as per the national guidelines for vaccination and respecting other local/national recommendations about the ideal timing for vaccination
Arm type:	Other
IMP arm information :	Comirnaty/Spikevax
Numbers of subjects in the arm	
Started	152
Completed	77
Not completed	75
Adverse event, not serious	0
Adverse event, serious fatal	0
Adverse event, serious non-fatal	0
Consent withdrawn by subject	8
Physician decision	0
Protocol violation	32
Study terminated by sponsor	20
Lost to follow-up	6
Death	4
Technical problems	1
Other:	4
Not evaluable	*3*
Removed by error	*1*

4 BASELINE CHARACTERISTICS

Baseline characteristics reporting groups	
Reporting group title	Included patients
Reporting group description	All included patients
Number of subjects	Cohort A.1 + A.2: N=73 Cohort A.3: N=39 Cohort B: N=11 Cohort C: N=29 152 in total

	Total (N=152)	A.1+A.2 (N=73)	A.3 (N=39)	B (N=11)	C (N=29)
Age (Units: years)					
N	152	73	39	11	29
Mean (SD)	60.4 (11.48)	61.4 (10.18)	58.1 (12.74)	62.1 (16.95)	60.1 (10.44)
Median (IQR)	62.0 (54.0, 68.0)	62.0 (54.0, 69.0)	62.0 (50.0, 67.0)	63.0 (49.0, 77.0)	60.0 (54.0, 67.0)
Range	24.0, 86.0	38.0, 86.0	31.0, 83.0	26.0, 83.0	24.0, 79.0
Missing	0	0	0	0	0
Age category, n (%) (Units: Subjects)					
18-64	90 (59.2%)	42 (57.5%)	24 (61.5%)	6 (54.5%)	18 (62.1%)
65-84	61 (40.1%)	30 (41.1%)	15 (38.5%)	5 (45.5%)	11 (37.9%)
>85	1 (0.7%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age class, n (%) (Units: Subjects)					
18-55	48 (31.6%)	23 (31.5%)	13 (33.3%)	3 (27.3%)	9 (31.0%)
56-75	93 (61.2%)	44 (60.3%)	25 (64.1%)	5 (45.5%)	19 (65.5%)
>75	11 (7.2%)	6 (8.2%)	1 (2.6%)	3 (27.3%)	1 (3.4%)
sex, n (%) (Units: Subjects)					
F	124 (81.6%)	65 (89.0%)	34 (87.2%)	3 (27.3%)	22 (75.9%)
M	28 (18.4%)	8 (11.0%)	5 (12.8%)	8 (72.7%)	7 (24.1%)
race, n (%) (Units: Subjects)					
ASIAN	2 (1.3%)	0 (0.0%)	2 (5.1%)	0 (0.0%)	0 (0.0%)
BLACK OR AFRICAN AMERICAN	2 (1.3%)	1 (1.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
NOT REPORTED	1 (0.7%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
WHITE	147 (96.7%)	72 (98.6%)	35 (89.7%)	11 (100.0%)	29 (100.0%)
ECOG PS at screening, n (%) (Units: Subjects)					
0	78 (52.0%)	37 (50.7%)	17 (43.6%)	5 (50.0%)	19 (67.9%)
1	69 (46.0%)	34 (46.6%)	21 (53.8%)	5 (50.0%)	9 (32.1%)
2	3 (2.0%)	2 (2.7%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Missing	2	0	0	1	1
Ecog class, n (%) (Units: Subjects)					
0-1	147 (98.0%)	71 (97.3%)	38 (97.4%)	10 (100.0%)	28 (100.0%)
2	3 (2.0%)	2 (2.7%)	1 (2.6%)	0 (0.0%)	0 (0.0%)

	Total (N=152)	A.1+A.2 (N=73)	A.3 (N=39)	B (N=11)	C (N=29)
Missing	2	0	0	1	1
BMI at screening (Units: m²/kg)					
N	132	62	36	8	26
Mean (SD)	26.6 (6.19)	26.4 (5.35)	25.3 (5.71)	24.0 (3.75)	29.4 (8.27)
Median (IQR)	25.3 (22.2, 29.5)	25.1 (22.5, 29.7)	24.5 (21.3, 27.5)	22.6 (21.1, 27.1)	27.0 (24.6, 32.3)
Range	16.4, 53.9	17.3, 43.6	16.4, 40.2	20.2, 30.1	19.5, 53.9
Missing	20	11	3	3	3
BMI ≥25m²/kg, n (%) (Units: Subjects)					
no	63 (47.7%)	31 (50.0%)	19 (52.8%)	5 (62.5%)	8 (30.8%)
yes	69 (52.3%)	31 (50.0%)	17 (47.2%)	3 (37.5%)	18 (69.2%)
Missing	20	11	3	3	3
smoking, n (%) (Units: Subjects)					
CURRENT	24 (19.2%)	10 (16.9%)	5 (16.7%)	4 (40.0%)	5 (19.2%)
FORMER	26 (20.8%)	10 (16.9%)	8 (26.7%)	3 (30.0%)	5 (19.2%)
NEVER	75 (60.0%)	39 (66.1%)	17 (56.7%)	3 (30.0%)	16 (61.5%)
Missing	27	14	9	1	3
ALC at screening (Units: µL)					
N	134	63	36	11	24
Mean (SD)	1553.5 (900.23)	1553.9 (641.81)	1287.0 (765.58)	1913.6 (2002.11)	1787.0 (843.30)
Median (IQR)	1395.0 (1020.0, 1820.0)	1440.0 (1100.0, 1830.0)	1160.0 (770.0, 1583.0)	1120.0 (750.0, 1810.0)	1680.0 (1215.0, 2145.0)
Range	310.0, 6100.0	440.0, 3610.0	310.0, 4590.0	440.0, 6100.0	620.0, 4220.0
Missing	18	10	3	0	5
ALC at screening, n (%) (Units: Subjects)					
<1000	32 (23.9%)	12 (19.0%)	13 (36.1%)	5 (45.5%)	2 (8.3%)
>=1000	102 (76.1%)	51 (81.0%)	23 (63.9%)	6 (54.5%)	22 (91.7%)
Missing	18	10	3	0	5
Lymphopenia at baseline, n (%) (Units: Subjects)					
N	150 (98.7%)	72 (98.6%)	38 (97.4%)	11 (100.0%)	29 (100.0%)
Y	2 (1.3%)	1 (1.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Hypogammaglobulinaemia at baseline, n (%) (Units: Subjects)					
N	151 (99.3%)	72 (98.6%)	39 (100.0%)	11 (100.0%)	29 (100.0%)
Y	1 (0.7%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension* at inclusion, n (%) (Units: Subjects)					
No	100 (65.8%)	47 (64.4%)	24 (61.5%)	8 (72.7%)	21 (72.4%)
Yes	52 (34.2%)	26 (35.6%)	15 (38.5%)	3 (27.3%)	8 (27.6%)
Hypercholesterolaemia* at inclusion, n (%) (Units: Subjects)					
No	120 (78.9%)	58 (79.5%)	33 (84.6%)	9 (81.8%)	20 (69.0%)
Yes	32 (21.1%)	15 (20.5%)	6 (15.4%)	2 (18.2%)	9 (31.0%)
Depression at inclusion*, n (%) (Units: Subjects)					
No	126 (82.9%)	57 (78.1%)	36 (92.3%)	10 (90.9%)	23 (79.3%)
Yes	26 (17.1%)	16 (21.9%)	3 (7.7%)	1 (9.1%)	6 (20.7%)

	Total (N=152)	A.1+A.2 (N=73)	A.3 (N=39)	B (N=11)	C (N=29)
Hypothyroidism at inclusion*, n (%) (Units: Subjects)					
No	132 (86.8%)	61 (83.6%)	33 (84.6%)	10 (90.9%)	28 (96.6%)
Yes	20 (13.2%)	12 (16.4%)	6 (15.4%)	1 (9.1%)	1 (3.4%)
N prior vaccin doses, n (%) (Units: Subjects)					
2	25 (16.4%)	7 (9.6%)	8 (20.5%)	5 (45.5%)	5 (17.2%)
3	61 (40.1%)	29 (39.7%)	17 (43.6%)	3 (27.3%)	12 (41.4%)
4	56 (36.8%)	31 (42.5%)	12 (30.8%)	2 (18.2%)	11 (37.9%)
5	10 (6.6%)	6 (8.2%)	2 (5.1%)	1 (9.1%)	1 (3.4%)
N months between last vaccination prior inclusion and date inclusion, n (%) (Units: Subjects)					
<6 months	79 (52.0%)	34 (46.6%)	27 (69.2%)	6 (54.5%)	12 (41.4%)
6 to 9 months	44 (28.9%)	23 (31.5%)	8 (20.5%)	1 (9.1%)	12 (41.4%)
>9 months	29 (19.1%)	16 (21.9%)	4 (10.3%)	4 (36.4%)	5 (17.2%)

* as reported in the medical history.

EVALUABLE SUBJECTS (N=115)

Subject analysis sets	
Subject analysis set title	EVALUABLE SUBJECTS
Subject analysis set type	Modified intention-to-treat
Subject analysis set description	Evaluable subjects: all subjects who received at least two doses of an mRNA anti-SARS-CoV-2 vaccine and from which peripheral blood sample was collected during study
Number of subjects	Cohort A.1 + A.2: N=59 Cohort A.3: N=22 Cohort B: N=9 Cohort C: N=25 115 in total

		Cohort			
	Total (N=115)	A1+A2 (N=59)	A3 (N=22)	B (N=9)	C (N=25)
Age (Units: years)					
N	115	59	22	9	25
Mean (SD)	59.8 (11.58)	60.7 (10.28)	57.4 (13.26)	60.8 (17.84)	59.8 (10.69)
Median (IQR)	61.0 (53.0, 68.0)	62.0 (54.0, 68.0)	60.5 (50.0, 67.0)	63.0 (49.0, 73.0)	59.0 (54.0, 67.0)
Range	24.0, 86.0	38.0, 86.0	31.0, 83.0	26.0, 83.0	24.0, 79.0
Missing	0	0	0	0	0
Age categories, n (%) (Units: Subjects)					
In utero	-	-	-	-	-
Preterm newborn - gestational age <37 wk	-	-	-	-	-
Newborns (0-27 days)	-	-	-	-	-
Infants and toddlers (28 days - 23 months)	-	-	-	-	-
Children (2-11 years)	-	-	-	-	-
Adolescents (12-17 years)	-	-	-	-	-
Adults (between 18 and 64 years)	70 (60.9%)	35 (59.3%)	15 (68.2%)	5 (55.6%)	15 (60.0%)
From 65 to 84 years	44 (38.3%)	23 (39.0%)	7 (31.8%)	4 (44.4%)	10 (40.0%)
85 years and over	1 (0.9%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age class, n (%) (Units: Subjects)					
18-55	38 (33.0%)	19 (32.2%)	8 (36.4%)	3 (33.3%)	8 (32.0%)
56-75	69 (60.0%)	36 (61.0%)	13 (59.1%)	4 (44.4%)	16 (64.0%)

		Cohort			
	Total (N=115)	A1+A2 (N=59)	A3 (N=22)	B (N=9)	C (N=25)
>75	8 (7.0%)	4 (6.8%)	1 (4.5%)	2 (22.2%)	1 (4.0%)
sex, n (%) (Units: Subjects)					
F	95 (82.6%)	54 (91.5%)	20 (90.9%)	2 (22.2%)	19 (76.0%)
M	20 (17.4%)	5 (8.5%)	2 (9.1%)	7 (77.8%)	6 (24.0%)
race, n (%) (Units: Subjects)					
ASIAN	2 (1.7%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	0 (0.0%)
BLACK OR AFRICAN AMERICAN	2 (1.7%)	1 (1.7%)	1 (4.5%)	0 (0.0%)	0 (0.0%)
WHITE	111 (96.5%)	58 (98.3%)	19 (86.4%)	9 (100.0%)	25 (100.0%)
ECOG PS at screening, n (%) (Units: Subjects)					
0	63 (55.3%)	30 (50.8%)	10 (45.5%)	5 (62.5%)	18 (72.0%)
1	48 (42.1%)	27 (45.8%)	11 (50.0%)	3 (37.5%)	7 (28.0%)
2	3 (2.6%)	2 (3.4%)	1 (4.5%)	0 (0.0%)	0 (0.0%)
Missing	1	0	0	1	0
ECOG PS class, n (%) (Units: Subjects)					
0-1	111 (97.4%)	57 (96.6%)	21 (95.5%)	8 (100.0%)	25 (100.0%)
2	3 (2.6%)	2 (3.4%)	1 (4.5%)	0 (0.0%)	0 (0.0%)
Missing	1	0	0	1	0
BMI at screening (Units: m^2/kg)					
N	98	50	20	6	22
Mean (SD)	26.7 (6.25)	26.1 (4.90)	25.4 (5.89)	24.9 (3.91)	29.7 (8.78)
Median (IQR)	25.3 (22.3, 29.7)	25.1 (22.5, 29.4)	24.7 (21.8, 28.1)	24.2 (22.0, 28.9)	27.0 (24.6, 32.3)
Range	16.9, 53.9	17.3, 38.9	16.9, 40.2	20.2, 30.1	19.5, 53.9
Missing	17	9	2	3	3
BMI ≥25m^2/kg, n (%) (Units: Subjects)					
no	45 (45.9%)	25 (50.0%)	10 (50.0%)	3 (50.0%)	7 (31.8%)
yes	53 (54.1%)	25 (50.0%)	10 (50.0%)	3 (50.0%)	15 (68.2%)
Missing	17	9	2	3	3
smoking, n (%) (Units: Subjects)					
CURRENT	16 (16.5%)	7 (14.3%)	2 (11.1%)	4 (50.0%)	3 (13.6%)
FORMER	19 (19.6%)	9 (18.4%)	3 (16.7%)	2 (25.0%)	5 (22.7%)
NEVER	62 (63.9%)	33 (67.3%)	13 (72.2%)	2 (25.0%)	14 (63.6%)
Missing	18	10	4	1	3
ALC at screening (µL)					
N	100	51	19	9	21
Mean (SD)	1592.8 (942.06)	1544.6 (657.44)	1363.3 (914.13)	2131.1 (2170.10)	1686.5 (693.59)
Median (IQR)	1395.0 (1010.0, 1880.0)	1430.0 (1060.0, 1900.0)	1140.0 (790.0, 1610.0)	1160.0 (900.0, 1810.0)	1670.0 (1280.0, 2110.0)
Range	440.0, 6100.0	440.0, 3610.0	520.0, 4590.0	440.0, 6100.0	620.0, 3540.0
Missing	15	8	3	0	4
ALC class, n (%) (Units: Subjects)					
<1000	24 (24.0%)	11 (21.6%)	7 (36.8%)	4 (44.4%)	2 (9.5%)
>=1000	76 (76.0%)	40 (78.4%)	12 (63.2%)	5 (55.6%)	19 (90.5%)
Missing	15	8	3	0	4
Lymphopenia at baseline, n (%) (Units: Subjects)					
N	114 (99.1%)	58 (98.3%)	22 (100.0%)	9 (100.0%)	25 (100.0%)

		Cohort			
	Total (N=115)	A1+A2 (N=59)	A3 (N=22)	B (N=9)	C (N=25)
Y	1 (0.9%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypogammaglobulinaemia at baseline, n (%) (Units: Subjects)					
N	114 (99.1%)	58 (98.3%)	22 (100.0%)	9 (100.0%)	25 (100.0%)
Y	1 (0.9%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension at inclusion*, n (%) (Units: Subjects)					
No	82 (71.3%)	42 (71.2%)	15 (68.2%)	7 (77.8%)	18 (72.0%)
Yes	33 (28.7%)	17 (28.8%)	7 (31.8%)	2 (22.2%)	7 (28.0%)
Hypercholesterolaemia at inclusion*, n (%) (Units: Subjects)					
No	93 (80.9%)	48 (81.4%)	19 (86.4%)	8 (88.9%)	18 (72.0%)
Yes	22 (19.1%)	11 (18.6%)	3 (13.6%)	1 (11.1%)	7 (28.0%)
Depression at inclusion*, n (%) (Units: Subjects)					
No	92 (80.0%)	44 (74.6%)	19 (86.4%)	9 (100.0%)	20 (80.0%)
Yes	23 (20.0%)	15 (25.4%)	3 (13.6%)	0 (0.0%)	5 (20.0%)
Hypothyroidism at inclusion*, n (%) (Units: Subjects)					
No	105 (91.3%)	52 (88.1%)	20 (90.9%)	8 (88.9%)	25 (100.0%)
Yes	10 (8.7%)	7 (11.9%)	2 (9.1%)	1 (11.1%)	0 (0.0%)
N prior vaccin doses, n (%) (Units: Subjects)					
2	24 (20.9%)	7 (11.9%)	8 (36.4%)	4 (44.4%)	5 (20.0%)
3	44 (38.3%)	23 (39.0%)	8 (36.4%)	3 (33.3%)	10 (40.0%)
4	38 (33.0%)	24 (40.7%)	4 (18.2%)	1 (11.1%)	9 (36.0%)
5	9 (7.8%)	5 (8.5%)	2 (9.1%)	1 (11.1%)	1 (4.0%)
N months between last vaccination prior inclusion and date inclusion, n (%) (Units: Subjects)					
<6 months	42 (36.5%)	20 (33.9%)	10 (45.5%)	4 (44.4%)	8 (32.0%)
6 to 9 months	44 (38.3%)	23 (39.0%)	8 (36.4%)	1 (11.1%)	12 (48.0%)
>9 months	29 (25.2%)	16 (27.1%)	4 (18.2%)	4 (44.4%)	5 (20.0%)

* as reported in the medical history.

	Total (N=115)	cohort A1+A2 (N=59)	A3 (N=22)	B (N=9)	C (N=25)
Solid_Hemato, n (%) (Units: Subjects)					
HAEMATOLOGICAL MALIGNANCY	11 (9.6%)	0 (0.0%)	0 (0.0%)	9 (100.0%)	2 (8.0%)
INVASIVE SOLID TUMOUR	104 (90.4%)	59 (100.0%)	22 (100.0%)	0 (0.0%)	23 (92.0%)

Haematological malignancies

	Total (N=11)	cohort B (N=9)	C (N=2)
Primary location Haematological malignancy, n (%)			
BLOOD	6 (54.5%)	6 (66.7%)	0 (0.0%)
LYMPH NODES	5 (45.5%)	3 (33.3%)	2 (100.0%)
Histology Hematological malignancy, n (%)			
LEUKEMIA	3 (27.3%)	3 (33.3%)	0 (0.0%)
LYMPHOMA	5 (45.5%)	3 (33.3%)	2 (100.0%)
MYELOMA	2 (18.2%)	2 (22.2%)	0 (0.0%)
OTHER	1 (9.1%)	1 (11.1%)	0 (0.0%)

Solid tumours

	Total (N=104)	COHORT A1+A2 (N=59)	A3 (N=22)	C (N=23)
Primary_tumor_location, n (%)				
ANAL CANAL	1 (1.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
BLADDER	3 (2.9%)	0 (0.0%)	1 (4.5%)	2 (8.7%)
BREAST	79 (76.0%)	50 (84.7%)	13 (59.1%)	16 (69.6%)
COLON	1 (1.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
HEAD AND NECK	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
LUNG	10 (9.6%)	2 (3.4%)	4 (18.2%)	4 (17.4%)
OVARY	3 (2.9%)	2 (3.4%)	1 (4.5%)	0 (0.0%)
PANCREAS	1 (1.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
PERITONEAL CAVITY	1 (1.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
PROSTATE	3 (2.9%)	3 (5.1%)	0 (0.0%)	0 (0.0%)
RECTUM	1 (1.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
status cancer at enrolment, n (%)				
METASTATIC	41 (39.8%)	26 (44.8%)	13 (59.1%)	2 (8.7%)
NON-METASTATIC	62 (60.2%)	32 (55.2%)	9 (40.9%)	21 (91.3%)
Missing info	1	1		

5 END POINTS

Of the 115 subjects,

- 107 were evaluable at baseline (8 not evaluable)
- 52 were evaluable at post boot (2 not evaluable, 61 no post boost assessment)
- 56 were evaluable at final (9 not evaluable, 50 no post boost assessment)

Of the 115 subjects,

- 11 had changed cohort at the time of boost.

Cohort at baseline	Cohort at boost				
	A1+A2	A3	B	C	Total
A1+A2	55	4	-	-	59
A3	6	16	-	-	22
B	-	-	9	-	9
C	1	-	-	24	24
	62	20	9	24	115

⇨ 107 evaluable subjects at baseline
  - 56 A1+A2
  - 17 A3
  - 9 B
  - 25 C

⇨ 52 evaluable subjects at post boost
  - 25 A1+A2
  - 12 A3
  - 6 B
  - 9 C

⇨ 56 evaluable subjects at final
  - 30 A1+A2
  - 8 A3
  - 4 B
  - 14 C

5.1 Primary endpoint – Long-term immune response rate

End point type	Primary
End point description	The proportion of subjects that have detectable titers of specific antibody against SARS-CoV-2 spike protein, measured by Elecsys® Anti-SARS-CoV-2 S, between 3 and 12 months after the last dose (before ICF signature) of an mRNA anti-SARS-CoV-2 vaccine.
End point timeframe	*Baseline*

	Evaluable population
Number of subjects analysed	*107*

⇨ 107 evaluable subjects at baseline
- 56 A1+A2
- 17 A3
- 9 B
- 25 C

The lowest value at baseline for anti-SARS-CoV-2 spike was above the cutoff of 0.80 U/ml for each subject , indicating that all subjects has an immune response at baseline.

The immune response rate was 100% in all subjects, in each cohort, at baseline.

- Cohort A1+A2: 56/56 = 100% (95% CI, 94% to 100%).
- Cohort A3: 17/17 = 100% (95% CI, 80% to 100%)
- Cohort B: 9/9 = 100% (95% CI, 66% to 100%)
- Cohort C: 25/25 = 100% (95% CI, 86% to 100%)

5.1.1 Statistical analysis of end point

Not applicable: single-arm study. The aim was to estimate the immune response rate within each cohort.

5.2 Secondary endpoint – Duration of immune response

End point type	Secondary
End point description	*The proportion of subjects that have detectable titers of specific antibody against SARS-CoV-2 spike protein, measured by Elecsys® Anti-SARS-CoV-2 S, at the final study assessment timepoint, namely at 6 months (+/- 4 weeks) after the baseline assessment or at 6 months (+ 4 weeks/- 8 weeks) after the first booster dose after ICF signature, if a booster dose of the vaccine is administered during the study per local / national health policy guidelines.*
End point timeframe	*Final Assessment*

	Evaluable population
Number of subjects analysed	*56*

Duration of immune response cannot be determined, as no subject had a non-response during study.

5.2.1 Statistical analysis of end point

Not applicable: single-arm study.

5.3 Secondary endpoint –Immune response by cohort

End point type	Secondary
End point description	*The proportion of subjects that have detectable titers of specific antibody against SARS-CoV-2 spike protein, measured by Elecsys® Anti-SARS-CoV-2 S, by cohort (specified in section 3.):* *i) between 3 and 12 months after the last dose before ICF signature; and* *ii) at the final study assessment timepoint, namely at 6 months (+/- 4 weeks) after baseline assessment or 6 months (+ 4 weeks/- 8 weeks) after the first booster dose after ICF signature, if a booster dose is administered during the study per local / national health policy guidelines.*
End point timeframe	*Baseline, Post-boost and Final Assessment*

	Cohort A1+A2	Cohort A3	Cohort B	Cohort C
Baseline				
Number of subjects analysed	*56*	*17*	*9*	*25*
Immune response rate at baseline, %				
Number	*100%*	*100%*	*100%*	*100%*
Confidence interval (95%)	*94%-100%*	*80%-100%*	*66%-100%*	*86%-100%*
Post-boost				
	Cohort A1+A2	Cohort A3	Cohort B	Cohort C
Number of subjects analysed	*25*	*12*	*6*	*9*
Immune response rate at post-boost, %				
Number	*100%*	*100%*	*100%*	*100%*
Confidence interval (95%)	*86%-100%*	*74%-100%*	*54%-100%*	*66%-100%*

Final Assessment				
	Cohort A1+A2	Cohort A3	Cohort B	Cohort C
Number of subjects analysed	*30*	*8*	*4*	*14*
Immune response rate at final assessment, %				
Number	*100%*	*100%*	*100%*	*100%*
Confidence interval (95%)	*88%-100%*	*63%-100%*	*40%-100%*	*77%-100%*

5.3.1 Statistical analysis of end point

Not applicable: single-arm study. The aim was to estimate the immune response rate within each cohort.

5.4 Secondary endpoint – Clinical Efficacy

End point type	Secondary
End point description	*The proportion of asymptomatic subjects with SARS-CoV-2 positive test, confirmed COVID-19 or severe COVID-19 infection with onset at least 14 days after the last dose before ICF signature in subjects who had been without serologic or virological evidence of SARS-CoV-2 infection up to 14 days after the last dose before ICF signature. Whenever reported in the patient's charter/dossier, both the viral load and mutant strains of SARS-CoV-2 related data will be collected in the eCRF for any subjects with SARS-CoV-2 infection.*

37 subjects with nucleo baseline NON REACTIVE at baseline and a FU available:

- 11 becoming REACTIVE at pre-boost, post-boost or EOT.
- 26 stay non reactive

	A.1+A.2 (N=13)	A.3 (N=6)	B (N=7)	C (N=11)	Total (N=37)
Become Reactive during follow-up, n (%)					
No	11 (84.6%)	5 (83.3%)	5 (71.4%)	5 (45.5%)	26 (70.3%)
Yes	2 (15.4%)	1 (16.7%)	2 (28.6%)	6 (54.5%)	11 (29.7%)

5.4.1 Statistical analysis of end point

Not applicable: single-arm study.

5.5 Secondary endpoint – Safety

End point type	Secondary
End point description	*Safety of booster dose(s) of mRNA anti-SARS-CoV-2 vaccine after ICF signature, defined as the frequency, duration and severity of adverse reactions reported according to NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, if booster dose(s) of the vaccine are administered during the study per local / national health policy guidelines.*

No adverse events were registered in the 152 included subjects.

5.6 Exploratory statistical analyses

We explore the anti-SARS-CoV-2 spike as continuous value, to assess whether there are differences over time, and differences between cohorts

For further analyses, when a comparison involves a group of <5 patients, the comparison is marked in black.

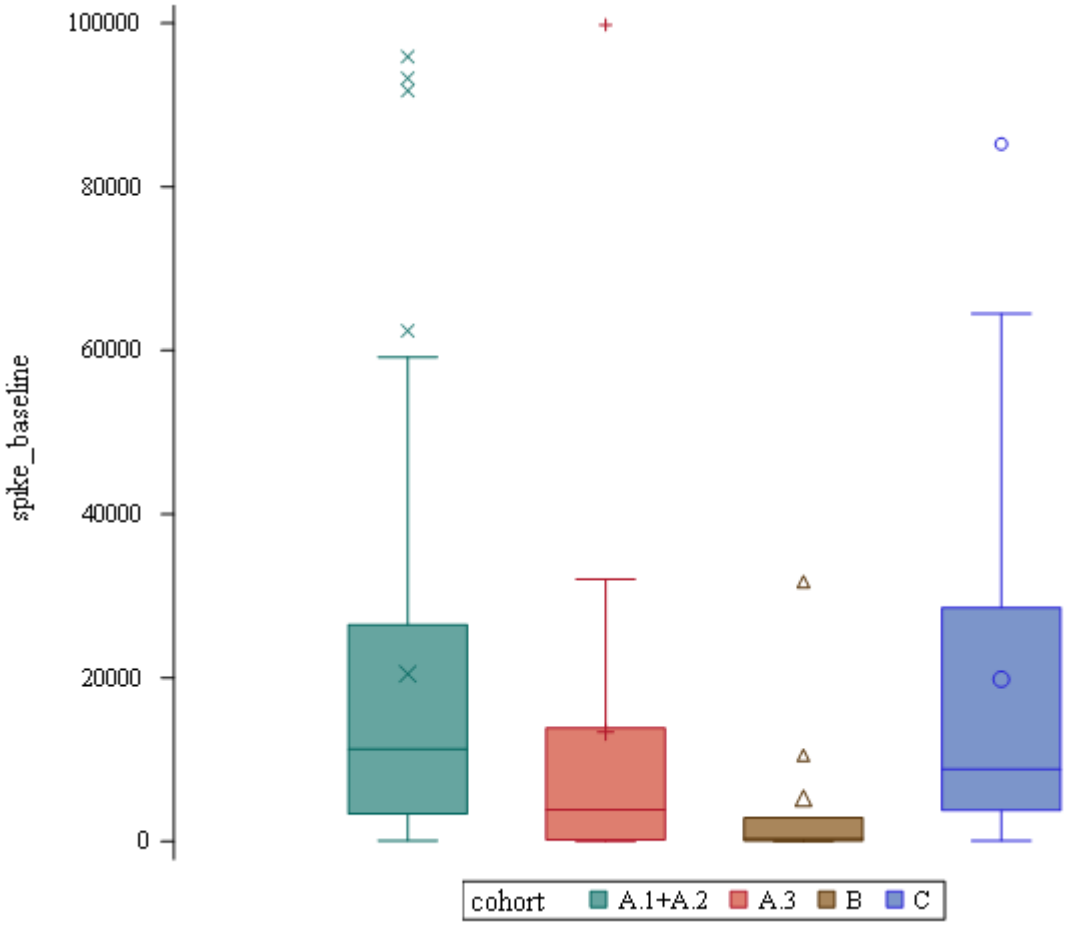
No adjustments for multiple testing have been made.

In the 107 subjects with baseline evaluable:

Comparison between the cohorts

		cohort				P-value						
	Total (N=107)	A1+A2 (N=56)	A3 (N=17)	B (N=9)	C (N=25)	Overall	A1+2 vs A3	A1+2 vs B	A1+2 vs C	A3 vs B	A3 vs C	B vs C
spike_baseline						0.0045[1]	0.03*	0.004*	0.71*	0.25*	0.07*	0.02*
N	107	56	17	9	25							
Mean (SD)	17911.4 (23193.96)	20469.4 (23950.74)	13355.6 (24790.91)	5288.0 (10471.46)	19823.7 (22838.34)							
Median (IQR)	9017.0 (2180.0, 26871.0)	11292.5 (3358.5, 26487.0)	3875.0 (202.0, 13863.0)	330.0 (107.0, 2888.0)	8828.0 (3785.0, 28582.0)							
Range	5.5, 99800.0	105.0, 95904.0	5.5, 99800.0	15.6, 31728.0	90.9, 85242.0							
Missing	0	0	0	0	0							
nucleo_baseline, n (%)						0.1970[2]						
NonReac	50 (47.2%)	22 (40.0%)	9 (52.9%)	7 (77.8%)	12 (48.0%)							
Reac	56 (52.8%)	33 (60.0%)	8 (47.1%)	2 (22.2%)	13 (52.0%)							
Missing	1	1	0	0	0							

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;
* Wilcoxon test p-value



Comparison between the cohorts, stratified by nucleo baseline (Reactive vs non-reactive)

			cohort				P-value						
Nucleo baseline		Total	A1+A2	A3	B	C	Overall	A1+2 vs A3	A1+2 vs B	A1+2 vs C	A3 vs B	A3 vs C	B vs C
NonReac		(N=50)	(N=22)	(N=9)	(N=7)	(N=12)							
	spike_baseline						0.0168[1]	0.28*	0.005*	0.76*	0.16*	0.20*	0.03*
	N	50	22	9	7	12							
	Mean (SD)	4531.7 (6733.56)	6583.5 (9264.49)	2740.3 (2640.04)	762.5 (1106.12)	4312.5 (3498.44)							
	Median (IQR)	2864.5 (700.0, 5618.0)	3182.0 (961.0, 8869.0)	3197.0 (202.0, 4766.0)	246.0 (52.0, 1699.0)	4533.5 (816.5, 7277.0)							
	Range	5.5, 38010.0	583.0, 38010.0	5.5, 7115.0	15.6, 2888.0	90.9, 9017.0							
	Missing	0	0	0	0	0							
Reac		(N=56)	(N=33)	(N=8)	(N=2)	(N=13)							
	spike_baseline						0.6545[1]						
	N	56	33	8	2	13							
	Mean (SD)	29889.6 (26220.50)	29858.7 (26562.07)	25297.9 (32999.04)	21127.0 (14992.08)	34141.7 (23859.46)							
	Median (IQR)	20800.0 (10865.5, 41482.5)	19193.0 (11205.0, 42893.0)	20367.0 (340.5, 30523.5)	21127.0 (10526.0, 31728.0)	28582.0 (18766.0, 46633.0)							
	Range	105.0, 99800.0	105.0, 95904.0	121.0, 99800.0	10526.0, 31728.0	3785.0, 85242.0							
	Missing	0	0	0	0	0							

[1]Kruskal-Wallis p-value;
* Wilxcoxon

Nucleo_baseline was missing for one subject.

Comparison between nucleo baseline reactive vs non-reactive

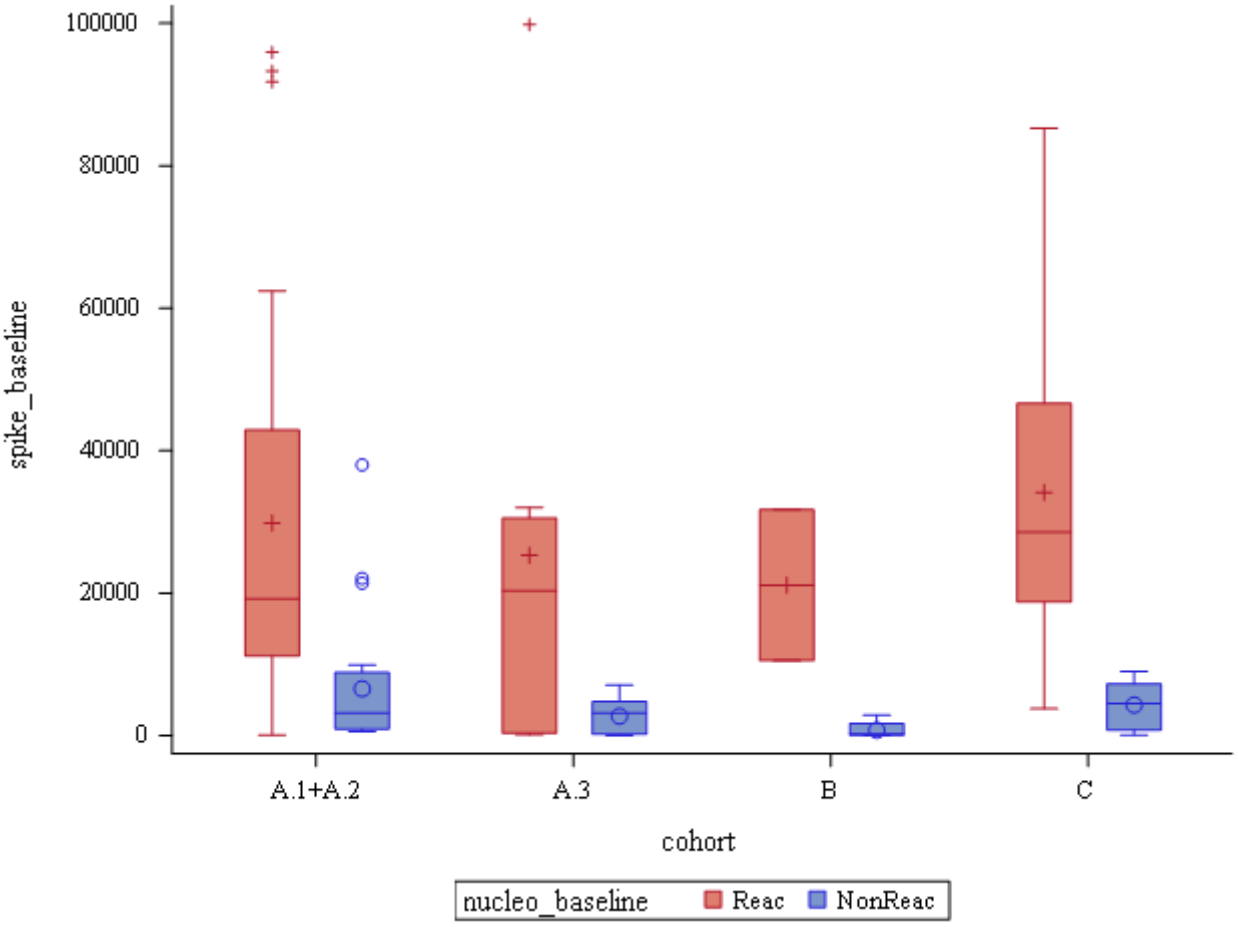
	nucleo_baseline			
	NonReac (N=50)	Reac (N=56)	Total (N=106)	P-value
spike_baseline				<.0001[1]
N	50	56	106	
Mean (SD)	4531.7 (6733.56)	29889.6 (26220.50)	17928.3 (23303.47)	
Median (IQR)	2864.5 (700.0, 5618.0)	20800.0 (10865.5, 41482.5)	8943.0 (2180.0, 26871.0)	
Range	5.5, 38010.0	105.0, 99800.0	5.5, 99800.0	
Missing	0	0	0	

[1]Kruskal-Wallis p-value;

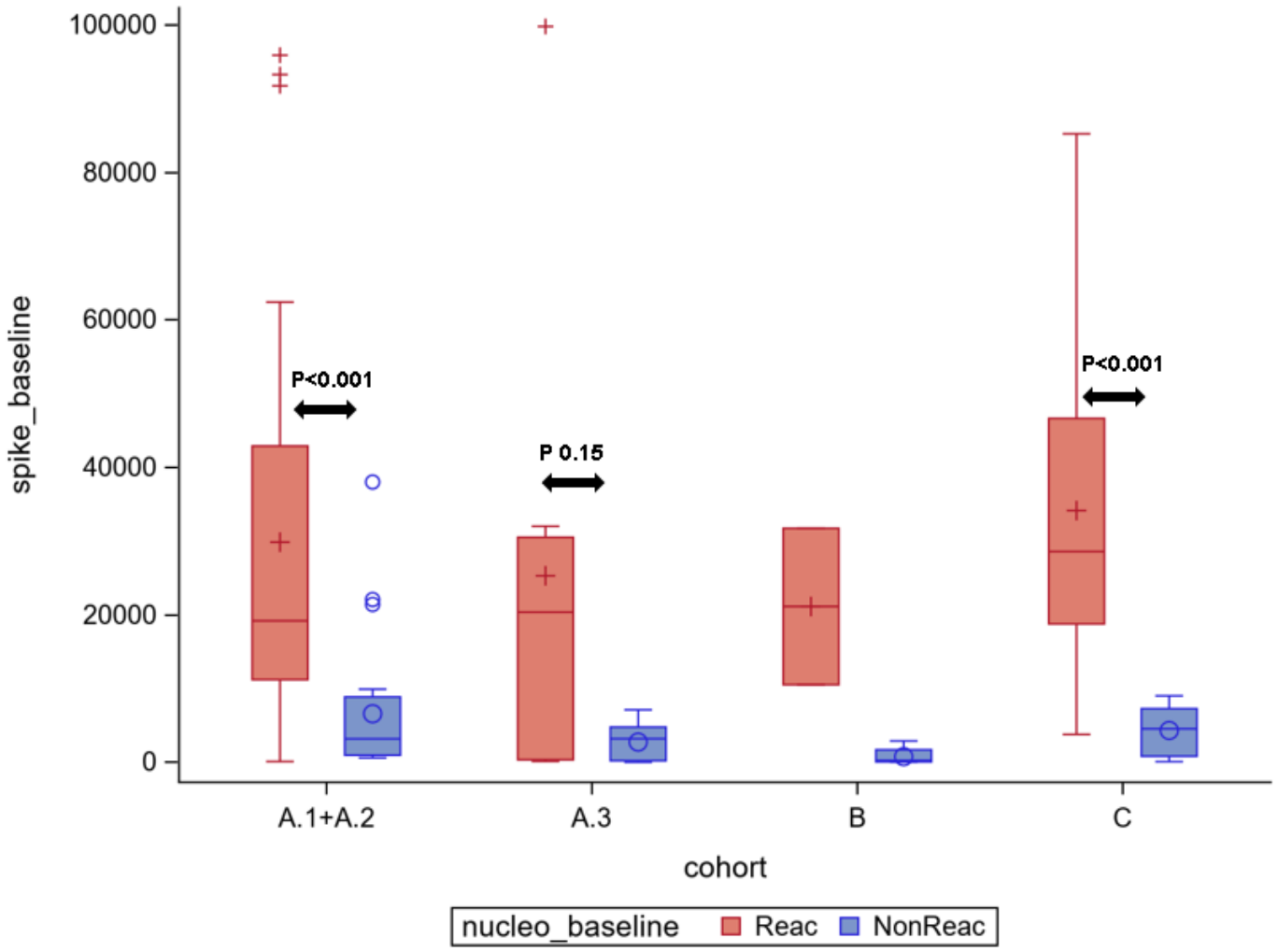
Comparison between nucleo baseline reactive vs non-reactive, stratified by cohort

		nucleo_baseline			
cohort		NonReac	Reac	Total	P-value
A.1+A.2		(N=22)	(N=33)	(N=55)	
	spike_baseline				<.0001[1]
	N	22	33	55	
	Mean (SD)	6583.5 (9264.49)	29858.7 (26562.07)	20548.6 (24164.08)	
	Median (IQR)	3182.0 (961.0, 8869.0)	19193.0 (11205.0, 42893.0)	11205.0 (3310.0, 30506.0)	
	Range	583.0, 38010.0	105.0, 95904.0	105.0, 95904.0	
	Missing	0	0	0	
A.3		(N=9)	(N=8)	(N=17)	
	spike_baseline				0.1489[1]
	N	9	8	17	
	Mean (SD)	2740.3 (2640.04)	25297.9 (32999.04)	13355.6 (24790.91)	
	Median (IQR)	3197.0 (202.0, 4766.0)	20367.0 (340.5, 30523.5)	3875.0 (202.0, 13863.0)	
	Range	5.5, 7115.0	121.0, 99800.0	5.5, 99800.0	
	Missing	0	0	0	
B		(N=7)	(N=2)	(N=9)	
	spike_baseline				[redacted]
	N	7	2	9	
	Mean (SD)	762.5 (1106.12)	21127.0 (14992.08)	5288.0 (10471.46)	
	Median (IQR)	246.0 (52.0, 1699.0)	21127.0 (10526.0, 31728.0)	330.0 (107.0, 2888.0)	
	Range	15.6, 2888.0	10526.0, 31728.0	15.6, 31728.0	
	Missing	0	0	0	
C		(N=12)	(N=13)	(N=25)	
	spike_baseline				0.0002[1]
	N	12	13	25	
	Mean (SD)	4312.5 (3498.44)	34141.7 (23859.46)	19823.7 (22838.34)	
	Median (IQR)	4533.5 (816.5, 7277.0)	28582.0 (18766.0, 46633.0)	8828.0 (3785.0, 28582.0)	
	Range	90.9, 9017.0	3785.0, 85242.0	90.9, 85242.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;



With p-values on the graph:



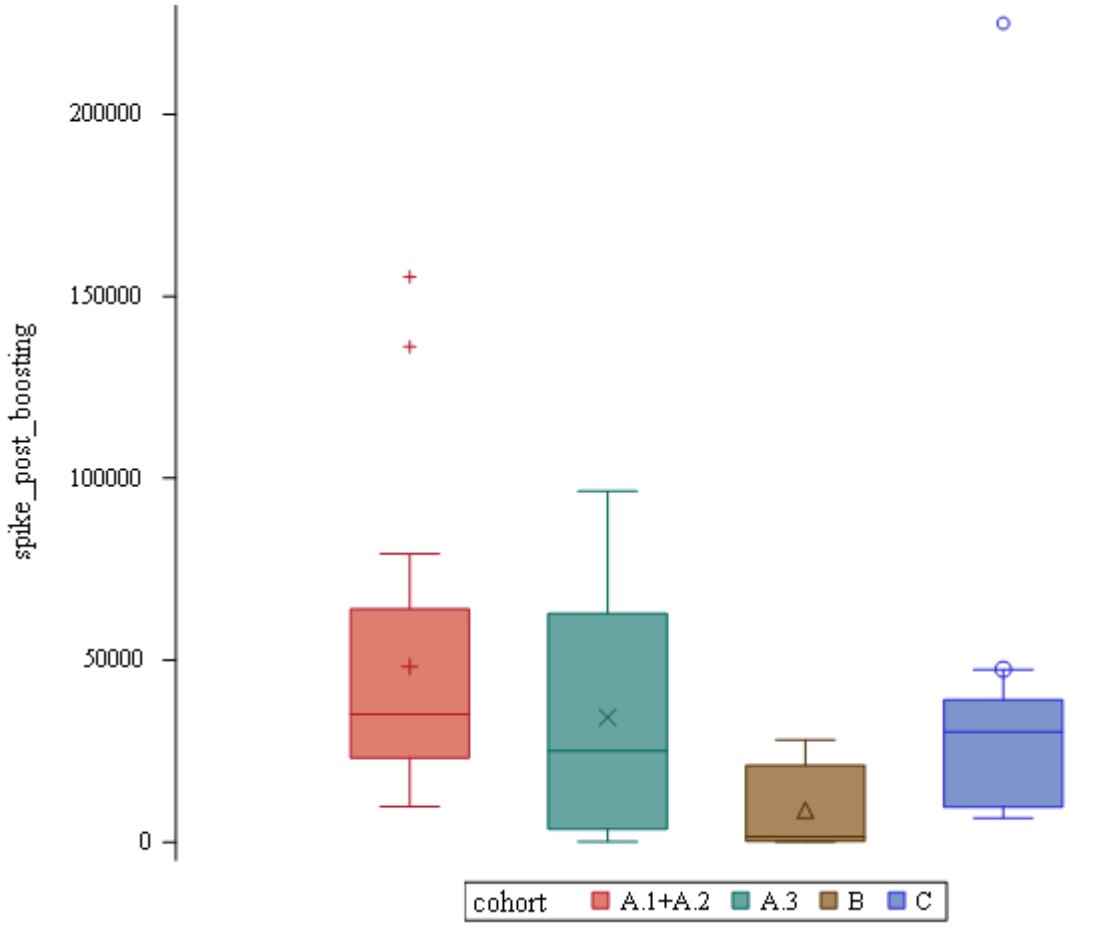
In the 52 subjects with post boost evaluable

Comparison between the cohorts at boost

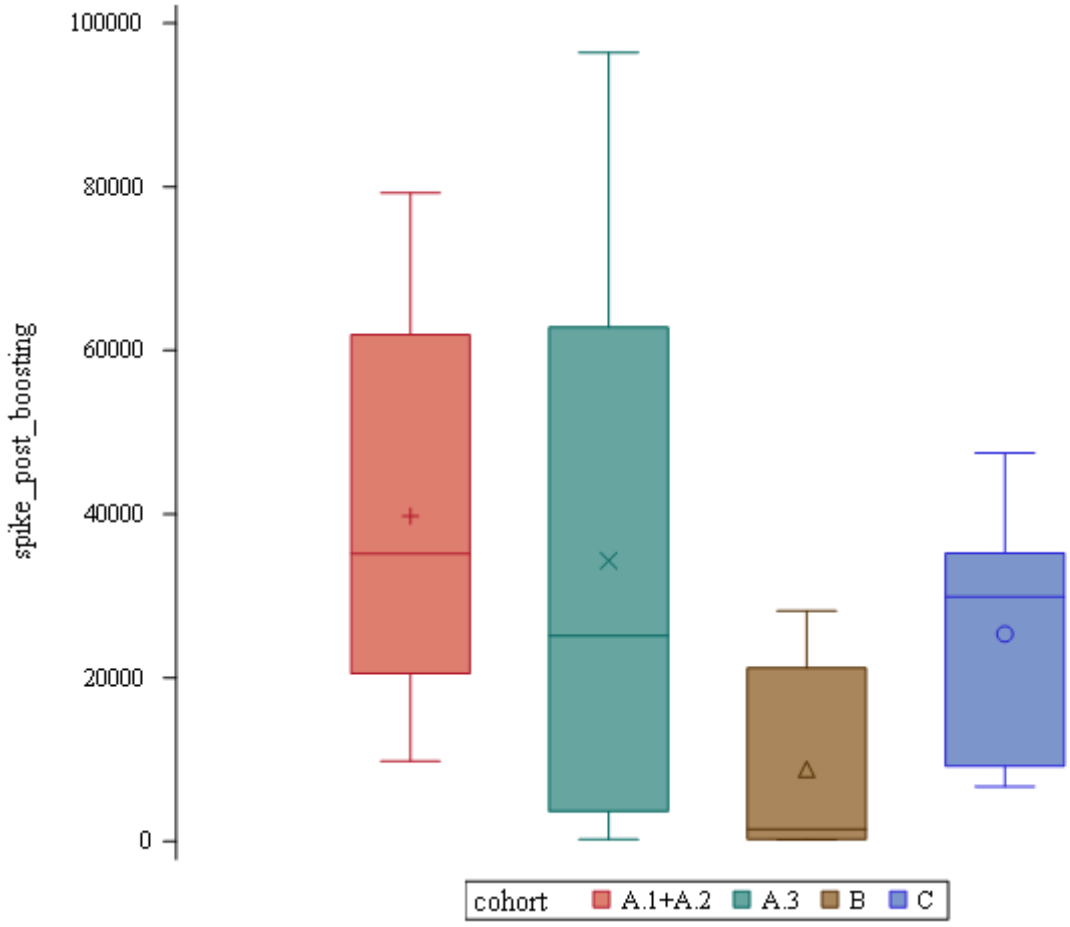
		Cohort at boost				P-value						
	Total (N=52)	A.1+A.2 (N=25)	A.3 (N=12)	B (N=6)	C (N=9)	Overall	A1+2 vs A3	A1+2 vs B	A1+2 vs C	A3 vs B	A3 vs C	B vs C
spike_post_boosting						0.0117[1]	0.18*	0.005*	0.23*	0.10*	0.55*	0.03*
N	52	25	12	6	9							
Mean (SD)	40355.6 (42217.42)	48241.1 (35718.40)	34315.4 (35690.11)	8807.7 (12524.01)	47536.8 (68057.51)							
Median (IQR)	30079.0 (13668.5, 56337.0)	35239.0 (23192.0, 64098.0)	25094.0 (3665.5, 62818.5)	1503.5 (287.0, 21182.0)	30414.0 (9722.0, 39142.0)							
Range	191.0, 225000.0	9822.0, 155332.0	238.0, 96425.0	191.0, 28179.0	6710.0, 225000.0							
Missing	0	0	0	0	0							
nucleo_post_boosting, n (%)						0.3867[2]						
NonReac	31 (62.0%)	14 (58.3%)	6 (50.0%)	4 (66.7%)	7 (87.5%)							
Reac	19 (38.0%)	10 (41.7%)	6 (50.0%)	2 (33.3%)	1 (12.5%)							
Missing	2	1	0	0	1							

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

* Wilcoxon



If we limit the Y-axis to 100,000:



Comparison between the cohorts at boost, stratified by nucleo post boosting (reactive vs non-reactive)

			Cohort at boost				P-value						
Nucleo Post boosting		Total	A.1+A.2	A.3	B	C	Overall	A1+2 vs A3	A1+2 vs B	A1+2 vs C	A3 vs B	A3 vs C	B vs C
NonReac		(N=31)	(N=14)	(N=6)	(N=4)	(N=7)							
	Spike post_boosting						0.0074[1]	0.02*	[redacted]	0.36*	[redacted]	0.06*	[redacted]
	N	31	14	6	4	7							
	Mean (SD)	23946.1 (19194.70)	34734.6 (18079.41)	9689.5 (12384.94)	6119.0 (10096.91)	24775.7 (16360.67)							
	Median (IQR)	20503.0 (6710.0, 33563.0)	29992.0 (19394.0, 41522.0)	3665.5 (380.0, 20444.0)	1503.5 (355.5, 11882.5)	30414.0 (8699.0, 39142.0)							
	Range	238.0, 69259.0	17515.0, 69259.0	238.0, 29744.0	287.0, 21182.0	6710.0, 47444.0							
	Missing	0	0	0	0	0							
Reac		(N=19)	(N=10)	(N=6)	(N=2)	(N=1)							
	Spike post_boosting						0.2326[1]						
	N	19	10	6	2	1							
	Mean (SD)	52371.5 (37633.54)	58364.0 (40922.48)	58941.3 (34546.94)	14185.0 (19790.50)	29401.0 (.)							
	Median (IQR)	48396.0 (28179.0, 76371.0)	49899.5 (35162.0, 76371.0)	62818.5 (34317.0, 91697.0)	14185.0 (191.0, 28179.0)	29401.0 (29401.0, 29401.0)							
	Range	191.0, 155332.0	9822.0, 155332.0	5572.0, 96425.0	191.0, 28179.0	29401.0, 29401.0							
	Missing	0	0	0	0	0							

[1]Kruskal-Wallis p-value;
* Wilcoxon

Comparison between nucelo post boosting (reactive vs non-reactive)

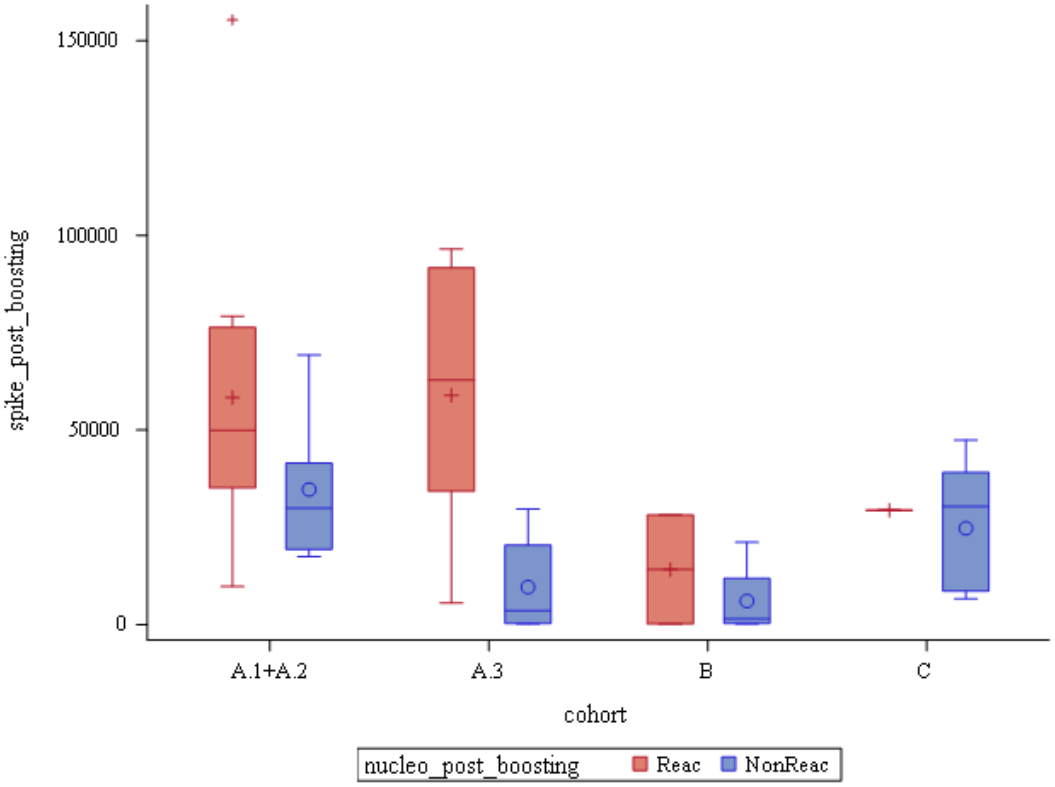
	nucleo_post_boosting NonReac (N=31)	Reac (N=19)	Total (N=50)	P-value
spike_post_boosting				0.0032[1]
N	31	19	50	
Mean (SD)	23946.1 (19194.70)	52371.5 (37633.54)	34747.7 (30660.92)	
Median (IQR)	20503.0 (6710.0, 33563.0)	48396.0 (28179.0, 76371.0)	29627.5 (9822.0, 48396.0)	
Range	238.0, 69259.0	191.0, 155332.0	191.0, 155332.0	
Missing	0	0	0	

[1]Kruskal-Wallis p-value;

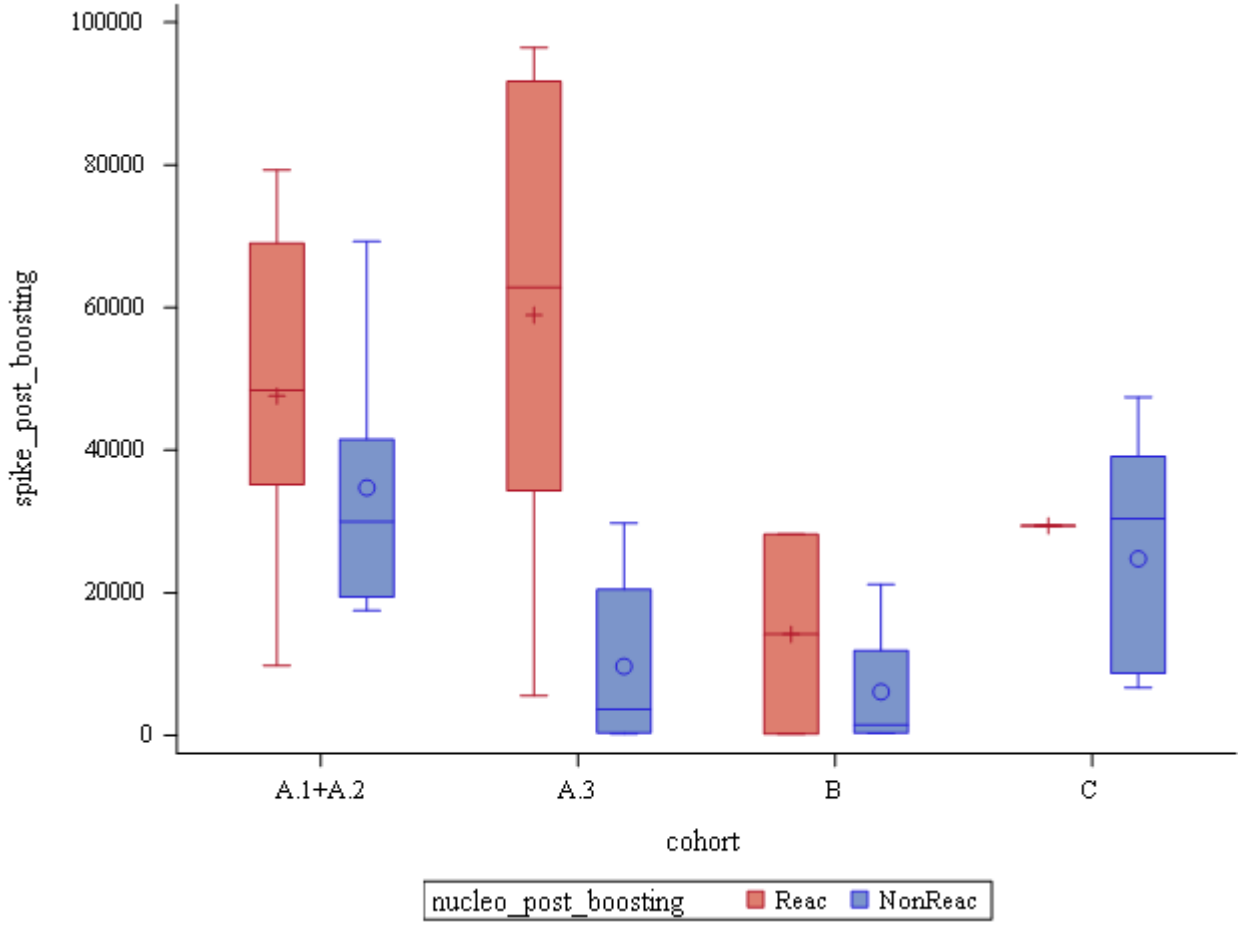
Comparison between nucleo post boosting (reactive vs non-reactive), stratified by cohort at boost

Cohort boost		nucleo_post_boosting NonReac	Reac	Total	P-value
A.1+A.2		(N=14)	(N=10)	(N=24)	
	spike_post_boosting				0.0695[1]
	N	14	10	24	
	Mean (SD)	34734.6 (18079.41)	58364.0 (40922.48)	44580.2 (31331.41)	
	Median (IQR)	29992.0 (19394.0, 41522.0)	49899.5 (35162.0, 76371.0)	35200.5 (21847.5, 62998.5)	
	Range	17515.0, 69259.0	9822.0, 155332.0	9822.0, 155332.0	
	Missing	0	0	0	
A.3		(N=6)	(N=6)	(N=12)	
	spike_post_boosting				0.0104[1]
	N	6	6	12	
	Mean (SD)	9689.5 (12384.94)	58941.3 (34546.94)	34315.4 (35690.11)	
	Median (IQR)	3665.5 (380.0, 20444.0)	62818.5 (34317.0, 91697.0)	25094.0 (3665.5, 62818.5)	
	Range	238.0, 29744.0	5572.0, 96425.0	238.0, 96425.0	
	Missing	0	0	0	
B		(N=4)	(N=2)	(N=6)	
	spike_post_boosting				[redacted]
	N	4	2	6	
	Mean (SD)	6119.0 (10096.91)	14185.0 (19790.50)	8807.7 (12524.01)	
	Median (IQR)	1503.5 (355.5, 11882.5)	14185.0 (191.0, 28179.0)	1503.5 (287.0, 21182.0)	
	Range	287.0, 21182.0	191.0, 28179.0	191.0, 28179.0	
	Missing	0	0	0	
C		(N=7)	(N=1)	(N=8)	
	spike_post_boosting				[redacted]
	N	7	1	8	
	Mean (SD)	24775.7 (16360.67)	29401.0 (.)	25353.9 (15235.06)	
	Median (IQR)	30414.0 (8699.0, 39142.0)	29401.0 (29401.0, 29401.0)	29907.5 (9210.5, 35220.5)	
	Range	6710.0, 47444.0	29401.0, 29401.0	6710.0, 47444.0	
	Missing	0	0	0	

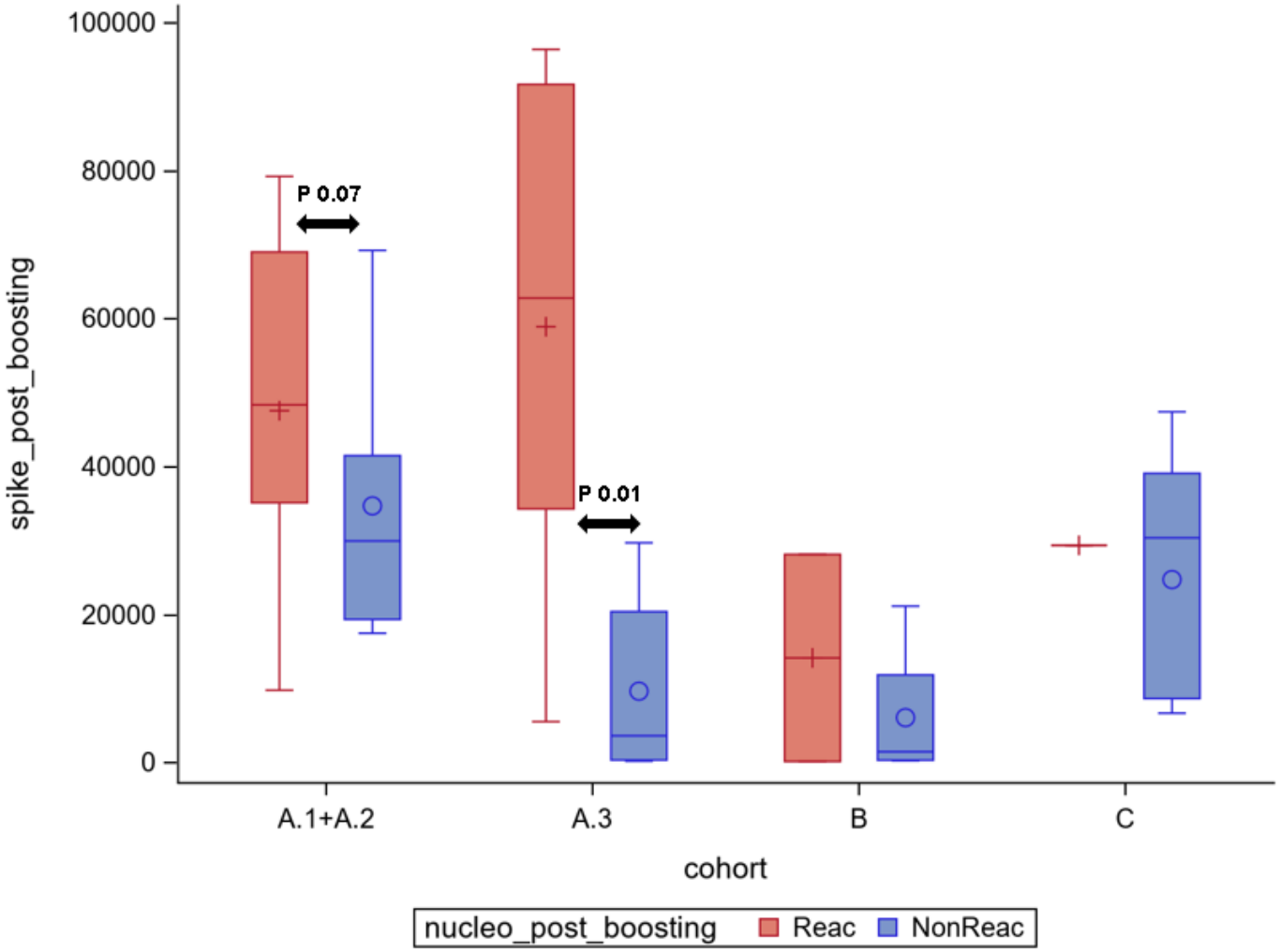
[1]Kruskal-Wallis p-value;



If we limit the Y-axis to 100,000:



If we limit to <100,000 and put p-values:

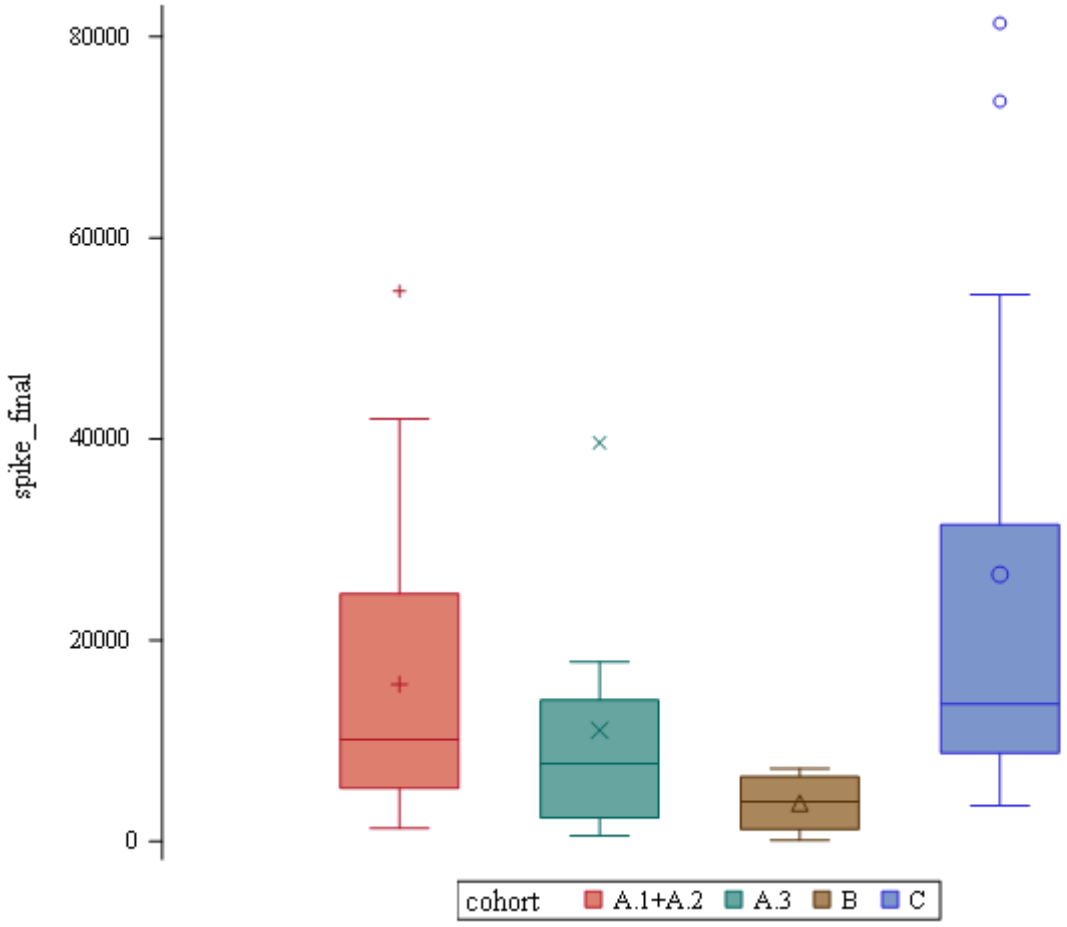


In the 56 subjects with final evaluable

Comparison between the cohorts at final

		Cohort at boost				P-value						
	Total (N=56)	A.1+A.2 (N=30)	A.3 (N=8)	B (N=4)	C (N=14)	Overall	A1+2 vs A3	A1+2 vs B	A1+2 vs C	A3 vs B	A3 vs C	B vs C
spike_final						0.0530[1]	0.28*	[redacted]	0.22*	[redacted]	0.11*	[redacted]
N	56	30	8	4	14							
Mean (SD)	16854.5 (17859.31)	15623.9 (13708.15)	11049.9 (12888.42)	3813.0 (3220.66)	26534.6 (25708.38)							
Median (IQR)	10023.5 (5040.0, 25813.5)	10105.5 (5302.0, 24628.0)	7719.5 (2333.5, 14040.5)	3941.0 (1193.0, 6433.0)	13659.0 (8792.0, 31475.0)							
Range	117.0, 81334.0	1296.0, 54691.0	582.0, 39630.0	117.0, 7253.0	3541.0, 81334.0							
Missing	0	0	0	0	0							
nucleo_final, n (%)						0.4332[2]						
NonReac	23 (41.1%)	15 (50.0%)	2 (25.0%)	2 (50.0%)	4 (28.6%)							
Reac	33 (58.9%)	15 (50.0%)	6 (75.0%)	2 (50.0%)	10 (71.4%)							

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;
* Wilcoxon



Comparison between the cohorts at final, stratified by nucleo final (reactive vs non-reactive)

			Cohort at boost				P-value						
Nucleo final		Total	A.1+A.2	A.3	B	C	Overall	A1+2 vs A3	A1+2 vs B	A1+2 vs C	A3 vs B	A3 vs C	B vs C
NonReac		(N=23)	(N=15)	(N=2)	(N=2)	(N=4)							
	spike_final						0.3476[1]						
	N	23	15	2	2	4							
	Mean (SD)	6784.2 (5687.32)	7856.8 (6534.53)	2053.0 (2080.31)	3941.0 (2364.57)	6549.0 (2913.67)							
	Median (IQR)	5302.0 (2269.0, 9287.0)	5368.0 (2016.0, 15297.0)	2053.0 (582.0, 3524.0)	3941.0 (2269.0, 5613.0)	6684.0 (4058.5, 9039.5)							
	Range	582.0, 19264.0	1389.0, 19264.0	582.0, 3524.0	2269.0, 5613.0	3541.0, 9287.0							
	Missing	0	0	0	0	0							
Reac		(N=33)	(N=15)	(N=6)	(N=2)	(N=10)							
	spike_final						0.0474[1]	0.21*	[redacted]	0.40*	[redacted]	0.09*	[redacted]
	N	33	15	6	2	10							
	Mean (SD)	23873.2 (20056.79)	23391.0 (14740.26)	14048.8 (13730.28)	3685.0 (5045.91)	34528.8 (26519.87)							
	Median (IQR)	17866.0 (8967.0, 31475.0)	24628.0 (8967.0, 33961.0)	10205.0 (5244.0, 17866.0)	3685.0 (117.0, 7253.0)	29374.5 (13238.0, 54363.0)							
	Range	117.0, 81334.0	1296.0, 54691.0	1143.0, 39630.0	117.0, 7253.0	8107.0, 81334.0							
	Missing	0	0	0	0	0							

[1]Kruskal-Wallis p-value;
* Wilcoxon

Comparison between nucleo final (reactive vs non-reactive)

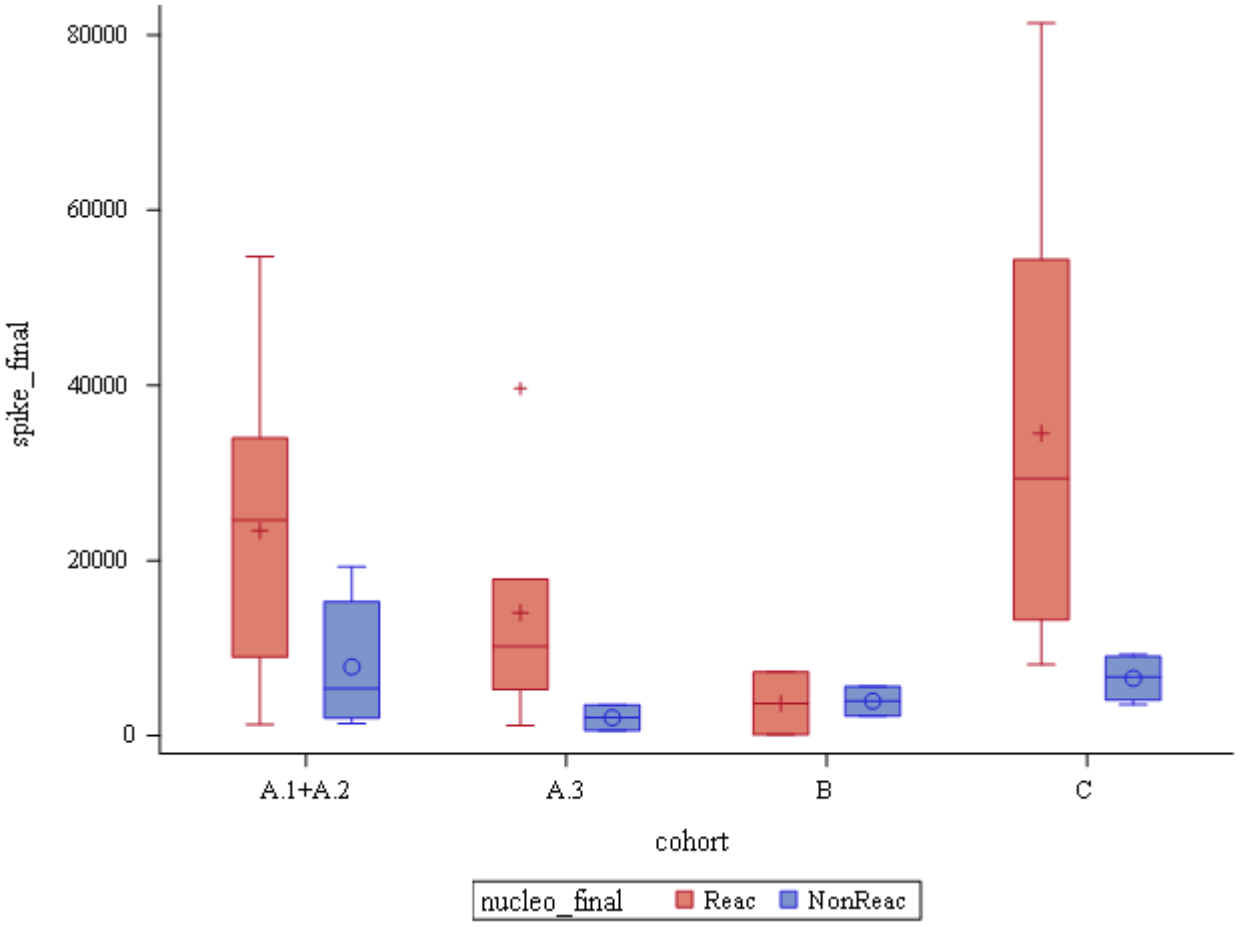
	nucleo_final			
	NonReac (N=23)	Reac (N=33)	Total (N=56)	P-value
spike_final				<.0001[1]
N	23	33	56	
Mean (SD)	6784.2 (5687.32)	23873.2 (20056.79)	16854.5 (17859.31)	
Median (IQR)	5302.0 (2269.0, 9287.0)	17866.0 (8967.0, 31475.0)	10023.5 (5040.0, 25813.5)	
Range	582.0, 19264.0	117.0, 81334.0	117.0, 81334.0	
Missing	0	0	0	

[1]Kruskal-Wallis p-value;

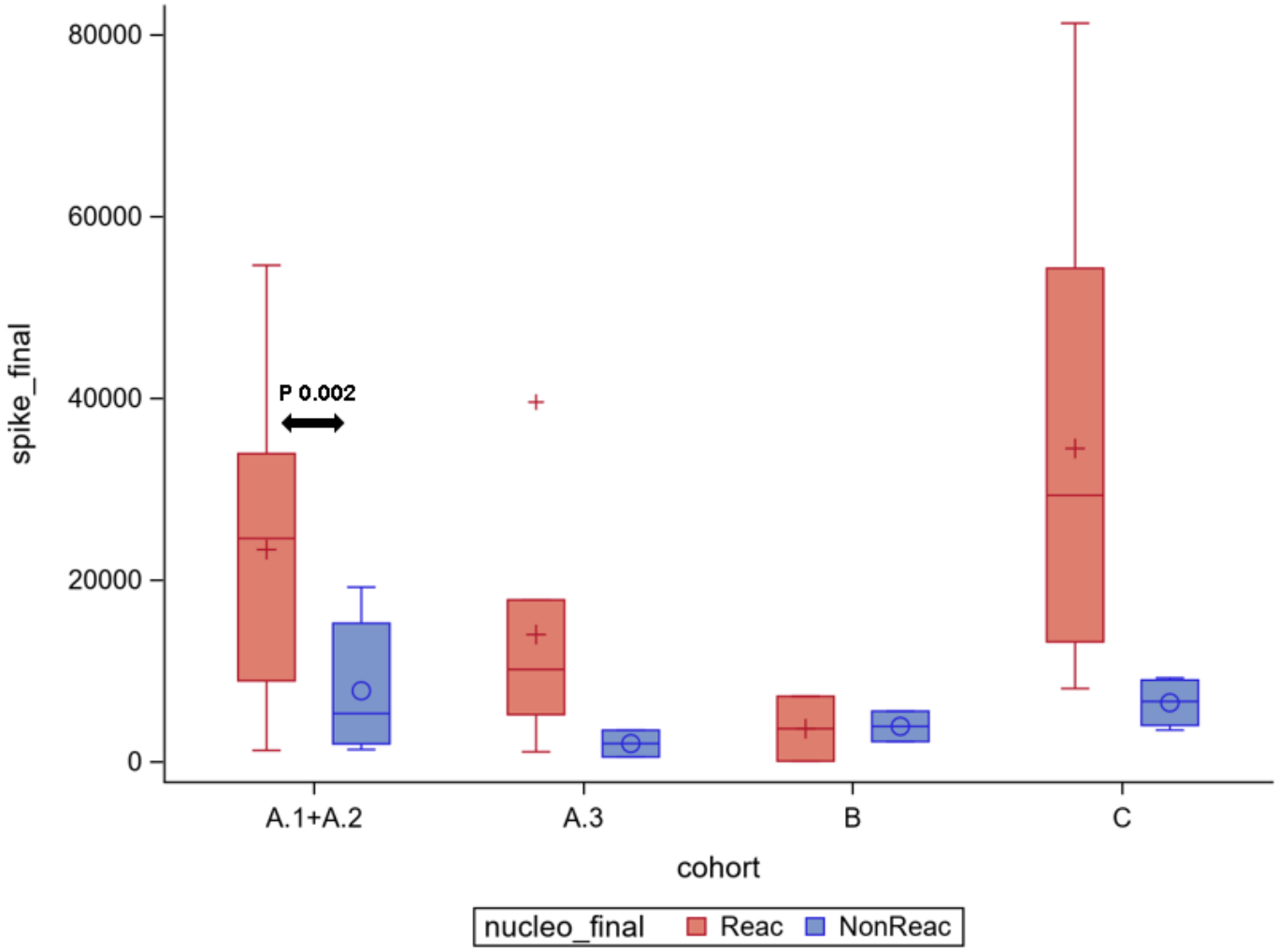
Comparison between nucleo final (reactive vs non-reactive), stratified by cohort at final

cohortboost		nucleo_final NonReac	Reac	Total	P-value
A.1+A.2		(N=15)	(N=15)	(N=30)	
	spike_final				0.0020[1]
	N	15	15	30	
	Mean (SD)	7856.8 (6534.53)	23391.0 (14740.26)	15623.9 (13708.15)	
	Median (IQR)	5368.0 (2016.0, 15297.0)	24628.0 (8967.0, 33961.0)	10105.5 (5302.0, 24628.0)	
	Range	1389.0, 19264.0	1296.0, 54691.0	1296.0, 54691.0	
	Missing	0	0	0	
A.3		(N=2)	(N=6)	(N=8)	
	spike_final				[redacted]
	N	2	6	8	
	Mean (SD)	2053.0 (2080.31)	14048.8 (13730.28)	11049.9 (12888.42)	
	Median (IQR)	2053.0 (582.0, 3524.0)	10205.0 (5244.0, 17866.0)	7719.5 (2333.5, 14040.5)	
	Range	582.0, 3524.0	1143.0, 39630.0	582.0, 39630.0	
	Missing	0	0	0	
B		(N=2)	(N=2)	(N=4)	
	spike_final				[redacted]
	N	2	2	4	
	Mean (SD)	3941.0 (2364.57)	3685.0 (5045.91)	3813.0 (3220.66)	
	Median (IQR)	3941.0 (2269.0, 5613.0)	3685.0 (117.0, 7253.0)	3941.0 (1193.0, 6433.0)	
	Range	2269.0, 5613.0	117.0, 7253.0	117.0, 7253.0	
	Missing	0	0	0	
C		(N=4)	(N=10)	(N=14)	
	spike_final				[redacted]
	N	4	10	14	
	Mean (SD)	6549.0 (2913.67)	34528.8 (26519.87)	26534.6 (25708.38)	
	Median (IQR)	6684.0 (4058.5, 9039.5)	29374.5 (13238.0, 54363.0)	13659.0 (8792.0, 31475.0)	
	Range	3541.0, 9287.0	8107.0, 81334.0	3541.0, 81334.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;



With p-values:

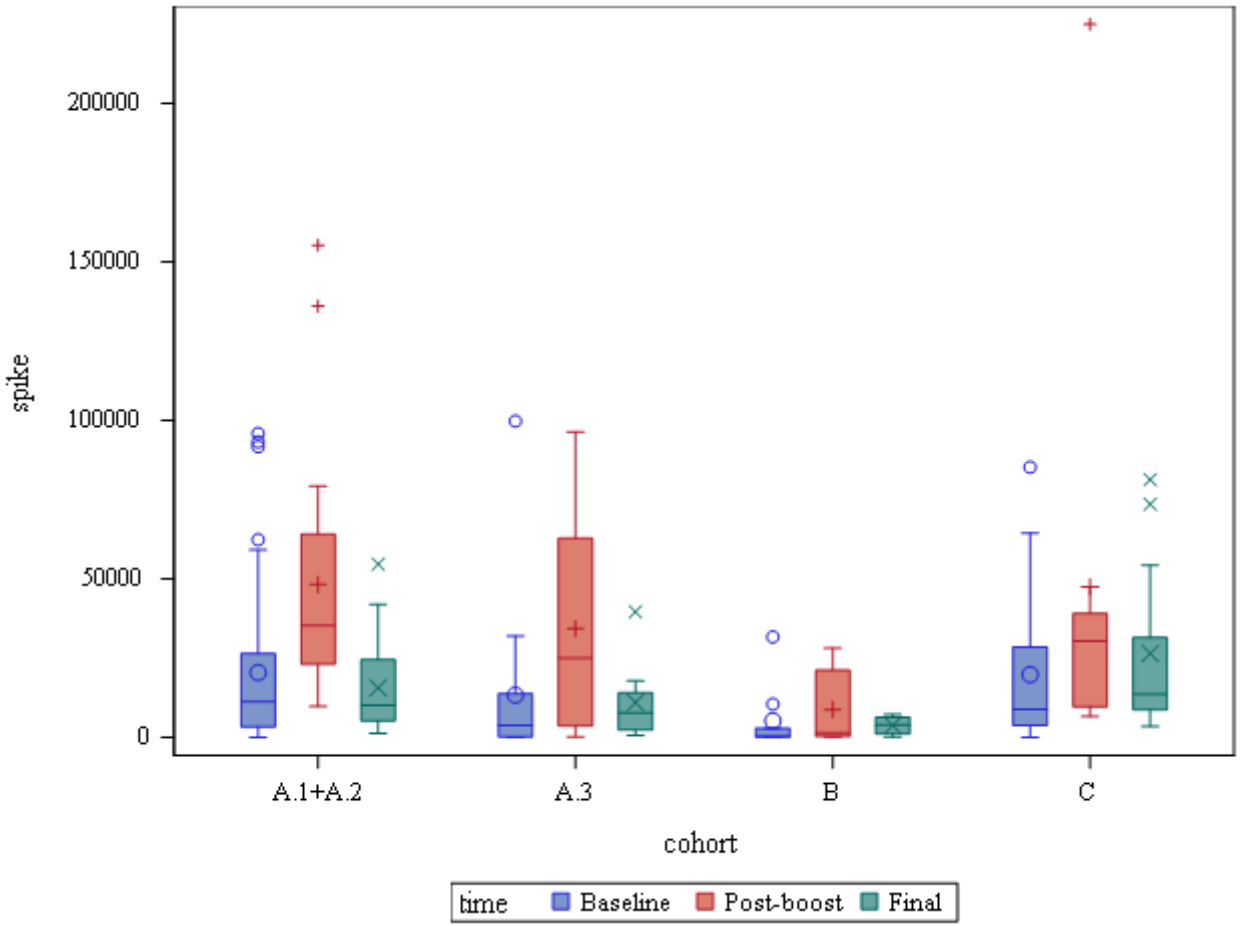


Evolution immune response over time

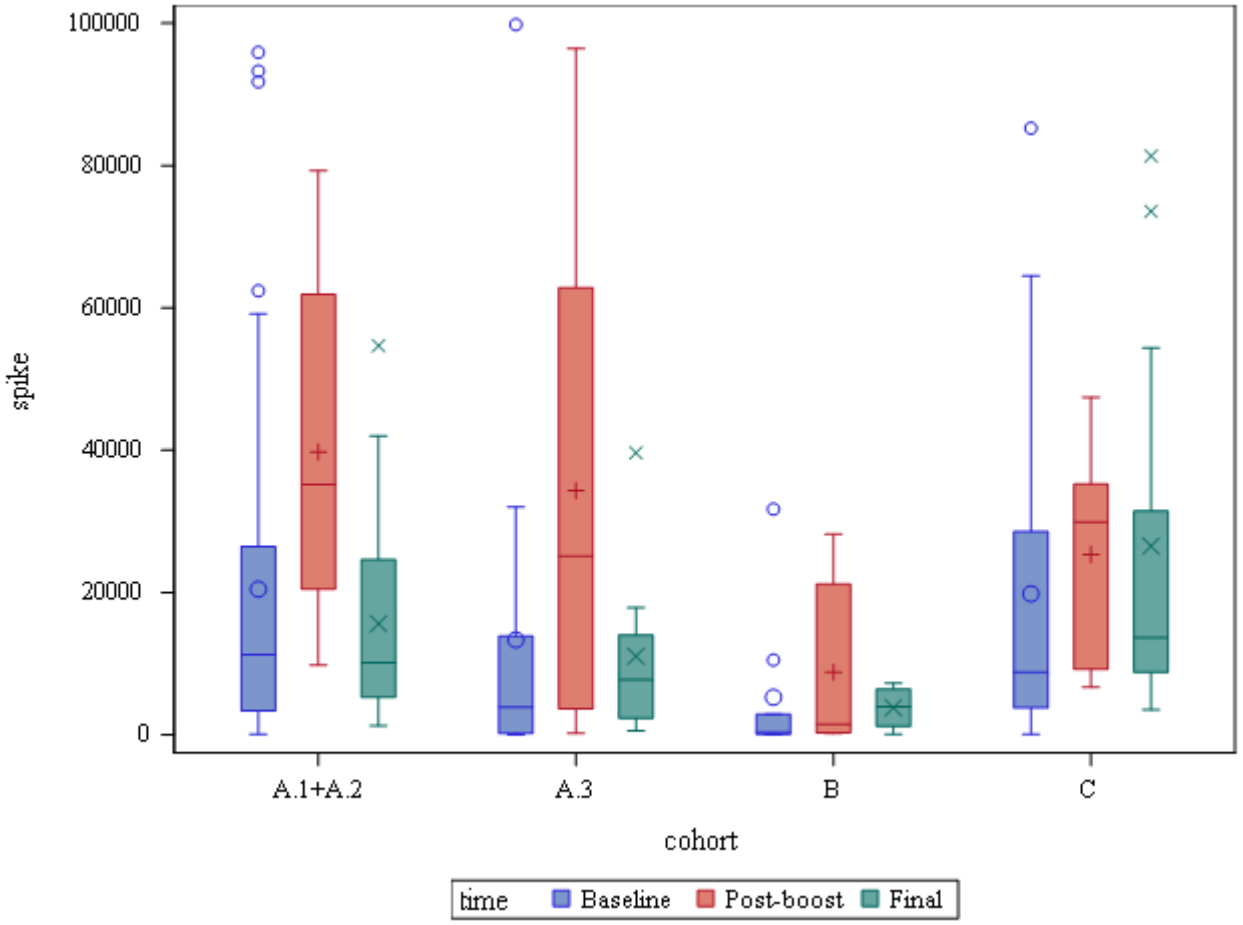
For subjects who change cohorts, the cohort is the cohort at the time of the spike measurement.

All cohorts

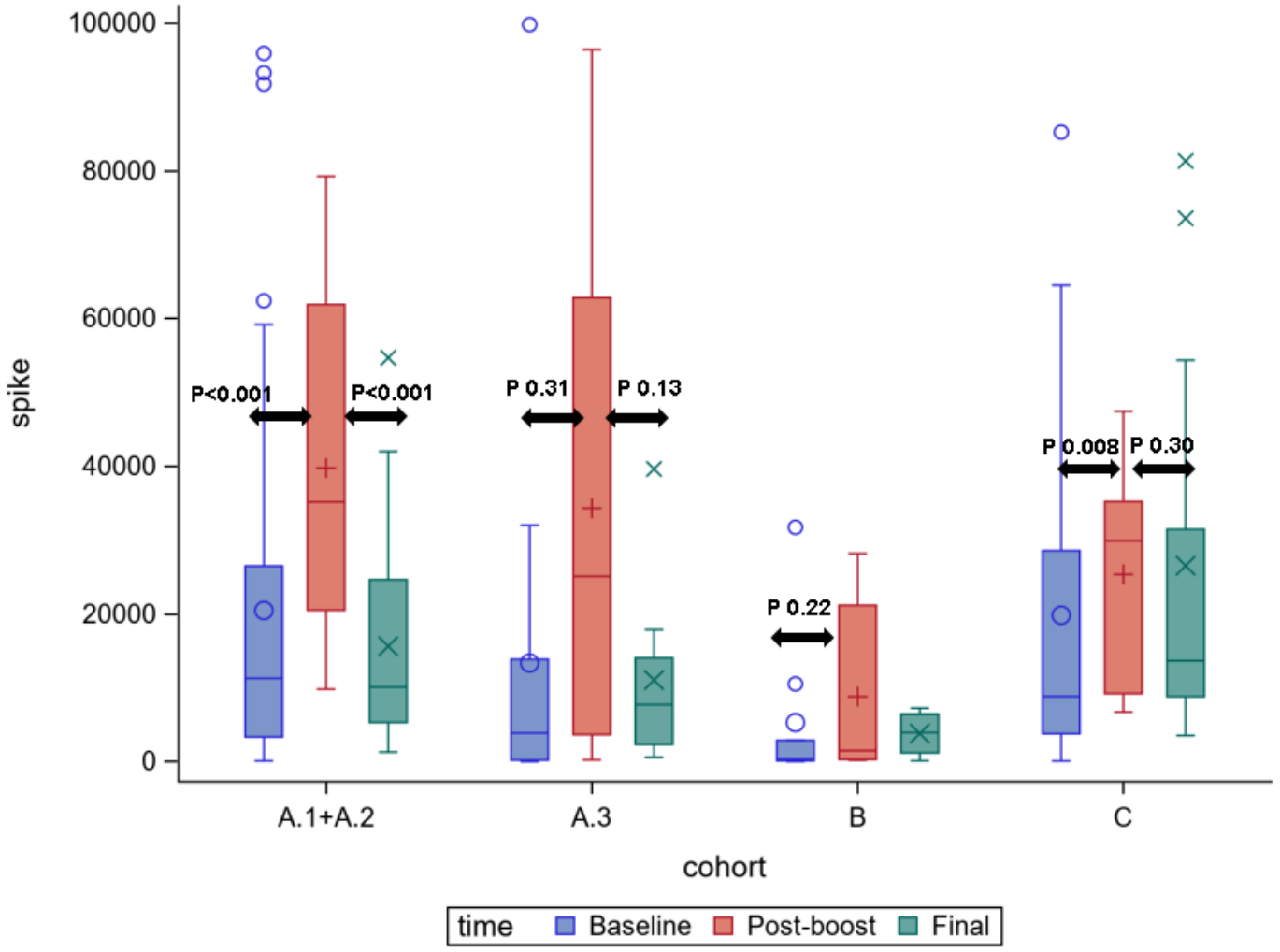
	N patients	P-value for difference in spike between the two time points
All cohorts	44 pts with baseline and post-boosting	<0.001
	52 pts with baseline and final	0.77
	28 pts with post-boosting and final	<0.001
A1+A2	15 pts with baseline and post-boosting in the same cohort	<0.001
	24 pts with baseline and final in the same cohort	0.42
	15 pts with post-boosting and final in the same cohort	<0.001
A3	5 pts with baseline and post-boosting in the same cohort	0.31
	4 pts with baseline and final in the same cohort	0.63
	5 pts with post-boosting and final in the same cohort	0.13
B	6 pts with baseline and post-boosting in the same cohort	0.22
	4 pts with baseline and final in the same cohort	0.88
	1 pt with post-boosting and final in the same cohort	
C	9 pts with baseline and post-boosting in the same cohort	0.008
	14 pts with baseline and final in the same cohort	0.95
	7 pts with post-boosting and final in the same cohort	0.30



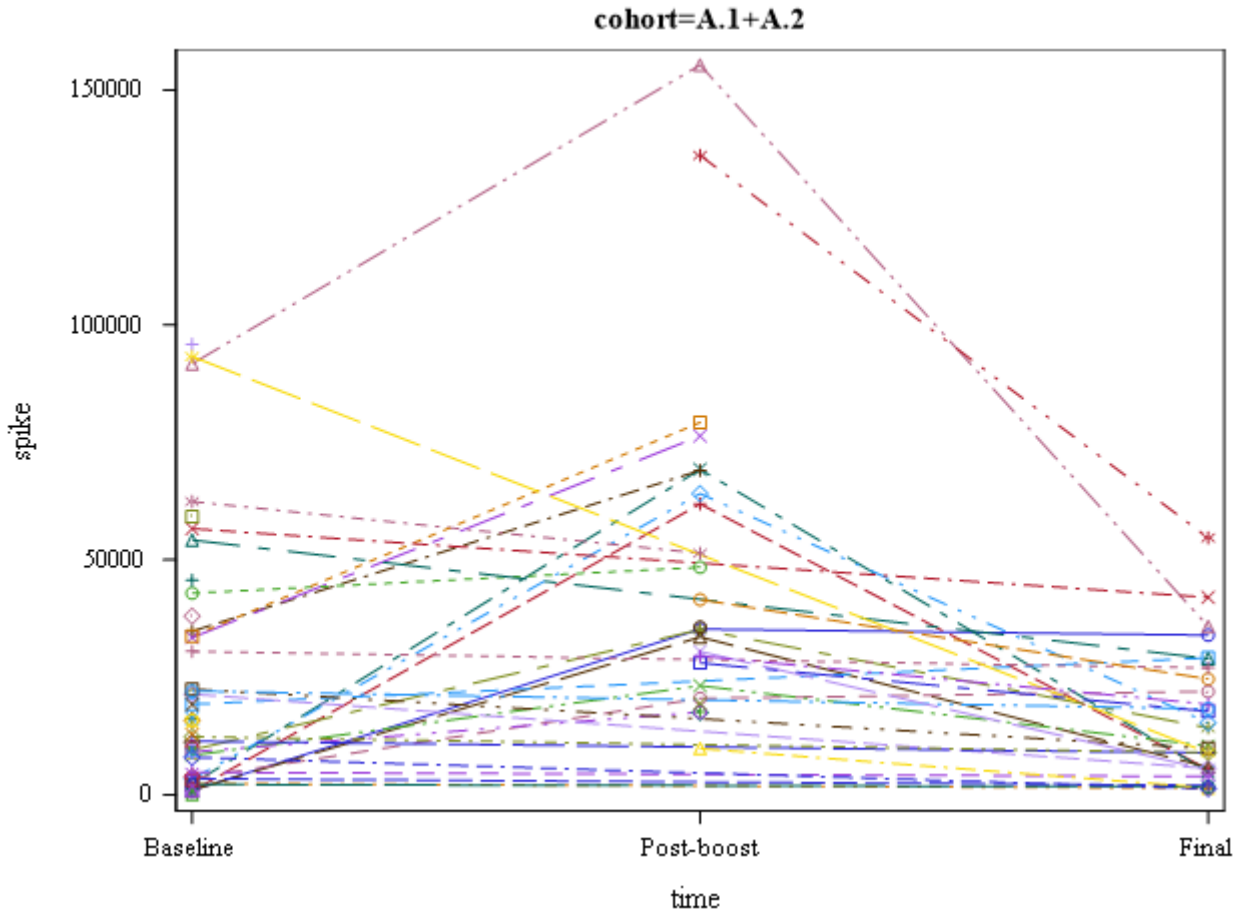
If we restrict to values < 100,000:



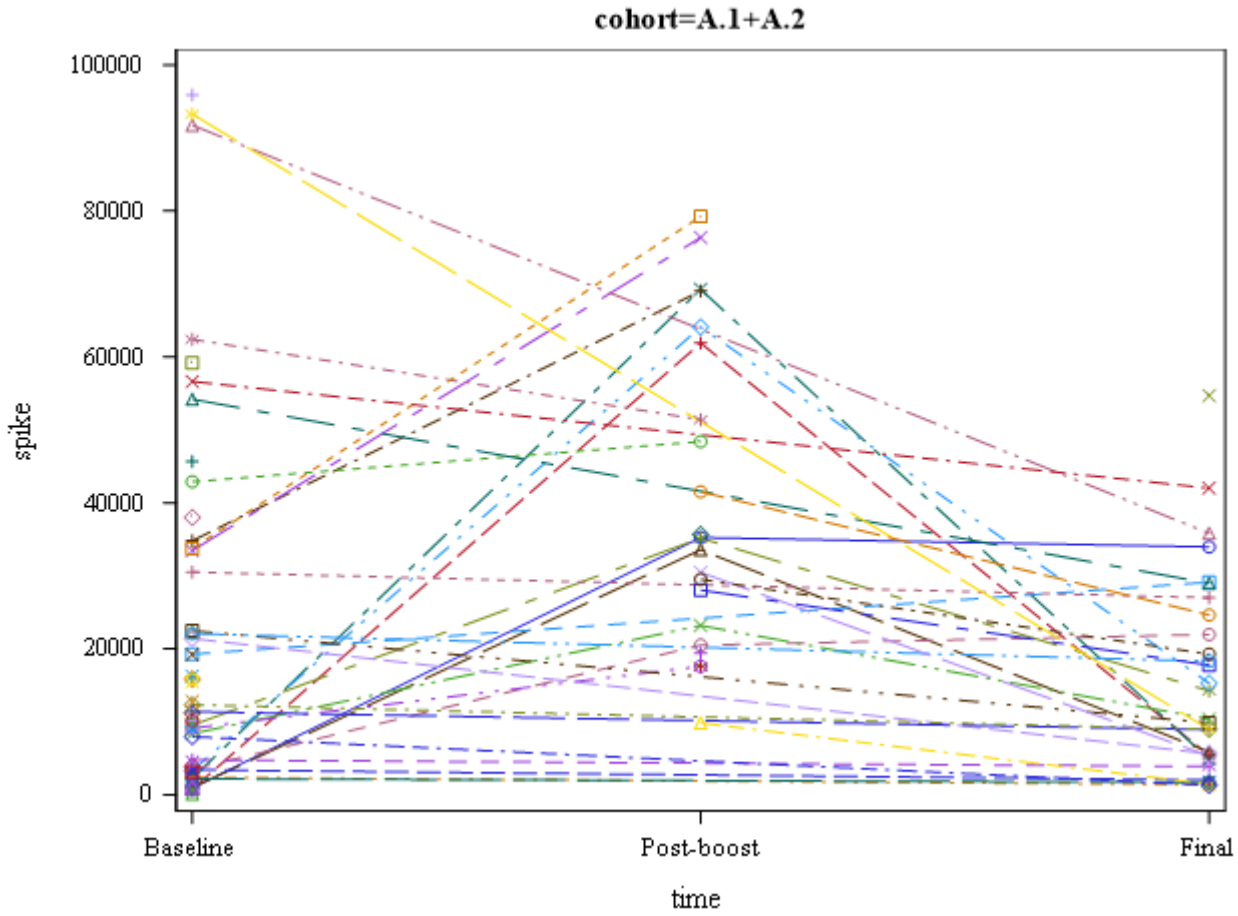
If we put the P-values (pairwise comparisons, signed rank test) on the graph:



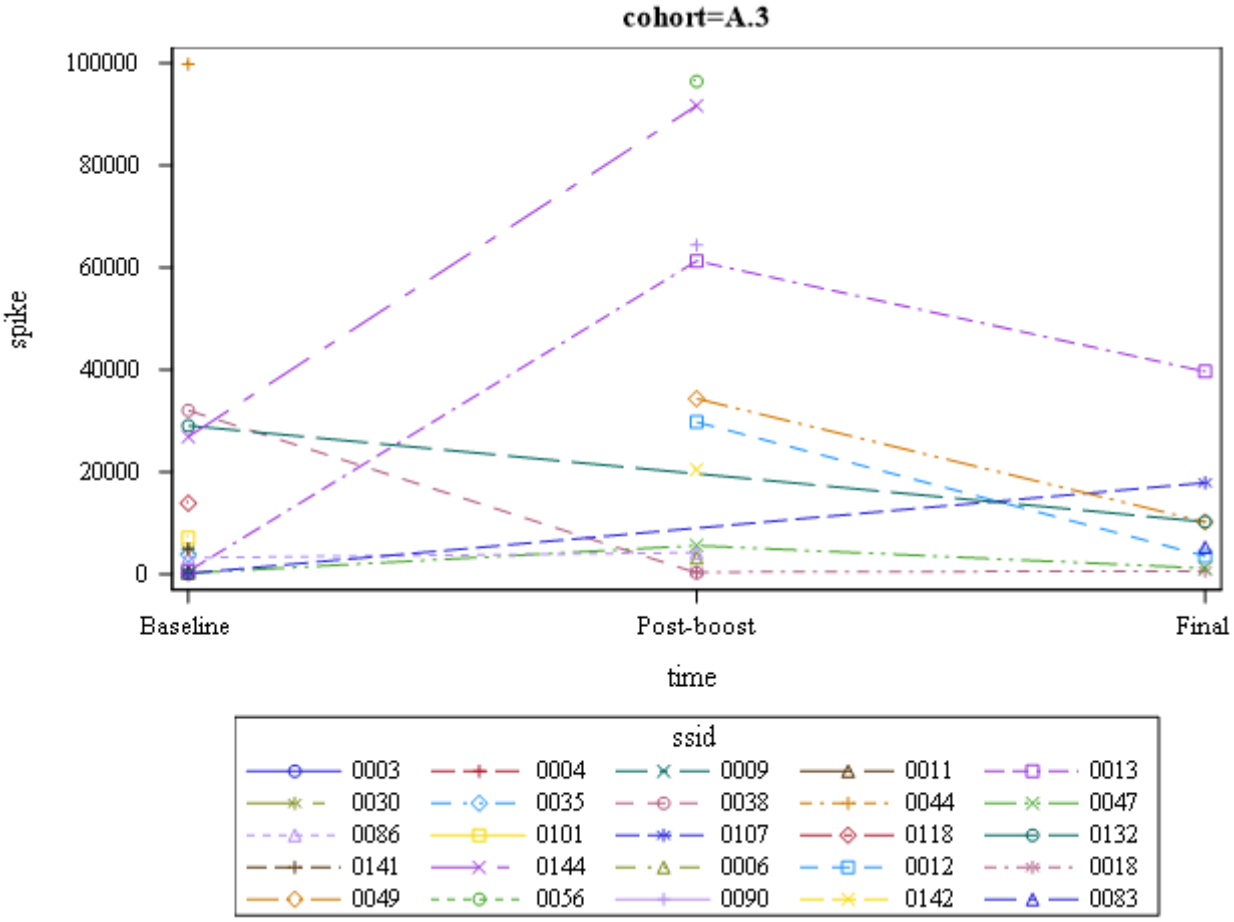
A1 + A2



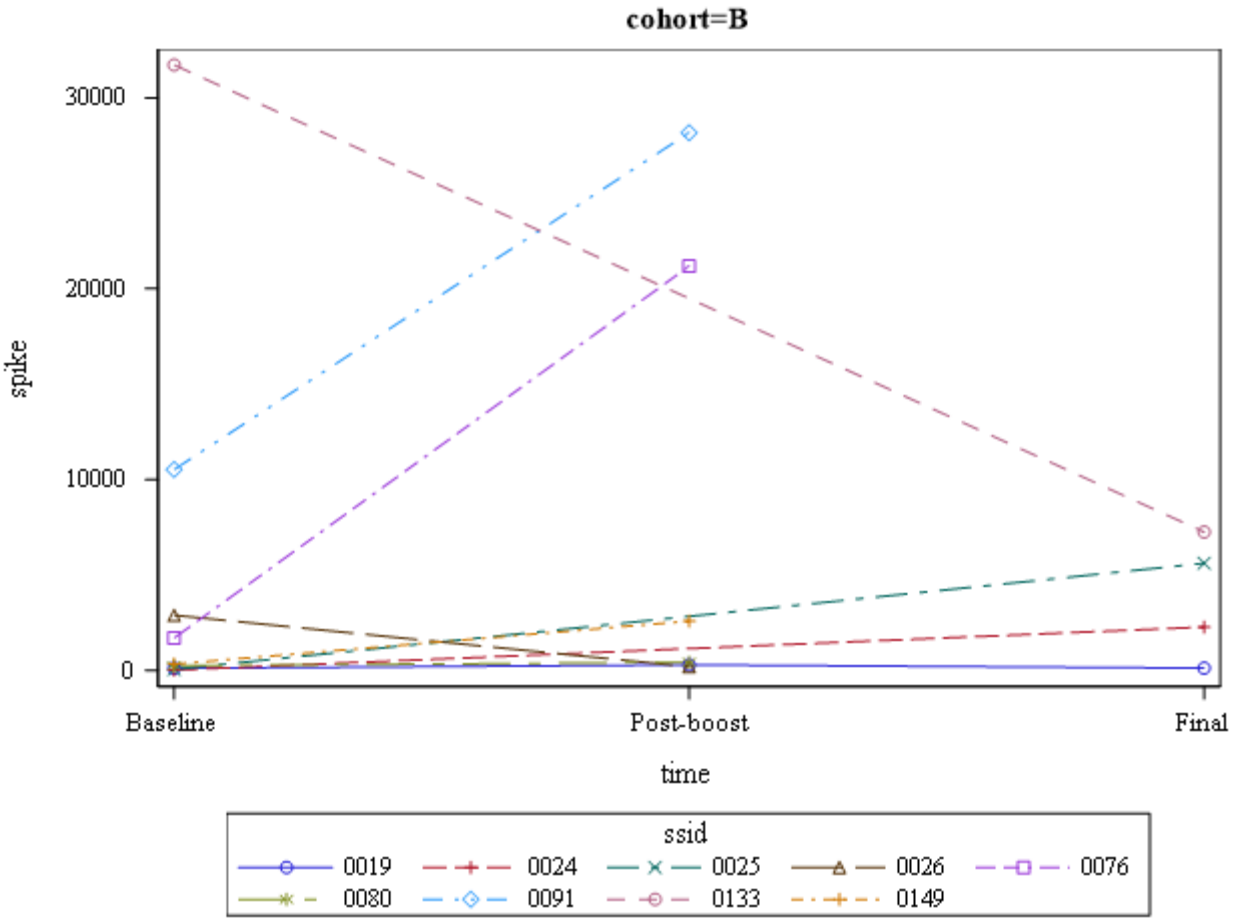
If we restrict to 100,000 on the Y-axis:



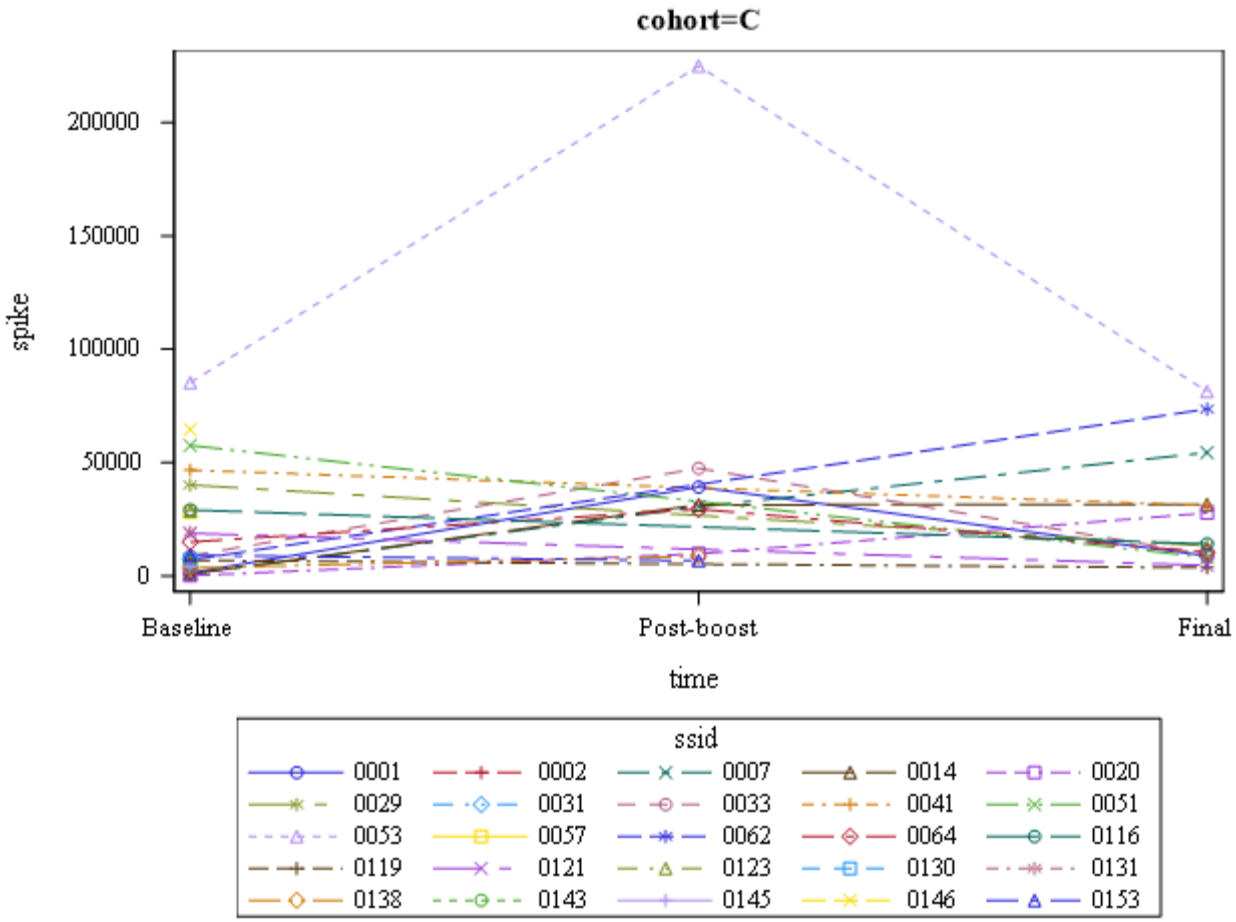
A3



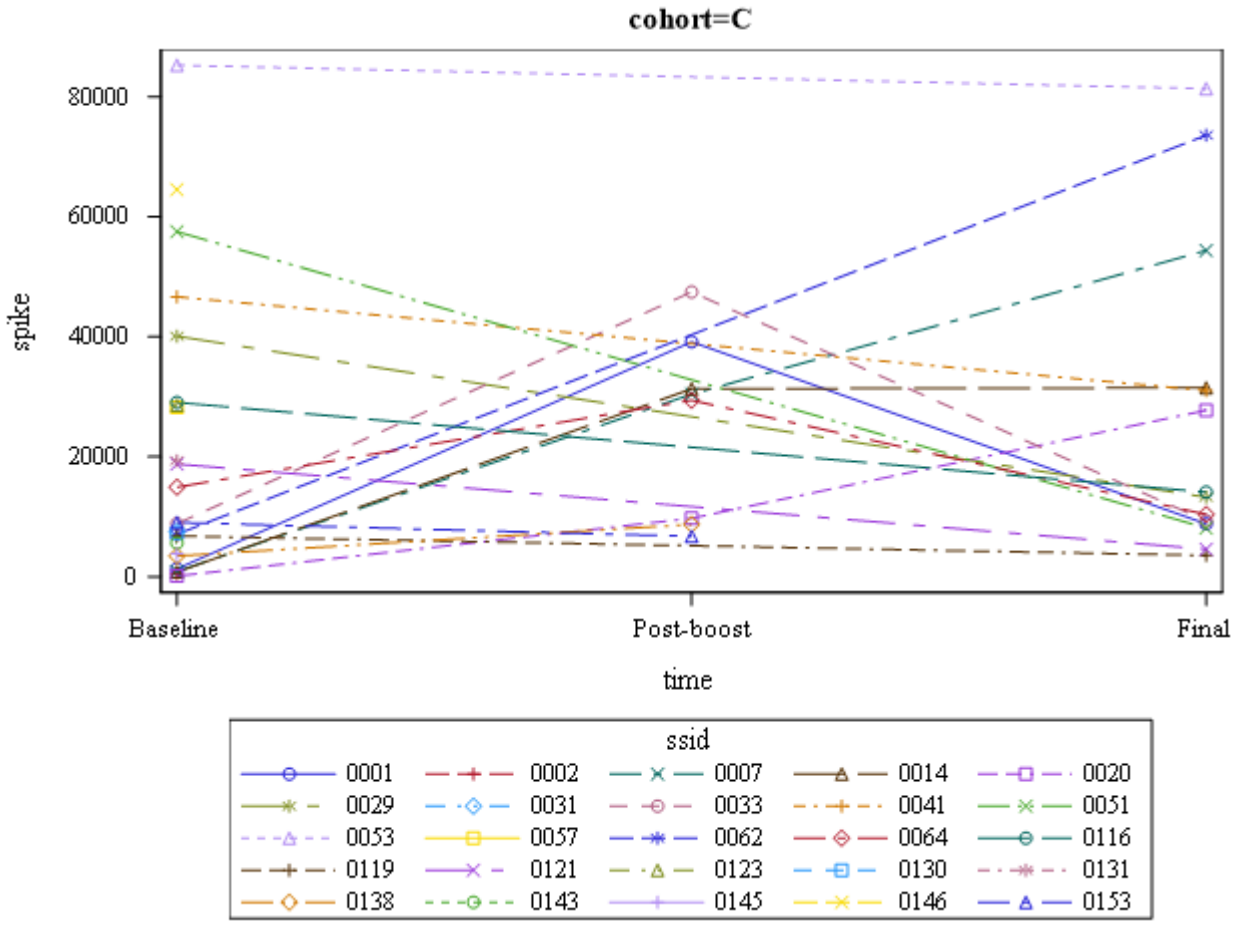
B



C



If we restrict to 10,000 on the Y-axis:



Immune response vs age class

Baseline

	ageclass a. 18-55 (N=33)	b. 56-75 (N=66)	c. >75 (N=8)	Total (N=107)	P-value
spike_baseline					0.1963[1]
N	33	66	8	107	
Mean (SD)	12569.4 (18924.15)	20277.0 (25066.51)	20430.4 (21910.46)	17911.4 (23193.96)	
Median (IQR)	7074.0 (776.0, 15479.0)	9425.5 (2888.0, 29032.0)	12621.5 (2974.0, 34869.0)	9017.0 (2180.0, 26871.0)	
Range	5.5, 95904.0	90.9, 99800.0	105.0, 62409.0	5.5, 99800.0	
Missing	0	0	0	0	
nucleo_baseline, n (%)					0.3751[2]
NonReac	19 (57.6%)	28 (43.1%)	3 (37.5%)	50 (47.2%)	
Reac	14 (42.4%)	37 (56.9%)	5 (62.5%)	56 (52.8%)	
Missing	0	1	0	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_baseline		ageclass a. 18-55	b. 56-75	c. >75	Total	P-value
NonReac		(N=19)	(N=28)	(N=3)	(N=50)	
	spike_baseline					0.6038[1]
	N	19	28	3	50	
	Mean (SD)	4004.0 (5521.98)	3805.5 (4359.54)	14652.7 (20400.11)	4531.7 (6733.56)	
	Median (IQR)	1297.0 (383.0, 7074.0)	2971.0 (889.0, 4860.5)	5618.0 (330.0, 38010.0)	2864.5 (700.0, 5618.0)	
	Range	5.5, 22072.0	90.9, 21402.0	330.0, 38010.0	5.5, 38010.0	
	Missing	0	0	0	0	
Reac		(N=14)	(N=37)	(N=5)	(N=56)	
	spike_baseline					0.4259[1]
	N	14	37	5	56	
	Mean (SD)	24193.9 (24219.07)	32854.5 (27315.58)	23897.0 (24330.61)	29889.6 (26220.50)	
	Median (IQR)	17336.0 (7961.0, 30506.0)	22468.0 (12322.0, 46633.0)	13863.0 (11380.0, 31728.0)	20800.0 (10865.5, 41482.5)	
	Range	121.0, 95904.0	125.0, 99800.0	105.0, 62409.0	105.0, 99800.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Post boost

	ageclass a. 18-55 (N=17)	b. 56-75 (N=33)	c. >75 (N=2)	Total (N=52)	P-value
spike_post_boosting					0.8915[1]
N	17	33	2	52	
Mean (SD)	34372.0 (23018.27)	44247.8 (49925.88)	26993.0 (34520.95)	40355.6 (42217.42)	
Median (IQR)	33563.0 (17677.0, 48396.0)	29401.0 (17515.0, 61271.0)	26993.0 (2583.0, 51403.0)	30079.0 (13668.5, 56337.0)	
Range	380.0, 69259.0	191.0, 225000.0	2583.0, 51403.0	191.0, 225000.0	
Missing	0	0	0	0	
nucleo_post_boosting, n (%)					1.0000[2]
NonReac	11 (64.7%)	19 (61.3%)	1 (50.0%)	31 (62.0%)	
Reac	6 (35.3%)	12 (38.7%)	1 (50.0%)	19 (38.0%)	
Missing	0	2	0	2	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_post_boosting		ageclass a. 18-55	b. 56-75	c. >75	Total	P-value
NonReac		(N=11)	(N=19)	(N=1)	(N=31)	
	spike_post_boosting					0.3205[1]
	N	11	19	1	31	
	Mean (SD)	29337.9 (23014.19)	21948.8 (16506.91)	2583.0 (.)	23946.1 (19194.70)	
	Median (IQR)	29744.0 (6710.0, 41522.0)	20444.0 (8699.0, 30473.0)	2583.0 (2583.0, 2583.0)	20503.0 (6710.0, 33563.0)	
	Range	380.0, 69259.0	238.0, 61899.0	2583.0, 2583.0	238.0, 69259.0	
	Missing	0	0	0	0	
Reac		(N=6)	(N=12)	(N=1)	(N=19)	
	spike_post_boosting					0.9326[1]
	N	6	12	1	19	
	Mean (SD)	43601.2 (21868.23)	56837.4 (45126.31)	51403.0 (.)	52371.5 (37633.54)	
	Median (IQR)	42034.0 (34317.0, 64366.0)	48216.5 (25685.5, 85476.5)	51403.0 (51403.0, 51403.0)	48396.0 (28179.0, 76371.0)	
	Range	9822.0, 69034.0	191.0, 155332.0	51403.0, 51403.0	191.0, 155332.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

	ageclass a. 18-55 (N=17)	b. 56-75 (N=37)	c. >75 (N=2)	Total (N=56)	P-value
spike_final					0.4554[1]
N	17	37	2	56	
Mean (SD)	14559.9 (18112.00)	18382.8 (18229.01)	8085.0 (1176.63)	16854.5 (17859.31)	
Median (IQR)	5866.0 (3524.0, 18292.0)	10359.0 (5368.0, 28977.0)	8085.0 (7253.0, 8917.0)	10023.5 (5040.0, 25813.5)	
Range	582.0, 73573.0	117.0, 81334.0	7253.0, 8917.0	117.0, 81334.0	
Missing	0	0	0	0	
nucleo_final, n (%)					0.0345[2]
NonReac	11 (64.7%)	12 (32.4%)	0 (0.0%)	23 (41.1%)	
Reac	6 (35.3%)	25 (67.6%)	2 (100.0%)	33 (58.9%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

If we test age as a continuous variable in nucleo_final Reactive versus Non-Reactive, e obtain a p-value of 0.07 (Wilcoxon test).

nucleo_final		ageclass a. 18-55	b. 56-75	c. >75	Total	P-value
NonReac		(N=11)	(N=12)	(N=0)	(N=23)	
	spike_final					0.9509[1]
	N	11	12		23	
	Mean (SD)	7213.9 (6598.21)	6390.3 (4975.82)		6784.2 (5687.32)	
	Median (IQR)	4836.0 (2269.0, 15297.0)	5335.0 (2778.5, 9039.5)		5302.0 (2269.0, 9287.0)	
	Range	582.0, 18292.0	1389.0, 19264.0		582.0, 19264.0	
	Missing	0	0		0	
Reac		(N=6)	(N=25)	(N=2)	(N=33)	
	spike_final					0.2501[1]
	N	6	25	2	33	
	Mean (SD)	28027.7 (25025.84)	24139.2 (19510.77)	8085.0 (1176.63)	23873.2 (20056.79)	
	Median (IQR)	25813.5 (10195.0, 31475.0)	17866.0 (10215.0, 33961.0)	8085.0 (7253.0, 8917.0)	17866.0 (8967.0, 31475.0)	
	Range	1296.0, 73573.0	117.0, 81334.0	7253.0, 8917.0	117.0, 81334.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs sex

Baseline

	sex			
	F (N=88)	M (N=19)	Total (N=107)	P-value
spike_baseline				0.0691[1]
N	88	19	107	
Mean (SD)	18876.9 (23966.50)	13439.6 (19133.34)	17911.4 (23193.96)	
Median (IQR)	9226.5 (3125.5, 27726.5)	2888.0 (246.0, 22468.0)	9017.0 (2180.0, 26871.0)	
Range	5.5, 99800.0	15.6, 59190.0	5.5, 99800.0	
Missing	0	0	0	
nucleo_baseline, n (%)				0.3228[2]
NonReac	39 (44.8%)	11 (57.9%)	50 (47.2%)	
Reac	48 (55.2%)	8 (42.1%)	56 (52.8%)	
Missing	1	0	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		sex			
nucleo_baseline		F	M	Total	P-value
NonReac		(N=39)	(N=11)	(N=50)	
	spike_baseline				0.0035[1]
	N	39	11	50	
	Mean (SD)	5434.0 (7328.77)	1332.8 (1907.10)	4531.7 (6733.56)	
	Median (IQR)	3310.0 (933.0, 7115.0)	330.0 (90.9, 2888.0)	2864.5 (700.0, 5618.0)	
	Range	5.5, 38010.0	15.6, 5618.0	5.5, 38010.0	
	Missing	0	0	0	
Reac		(N=48)	(N=8)	(N=56)	
	spike_baseline				0.5427[1]
	N	48	8	56	
	Mean (SD)	29856.8 (27323.53)	30086.4 (19726.37)	29889.6 (26220.50)	
	Median (IQR)	19223.0 (10332.5, 41482.5)	25340.0 (20519.5, 44613.0)	20800.0 (10865.5, 41482.5)	
	Range	105.0, 99800.0	556.0, 59190.0	105.0, 99800.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Post boost

	sex			
	F (N=43)	M (N=9)	Total (N=52)	P-value
spike_post_boosting				0.2219[1]
N	43	9	52	
Mean (SD)	42602.8 (43441.95)	29618.7 (36021.91)	40355.6 (42217.42)	
Median (IQR)	30414.0 (17677.0, 51403.0)	9722.0 (424.0, 61271.0)	30079.0 (13668.5, 56337.0)	
Range	238.0, 225000.0	191.0, 96425.0	191.0, 225000.0	
Missing	0	0	0	
nucleo_post_boosting, n (%)				0.7152[2]
NonReac	26 (63.4%)	5 (55.6%)	31 (62.0%)	
Reac	15 (36.6%)	4 (44.4%)	19 (38.0%)	
Missing	2	0	2	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		sex			
nucleo_post_boosting		F	M	Total	P-value
NonReac		(N=26)	(N=5)	(N=31)	
	spike_post_boosting				0.0532[1]
	N	26	5	31	
	Mean (SD)	26846.7 (18982.66)	8863.0 (13117.88)	23946.1 (19194.70)	
	Median (IQR)	24611.5 (17515.0, 35239.0)	2583.0 (424.0, 9722.0)	20503.0 (6710.0, 33563.0)	
	Range	238.0, 69259.0	287.0, 31299.0	238.0, 69259.0	
	Missing	0	0	0	
Reac		(N=15)	(N=4)	(N=19)	
	spike_post_boosting				[redacted]
	N	15	4	19	
	Mean (SD)	51520.4 (38355.15)	55563.3 (40190.53)	52371.5 (37633.54)	
	Median (IQR)	35672.0 (28179.0, 76371.0)	62818.5 (30731.0, 80395.5)	48396.0 (28179.0, 76371.0)	
	Range	5572.0, 155332.0	191.0, 96425.0	191.0, 155332.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

	sex			
	F (N=46)	M (N=10)	Total (N=56)	P-value
spike_final				0.5350[1]
N	46	10	56	
Mean (SD)	17548.6 (18667.83)	13661.7 (13890.31)	16854.5 (17859.31)	
Median (IQR)	10287.0 (5244.0, 24628.0)	7680.0 (4576.0, 27725.0)	10023.5 (5040.0, 25813.5)	
Range	582.0, 81334.0	117.0, 39630.0	117.0, 81334.0	
Missing	0	0	0	
nucleo_final, n (%)				1.0000[2]
NonReac	19 (41.3%)	4 (40.0%)	23 (41.1%)	
Reac	27 (58.7%)	6 (60.0%)	33 (58.9%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		sex			
nucleo_final		F	M	Total	P-value
NonReac		(N=19)	(N=4)	(N=23)	
	spike_final				[redacted]
	N	19	4	23	
	Mean (SD)	7038.2 (6120.69)	5577.5 (3173.95)	6784.2 (5687.32)	
	Median (IQR)	5302.0 (2016.0, 9287.0)	5094.5 (3422.5, 7732.5)	5302.0 (2269.0, 9287.0)	
	Range	582.0, 19264.0	2269.0, 9852.0	582.0, 19264.0	
	Missing	0	0	0	
Reac		(N=27)	(N=6)	(N=33)	
	spike_final				0.4552[1]
	N	27	6	33	
	Mean (SD)	24944.8 (20968.59)	19051.2 (15940.83)	23873.2 (20056.79)	
	Median (IQR)	17866.0 (10195.0, 33961.0)	17916.0 (7253.0, 31475.0)	17866.0 (8967.0, 31475.0)	
	Range	1143.0, 81334.0	117.0, 39630.0	117.0, 81334.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs overweight/obese

Baseline

	overweight_obese				
	Missing (N=16)	no (N=42)	yes (N=49)	Total (N=91)	P-value
spike_baseline					0.1972[1]
N	16	42	49	91	
Mean (SD)	22065.8 (29880.97)	11321.7 (11729.63)	22203.1 (26998.15)	17180.9 (21935.75)	
Median (IQR)	7951.0 (858.5, 47754.0)	9057.5 (2180.0, 16112.0)	9331.0 (3054.0, 31728.0)	9098.0 (2359.0, 22468.0)	
Range	5.5, 93273.0	52.0, 46633.0	15.6, 99800.0	15.6, 99800.0	
Missing	0	0	0	0	
nucleo_baseline, n (%)					1.0000[2]
NonReac	9	19 (46.3%)	22 (44.9%)	41 (45.6%)	
Reac	7	22 (53.7%)	27 (55.1%)	49 (54.4%)	
Missing	0	1	0	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		overweight_obese				
nucleo_baseline		Missing	no	yes	Total	P-value
NonReac		(N=9)	(N=19)	(N=22)	(N=41)	
	spike_baseline					0.4641[1]
	N	9	19	22	41	
	Mean (SD)	6718.6 (12141.15)	4597.1 (5409.30)	3580.7 (4643.11)	4051.7 (4974.81)	
	Median (IQR)	1699.0 (756.0, 7074.0)	3197.0 (700.0, 8869.0)	2706.5 (583.0, 4774.0)	3054.0 (700.0, 4955.0)	
	Range	5.5, 38010.0	52.0, 22072.0	15.6, 21402.0	15.6, 22072.0	
	Missing	0	0	0	0	
Reac		(N=7)	(N=22)	(N=27)	(N=49)	
	spike_baseline					0.0046[1]
	N	7	22	27	49	
	Mean (SD)	41797.9 (35044.08)	16911.6 (12992.09)	37376.9 (28208.29)	28188.4 (24710.97)	
	Median (IQR)	57498.0 (9520.0, 62409.0)	14829.5 (9098.0, 19327.0)	30506.0 (15479.0, 54202.0)	19327.0 (11380.0, 33733.0)	
	Range	556.0, 93273.0	105.0, 46633.0	125.0, 99800.0	105.0, 99800.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Post boost

	overweight_obese				
	Missing (N=11)	no (N=15)	yes (N=26)	Total (N=41)	P-value
spike_post_boosting					0.0304[1]
N	11	15	26	41	
Mean (SD)	31611.9 (22175.14)	22418.8 (20632.67)	54402.9 (52620.59)	42701.4 (46074.37)	
Median (IQR)	33563.0 (17515.0, 51403.0)	19394.0 (5572.0, 35239.0)	32808.0 (23192.0, 69259.0)	29744.0 (9822.0, 64098.0)	
Range	191.0, 61899.0	380.0, 79256.0	238.0, 225000.0	238.0, 225000.0	
Missing	0	0	0	0	
nucleo_post_boosting, n (%)					0.7397[2]
NonReac	7	10 (66.7%)	14 (58.3%)	24 (61.5%)	
Reac	4	5 (33.3%)	10 (41.7%)	15 (38.5%)	
Missing	0	0	2	2	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		overweight_obese				
nucleo_post_boosting		Missing	no	yes	Total	P-value
NonReac		(N=7)	(N=10)	(N=14)	(N=24)	
	spike_post_boosting					0.4124[1]
	N	7	10	14	24	
	Mean (SD)	28529.1 (20734.91)	17778.1 (14386.53)	26060.2 (21520.44)	22609.3 (18977.74)	
	Median (IQR)	21182.0 (17515.0, 47444.0)	18492.5 (4174.0, 29744.0)	28776.0 (8699.0, 31299.0)	20473.5 (5442.0, 30886.0)	
	Range	424.0, 61899.0	380.0, 41522.0	238.0, 69259.0	238.0, 69259.0	
	Missing	0	0	0	0	
Reac		(N=4)	(N=5)	(N=10)	(N=15)	
	spike_post_boosting					0.0864[1]
	N	4	5	10	15	
	Mean (SD)	37006.8 (26800.55)	31700.2 (29372.89)	68853.1 (39567.07)	56468.8 (39769.13)	
	Median (IQR)	43282.5 (17676.5, 56337.0)	28179.0 (9822.0, 35672.0)	66700.0 (34317.0, 91697.0)	48396.0 (28179.0, 79256.0)	
	Range	191.0, 61271.0	5572.0, 79256.0	23192.0, 155332.0	5572.0, 155332.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

	overweight_obese				
	Missing (N=8)	no (N=15)	yes (N=33)	Total (N=48)	P-value
spike_final					0.3918[1]
N	8	15	33	48	
Mean (SD)	20624.5 (24136.53)	12632.8 (11866.20)	17859.5 (18606.82)	16226.2 (16842.11)	
Median (IQR)	9115.0 (6986.5, 26926.0)	8917.0 (1693.0, 24628.0)	10359.0 (4836.0, 26999.0)	10205.0 (4224.5, 25813.5)	
Range	5368.0, 73573.0	582.0, 33961.0	117.0, 81334.0	117.0, 81334.0	
Missing	0	0	0	0	
nucleo_final, n (%)					1.0000[2]
NonReac	3	6 (40.0%)	14 (42.4%)	20 (41.7%)	
Reac	5	9 (60.0%)	19 (57.6%)	28 (58.3%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		overweight_obese				
nucleo_final		Missing	no	yes	Total	P-value
NonReac		(N=3)	(N=6)	(N=14)	(N=20)	
	spike_final					0.2160[1]
	N	3	6	14	20	
	Mean (SD)	6840.3 (2133.46)	5193.3 (6663.67)	7453.9 (5942.05)	6775.8 (6080.55)	
	Median (IQR)	5866.0 (5368.0, 9287.0)	2608.5 (1456.0, 5613.0)	5069.0 (3541.0, 9852.0)	4706.0 (2142.5, 9322.0)	
	Range	5368.0, 9287.0	582.0, 18292.0	1389.0, 19264.0	582.0, 19264.0	
	Missing	0	0	0	0	
Reac		(N=5)	(N=9)	(N=19)	(N=28)	
	spike_final					0.4170[1]
	N	5	9	19	28	
	Mean (SD)	28895.0 (28093.08)	17592.4 (12226.08)	25526.8 (21064.74)	22976.5 (18824.04)	
	Median (IQR)	14222.0 (8943.0, 39630.0)	14080.0 (8917.0, 29120.0)	21947.0 (10195.0, 35824.0)	19906.5 (9581.0, 31249.5)	
	Range	8107.0, 73573.0	1143.0, 33961.0	117.0, 81334.0	117.0, 81334.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs smoking status

Baseline

	Smoking status					
	Missing (N=16)	CURRENT (N=16)	FORMER (N=18)	NEVER (N=57)	Total (N=91)	P-value
spike_baseline						0.6403[1]
N	16	16	18	57	91	
Mean (SD)	12334.9 (21060.69)	14726.6 (19055.17)	15099.9 (17012.40)	21258.5 (26241.69)	18891.9 (23519.59)	
Median (IQR)	3464.5 (641.5, 16175.0)	8598.0 (2293.5, 14859.5)	10560.0 (556.0, 22273.0)	9520.0 (3310.0, 31728.0)	9122.0 (2359.0, 29032.0)	
Range	15.6, 85242.0	52.0, 59190.0	90.9, 62409.0	5.5, 99800.0	5.5, 99800.0	
Missing	0	0	0	0	0	
nucleo_baseline, n (%)						0.6852[2]
NonReac	10	8 (50.0%)	9 (50.0%)	23 (40.4%)	40 (44.0%)	
Reac	5	8 (50.0%)	9 (50.0%)	34 (59.6%)	51 (56.0%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_baseline		Smoking status Missing	CURRENT	FORMER	NEVER	Total	P-value
NonReac		(N=10)	(N=8)	(N=9)	(N=23)	(N=40)	
	spike_baseline						0.9365[1]
	N	10	8	9	23	40	
	Mean (SD)	4137.7 (6434.78)	3594.4 (3638.73)	5248.2 (7246.95)	4748.8 (7751.61)	4630.3 (6881.97)	
	Median (IQR)	2075.5 (583.0, 3875.0)	2293.5 (658.0, 6891.5)	2252.0 (164.0, 6769.0)	3310.0 (857.0, 4774.0)	3042.5 (766.0, 6193.5)	
	Range	15.6, 21402.0	52.0, 9017.0	90.9, 22072.0	5.5, 38010.0	5.5, 38010.0	
	Missing	0	0	0	0	0	
Reac		(N=5)	(N=8)	(N=9)	(N=34)	(N=51)	
	spike_baseline						0.7745[1]
	N	5	8	9	34	51	
	Mean (SD)	27973.8 (33058.83)	25858.9 (21944.67)	24951.7 (18550.62)	32426.8 (28461.10)	30077.4 (25854.06)	
	Median (IQR)	16238.0 (15796.0, 22468.0)	14859.5 (8849.5, 46151.0)	22273.0 (11380.0, 28212.0)	28807.0 (12322.0, 45672.0)	22273.0 (10526.0, 42893.0)	
	Range	125.0, 85242.0	7961.0, 59190.0	556.0, 62409.0	105.0, 99800.0	105.0, 99800.0	
	Missing	0	0	0	0	0	

[1]Kruskal-Wallis p-value;

Post boost

	Smoking status					
	Missing (N=5)	CURRENT (N=10)	FORMER (N=11)	NEVER (N=26)	Total (N=47)	P-value
spike_post_boosting						0.4769[1]
N	5	10	11	26	47	
Mean (SD)	77509.0 (84102.18)	26381.1 (19615.89)	42738.9 (35421.84)	37577.1 (38718.00)	36403.1 (34568.46)	
Median (IQR)	41522.0 (39142.0, 64366.0)	22187.0 (19394.0, 28179.0)	48396.0 (5572.0, 69259.0)	30079.0 (9822.0, 35239.0)	29511.0 (9722.0, 51403.0)	
Range	17515.0, 225000.0	191.0, 69034.0	287.0, 96425.0	238.0, 155332.0	191.0, 155332.0	
Missing	0	0	0	0	0	
nucleo_post_boosting, n (%)						0.1304[2]
NonReac	3	6 (60.0%)	4 (36.4%)	18 (72.0%)	28 (60.9%)	
Reac	1	4 (40.0%)	7 (63.6%)	7 (28.0%)	18 (39.1%)	
Missing	1	0	0	1	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		Smoking status					
nucleo_post_boosting		Missing	CURRENT	FORMER	NEVER	Total	P-value
NonReac		(N=3)	(N=6)	(N=4)	(N=18)	(N=28)	
	spike_post_boosting						0.6488[1]
	N	3	6	4	18	28	
	Mean (SD)	32726.3 (13227.04)	23869.2 (13465.46)	19923.0 (33185.76)	23402.3 (19083.92)	23005.3 (19670.55)	
	Median (IQR)	39142.0 (17515.0, 41522.0)	20813.0 (19394.0, 28041.0)	5073.0 (355.5, 39490.5)	25007.0 (4174.0, 31299.0)	20473.5 (5442.0, 30886.0)	
	Range	17515.0, 41522.0	6710.0, 47444.0	287.0, 69259.0	238.0, 64098.0	238.0, 69259.0	
	Missing	0	0	0	0	0	
Reac		(N=1)	(N=4)	(N=7)	(N=7)	(N=18)	
	spike_post_boosting						0.2688[1]
	N	1	4	7	7	18	
	Mean (SD)	64366.0 (.)	30149.0 (28646.15)	55776.6 (31546.41)	59951.6 (49087.76)	51705.2 (38609.08)	
	Median (IQR)	64366.0 (64366.0, 64366.0)	25685.5 (11691.5, 48606.5)	51403.0 (35672.0, 91697.0)	35162.0 (29401.0, 79256.0)	42034.0 (28179.0, 76371.0)	
	Range	64366.0, 64366.0	191.0, 69034.0	5572.0, 96425.0	9822.0, 155332.0	191.0, 155332.0	
	Missing	0	0	0	0	0	

[1]Kruskal-Wallis p-value;

Final

	Smoking status					
	Missing (N=8)	CURRENT (N=6)	FORMER (N=9)	NEVER (N=33)	Total (N=48)	P-value
spike_final						0.2519[1]
N	8	6	9	33	48	
Mean (SD)	19448.5 (26058.73)	8734.5 (5469.96)	12086.3 (13678.42)	19002.4 (17972.56)	16422.2 (16455.17)	
Median (IQR)	9322.0 (5423.5, 21247.0)	8697.0 (5613.0, 10359.0)	4836.0 (3541.0, 18292.0)	13238.0 (5368.0, 29120.0)	10205.0 (4706.0, 27362.0)	
Range	2269.0, 81334.0	1296.0, 17745.0	117.0, 39630.0	582.0, 73573.0	117.0, 73573.0	
Missing	0	0	0	0	0	
nucleo_final, n (%)						0.7333[2]
NonReac	4	3 (50.0%)	4 (44.4%)	12 (36.4%)	19 (39.6%)	
Reac	4	3 (50.0%)	5 (55.6%)	21 (63.6%)	29 (60.4%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		Smoking status					
nucleo_final		Missing	CURRENT	FORMER	NEVER	Total	P-value
NonReac		(N=4)	(N=3)	(N=4)	(N=12)	(N=19)	
	spike_final						0.1786[1]
	N	4	3	4	12	19	
	Mean (SD)	6629.0 (3421.92)	10881.7 (6221.22)	7811.3 (7009.52)	5469.2 (5848.33)	6816.8 (6129.88)	
	Median (IQR)	7197.5 (3936.0, 9322.0)	9287.0 (5613.0, 17745.0)	4706.0 (4058.5, 11564.0)	3698.5 (1574.5, 5617.0)	4836.0 (2016.0, 9287.0)	
	Range	2269.0, 9852.0	5613.0, 17745.0	3541.0, 18292.0	582.0, 19264.0	582.0, 19264.0	
	Missing	0	0	0	0	0	
Reac		(N=4)	(N=3)	(N=5)	(N=21)	(N=29)	
	spike_final						0.0463[1]
	N	4	3	5	21	29	
	Mean (SD)	32268.0 (33682.62)	6587.3 (4718.74)	15506.4 (17448.52)	26735.7 (18036.79)	22715.3 (18075.70)	
	Median (IQR)	21247.0 (11555.0, 52981.0)	8107.0 (1296.0, 10359.0)	8917.0 (1143.0, 27725.0)	26999.0 (10369.0, 33961.0)	14222.0 (8967.0, 31475.0)	
	Range	5244.0, 81334.0	1296.0, 10359.0	117.0, 39630.0	7253.0, 73573.0	117.0, 73573.0	
	Missing	0	0	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs ALC class

Baseline

	ALC at screening				
	Missing (N=14)	a. <1000 (N=21)	b. >=1000 (N=72)	Total (N=93)	P-value
spike_baseline					0.5201[1]
N	14	21	72	93	
Mean (SD)	11726.5 (24680.44)	14414.5 (16259.63)	20133.9 (24514.90)	18842.4 (22957.65)	
Median (IQR)	1606.5 (556.0, 9331.0)	9098.0 (2359.0, 21402.0)	9717.5 (3182.0, 28807.0)	9520.0 (3054.0, 28212.0)	
Range	5.5, 91756.0	121.0, 62409.0	15.6, 99800.0	15.6, 99800.0	
Missing	0	0	0	0	
nucleo_baseline, n (%)					0.3187[2]
NonReac	9	11 (55.0%)	30 (41.7%)	41 (44.6%)	
Reac	5	9 (45.0%)	42 (58.3%)	51 (55.4%)	
Missing	0	1	0	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		ALC at screening				
nucleo_baseline		Missing	a. <1000	b. >=1000	Total	P-value
NonReac		(N=9)	(N=11)	(N=30)	(N=41)	
	spike_baseline					0.8830[1]
	N	9	11	30	41	
	Mean (SD)	1966.4 (2598.26)	7372.8 (11765.05)	4259.6 (4673.06)	5094.9 (7237.85)	
	Median (IQR)	776.0 (164.0, 2252.0)	3197.0 (481.0, 4774.0)	3182.0 (857.0, 7115.0)	3197.0 (857.0, 6769.0)	
	Range	5.5, 7074.0	246.0, 38010.0	15.6, 22072.0	15.6, 38010.0	
	Missing	0	0	0	0	
Reac		(N=5)	(N=9)	(N=42)	(N=51)	
	spike_baseline					0.4585[1]
	N	5	9	42	51	
	Mean (SD)	29294.6 (36959.71)	22832.4 (18429.84)	31472.7 (26630.58)	29947.9 (25435.13)	
	Median (IQR)	11380.0 (9331.0, 33450.0)	18766.0 (10526.0, 29034.0)	22370.5 (12322.0, 45672.0)	22273.0 (11205.0, 42893.0)	
	Range	556.0, 91756.0	121.0, 62409.0	105.0, 99800.0	105.0, 99800.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Post boost

ALC at boost is available in 14 subjects. (Only 27% of the post boost subjects had an ALC measurement at that time registered in the database.)

		ALCclass_boost			
	Missing (N=38)	a. <1000 (N=8)	b. >=1000 (N=6)	Total (N=14)	P-value
spike_post_boosting					0.3662[1]
N	38	8	6	14	
Mean (SD)	40710.3 (43700.00)	27268.5 (25246.05)	55558.3 (51021.71)	39392.7 (39439.88)	
Median (IQR)	29627.5 (9822.0, 61271.0)	29326.0 (1503.5, 43537.5)	35200.5 (28041.0, 61899.0)	32817.5 (17677.0, 51403.0)	
Range	191.0, 225000.0	380.0, 69034.0	17677.0, 155332.0	380.0, 155332.0	
Missing	0	0	0	0	
nucleo_post_boosting, n (%)					0.6270[2]
NonReac	23	4 (50.0%)	4 (66.7%)	8 (57.1%)	
Reac	13	4 (50.0%)	2 (33.3%)	6 (42.9%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_post_boosting		ALCclass_boost				
		Missing	a. <1000	b. >=1000	Total	P-value
NonReac		(N=23)	(N=4)	(N=4)	(N=8)	
	spike_post_boosting					[redacted]
	N	23	4	4	8	
	Mean (SD)	24591.8 (18843.67)	8465.0 (14707.99)	35714.0 (18886.40)	22089.5 (21394.52)	
	Median (IQR)	20503.0 (8699.0, 33563.0)	1503.5 (402.0, 16528.0)	31640.0 (22859.0, 48569.0)	22859.0 (1503.5, 32856.0)	
	Range	238.0, 69259.0	380.0, 30473.0	17677.0, 61899.0	380.0, 61899.0	
	Missing	0	0	0	0	
Reac		(N=13)	(N=4)	(N=2)	(N=6)	
	spike_post_boosting					[redacted]
	N	13	4	2	6	
	Mean (SD)	47713.6 (33130.17)	46072.0 (18110.70)	95247.0 (84973.02)	62463.7 (47809.30)	
	Median (IQR)	48396.0 (23192.0, 76371.0)	43537.5 (31925.5, 60218.5)	95247.0 (35162.0, 155332.0)	43537.5 (35162.0, 69034.0)	
	Range	191.0, 96425.0	28179.0, 69034.0	35162.0, 155332.0	28179.0, 155332.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Final

ALC at final is available in 14 subjects. (Only 25% of the subjectsat EOT had an ALC at that time point registered in the database)

	ALCclass_final				
	Missing (N=42)	a. <1000 (N=6)	b. >=1000 (N=8)	Total (N=14)	P-value
spike_final					0.5186[1]
N	42	6	8	14	
Mean (SD)	18844.6 (19236.15)	7795.0 (8849.87)	13201.0 (13169.89)	10884.1 (11455.34)	
Median (IQR)	10364.0 (5603.0, 27725.0)	4384.0 (2016.0, 10215.0)	7904.0 (3264.5, 23432.5)	5428.5 (2016.0, 17745.0)	
Range	117.0, 81334.0	1143.0, 24628.0	582.0, 35824.0	582.0, 35824.0	
Missing	0	0	0	0	
nucleo_final, n (%)					0.5921[2]
NonReac	16	2 (33.3%)	5 (62.5%)	7 (50.0%)	
Reac	26	4 (66.7%)	3 (37.5%)	7 (50.0%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		ALCclass_final				
nucleo_final		Missing	a. <1000	b. >=1000	Total	P-value
NonReac		(N=16)	(N=2)	(N=5)	(N=7)	
	spike_final					[redacted]
	N	16	2	5	7	
	Mean (SD)	7501.7 (5658.67)	2770.0 (1066.32)	6093.8 (6843.07)	5144.1 (5834.24)	
	Median (IQR)	5485.5 (3707.0, 9569.5)	2770.0 (2016.0, 3524.0)	4836.0 (1693.0, 5613.0)	3524.0 (1693.0, 5613.0)	
	Range	1389.0, 19264.0	2016.0, 3524.0	582.0, 17745.0	582.0, 17745.0	
	Missing	0	0	0	0	
Reac		(N=26)	(N=4)	(N=3)	(N=7)	
	spike_final					[redacted]
	N	26	4	3	7	
	Mean (SD)	25824.9 (21321.81)	10307.5 (10242.27)	25046.3 (13291.26)	16624.1 (13168.31)	
	Median (IQR)	19906.5 (8967.0, 33961.0)	7729.5 (3193.5, 17421.5)	29120.0 (10195.0, 35824.0)	10215.0 (5244.0, 29120.0)	
	Range	117.0, 81334.0	1143.0, 24628.0	10195.0, 35824.0	1143.0, 35824.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs metastatic status (in solid tumors)

Baseline

	status cancer at enrolment				
	Missing (N=1)	METASTATIC (N=39)	NON-METASTATIC (N=56)	Total (N=95)	P-value
spike_baseline					0.6069[1]
N	1	39	56	95	
Mean (SD)	583.0 (.)	17190.3 (22373.39)	20720.0 (25130.74)	19271.0 (23977.72)	
Median (IQR)	583.0 (583.0, 583.0)	9098.0 (3054.0, 22468.0)	9425.5 (2904.0, 31241.0)	9331.0 (3054.0, 28212.0)	
Range	583.0, 583.0	105.0, 93273.0	5.5, 99800.0	5.5, 99800.0	
Missing	0	0	0	0	
nucleo_baseline, n (%)					1.0000[2]
NonReac	1	17 (44.7%)	24 (42.9%)	41 (43.6%)	
Reac	0	21 (55.3%)	32 (57.1%)	53 (56.4%)	
Missing	0	1	0	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		status cancer at enrolment				
nucleo_baseline		Missing (N=1)	METASTATIC (N=17)	NON-METASTATIC (N=24)	Total (N=41)	P-value
NonReac	**spike_baseline**					0.9578[1]
	N	1	17	24	41	
	Mean (SD)	583.0 (.)	6160.7 (9631.96)	4454.9 (4888.11)	5162.2 (7181.40)	
	Median (IQR)	583.0 (583.0, 583.0)	3310.0 (933.0, 4766.0)	2904.0 (889.0, 7094.5)	3310.0 (921.0, 6769.0)	
	Range	583.0, 583.0	164.0, 38010.0	5.5, 22072.0	5.5, 38010.0	
	Missing	0	0	0	0	
Reac		(N=0)	(N=21)	(N=32)	(N=53)	
	spike_baseline					0.3443[1]
	N		21	32	53	
	Mean (SD)		26170.3 (26243.59)	32918.9 (27282.63)	30244.9 (26828.00)	
	Median (IQR)		19327.0 (9098.0, 30506.0)	23702.5 (12562.5, 50417.5)	19327.0 (11205.0, 42893.0)	
	Range		105.0, 93273.0	121.0, 99800.0	105.0, 99800.0	
	Missing		0	0	0	

[1]Kruskal-Wallis p-value;

	status cancer at enrolment METASTATIC (N=17)	NON-METASTATIC (N=28)	Total (N=45)	P-value
spike_post_boosting				0.9627[1]
N	17	28	45	
Mean (SD)	45810.8 (41953.96)	45005.3 (44612.12)	45309.6 (43144.98)	
Median (IQR)	30473.0 (19394.0, 64366.0)	33940.0 (19090.0, 54833.5)	33563.0 (19394.0, 61899.0)	
Range	238.0, 155332.0	380.0, 225000.0	238.0, 225000.0	
Missing	0	0	0	
nucleo_post_boosting, n (%)				0.5277[2]
NonReac	9 (52.9%)	17 (65.4%)	26 (60.5%)	
Reac	8 (47.1%)	9 (34.6%)	17 (39.5%)	
Missing	0	2	2	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_post_boosting		status cancer at enrolment METASTATIC	NON-METASTATIC	Total	P-value
NonReac		(N=9)	(N=17)	(N=26)	
	spike_post_boosting				0.4035[1]
	N	9	17	26	
	Mean (SD)	23504.6 (20606.08)	29388.3 (18160.42)	27351.6 (18844.00)	
	Median (IQR)	20444.0 (4174.0, 30473.0)	29744.0 (17591.0, 35239.0)	28776.0 (17515.0, 35239.0)	
	Range	238.0, 64098.0	380.0, 69259.0	238.0, 69259.0	
	Missing	0	0	0	
Reac		(N=8)	(N=9)	(N=17)	
	spike_post_boosting				0.1779[1]
	N	8	9	17	
	Mean (SD)	70905.4 (46674.03)	44382.9 (21252.55)	56864.1 (36947.52)	
	Median (IQR)	71811.0 (37297.5, 94061.0)	35672.0 (34317.0, 61271.0)	51403.0 (34317.0, 76371.0)	
	Range	5572.0, 155332.0	9822.0, 76371.0	5572.0, 155332.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

	status cancer at enrolment METASTATIC (N=19)	NON-METASTATIC (N=33)	Total (N=52)	P-value
spike_final				0.2503[1]
N	19	33	52	
Mean (SD)	12529.6 (10320.44)	20925.4 (20925.16)	17857.7 (18138.22)	
Median (IQR)	9852.0 (5244.0, 17866.0)	13238.0 (5368.0, 31024.0)	10287.0 (5273.0, 27362.0)	
Range	1143.0, 35824.0	582.0, 81334.0	582.0, 81334.0	
Missing	0	0	0	
nucleo_final, n (%)				0.7744[2]
NonReac	7 (36.8%)	14 (42.4%)	21 (40.4%)	
Reac	12 (63.2%)	19 (57.6%)	31 (59.6%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_final		status cancer at enrolment METASTATIC (N=7)	NON-METASTATIC (N=14)	Total (N=21)	P-value
NonReac	**spike_final**				0.4556[1]
	N	7	14	21	
	Mean (SD)	8215.4 (6323.60)	6474.7 (5779.52)	7055.0 (5866.45)	
	Median (IQR)	5603.0 (2016.0, 15297.0)	4706.0 (3524.0, 8792.0)	5302.0 (3524.0, 9287.0)	
	Range	1693.0, 17745.0	582.0, 19264.0	582.0, 19264.0	
	Missing	0	0	0	
Reac		(N=12)	(N=19)	(N=31)	
	spike_final				0.0150[1]
	N	12	19	31	
	Mean (SD)	15046.2 (11564.04)	31573.3 (21730.27)	25175.7 (19983.00)	
	Median (IQR)	10287.0 (7080.5, 25813.5)	28977.0 (13238.0, 42014.0)	21947.0 (10195.0, 33961.0)	
	Range	1143.0, 35824.0	8107.0, 81334.0	1143.0, 81334.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs Lymphopenia

Post boost

	Did the subject experience any lymphopenia since last visit? N (N=38)	Y (N=14)	Total (N=52)	P-value
spike_post_boosting				0.8852[1]
N	38	14	52	
Mean (SD)	40710.3 (43700.00)	39392.7 (39439.88)	40355.6 (42217.42)	
Median (IQR)	29627.5 (9822.0, 61271.0)	32817.5 (17677.0, 51403.0)	30079.0 (13668.5, 56337.0)	
Range	191.0, 225000.0	380.0, 155332.0	191.0, 225000.0	
Missing	0	0	0	
nucleo_post_boosting, n (%)				0.7500[2]
NonReac	23 (63.9%)	8 (57.1%)	31 (62.0%)	
Reac	13 (36.1%)	6 (42.9%)	19 (38.0%)	
Missing	2	0	2	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_post_boosting		Did the subject experience any lymphopenia since last visit? N	Y	Total	P-value
NonReac		(N=23)	(N=8)	(N=31)	
	spike_post_boosting				0.6845[1]
	N	23	8	31	
	Mean (SD)	24591.8 (18843.67)	22089.5 (21394.52)	23946.1 (19194.70)	
	Median (IQR)	20503.0 (8699.0, 33563.0)	22859.0 (1503.5, 32856.0)	20503.0 (6710.0, 33563.0)	
	Range	238.0, 69259.0	380.0, 61899.0	238.0, 69259.0	
	Missing	0	0	0	
Reac		(N=13)	(N=6)	(N=19)	
	spike_post_boosting				0.5987[1]
	N	13	6	19	
	Mean (SD)	47713.6 (33130.17)	62463.7 (47809.30)	52371.5 (37633.54)	
	Median (IQR)	48396.0 (23192.0, 76371.0)	43537.5 (35162.0, 69034.0)	48396.0 (28179.0, 76371.0)	
	Range	191.0, 96425.0	28179.0, 155332.0	191.0, 155332.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Final

	Did the subject experience any lymphopenia since last visit? N (N=42)	Y (N=14)	Total (N=56)	P-value
spike_final				0.0997[1]
N	42	14	56	
Mean (SD)	18844.6 (19236.15)	10884.1 (11455.34)	16854.5 (17859.31)	
Median (IQR)	10364.0 (5603.0, 27725.0)	5428.5 (2016.0, 17745.0)	10023.5 (5040.0, 25813.5)	
Range	117.0, 81334.0	582.0, 35824.0	117.0, 81334.0	
Missing	0	0	0	
nucleo_final, n (%)				0.5350[2]
NonReac	16 (38.1%)	7 (50.0%)	23 (41.1%)	
Reac	26 (61.9%)	7 (50.0%)	33 (58.9%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_final		Did the subject experience any lymphopenia since last visit? N	Y	Total	P-value
NonReac		(N=16)	(N=7)	(N=23)	
	spike_final				0.1814[1]
	N	16	7	23	
	Mean (SD)	7501.7 (5658.67)	5144.1 (5834.24)	6784.2 (5687.32)	
	Median (IQR)	5485.5 (3707.0, 9569.5)	3524.0 (1693.0, 5613.0)	5302.0 (2269.0, 9287.0)	
	Range	1389.0, 19264.0	582.0, 17745.0	582.0, 19264.0	
	Missing	0	0	0	
Reac		(N=26)	(N=7)	(N=33)	
	spike_final				0.3111[1]
	N	26	7	33	
	Mean (SD)	25824.9 (21321.81)	16624.1 (13168.31)	23873.2 (20056.79)	
	Median (IQR)	19906.5 (8967.0, 33961.0)	10215.0 (5244.0, 29120.0)	17866.0 (8967.0, 31475.0)	
	Range	117.0, 81334.0	1143.0, 35824.0	117.0, 81334.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs Hypogammaglobulinaemia

Post boost

	Did the subject experience any Hypogammaglobulinaemia since last visit? N (N=49)	Y (N=3)	Total (N=52)	P-value
spike_post_boosting				[redacted]
N	49	3	52	
Mean (SD)	40913.0 (43447.08)	31251.0 (3661.52)	40355.6 (42217.42)	
Median (IQR)	29744.0 (9822.0, 61271.0)	30473.0 (28041.0, 35239.0)	30079.0 (13668.5, 56337.0)	
Range	191.0, 225000.0	28041.0, 35239.0	191.0, 225000.0	
Missing	0	0	0	
nucleo_post_boosting, n (%)				[redacted]
NonReac	28 (59.6%)	3 (100.0%)	31 (62.0%)	
Reac	19 (40.4%)	0 (0.0%)	19 (38.0%)	
Missing	2	0	2	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_post_boosting		Did the subject experience any Hypogammaglobulinaemia since last visit? N	Y	Total	P-value
NonReac		(N=28)	(N=3)	(N=31)	
	spike_post_boosting				[redacted]
	N	28	3	31	
	Mean (SD)	23163.4 (20045.36)	31251.0 (3661.52)	23946.1 (19194.70)	
	Median (IQR)	19919.0 (5442.0, 32431.0)	30473.0 (28041.0, 35239.0)	20503.0 (6710.0, 33563.0)	
	Range	238.0, 69259.0	28041.0, 35239.0	238.0, 69259.0	
	Missing	0	0	0	
Reac		(N=19)	(N=0)	(N=19)	
	spike_post_boosting				
	N	19		19	
	Mean (SD)	52371.5 (37633.54)		52371.5 (37633.54)	
	Median (IQR)	48396.0 (28179.0, 76371.0)		48396.0 (28179.0, 76371.0)	
	Range	191.0, 155332.0		191.0, 155332.0	
	Missing	0		0	

[1]Kruskal-Wallis p-value;

	Did the subject experience any Hypogammaglobulinaemia since last visit? N (N=51)	Y (N=5)	Total (N=56)	P-value
spike_final				0.4464[1]
N	51	5	56	
Mean (SD)	17344.7 (18310.48)	11854.6 (12664.66)	16854.5 (17859.31)	
Median (IQR)	10195.0 (5302.0, 26999.0)	4836.0 (3524.0, 17745.0)	10023.5 (5040.0, 25813.5)	
Range	117.0, 81334.0	1693.0, 31475.0	117.0, 81334.0	
Missing	0	0	0	
nucleo_final, n (%)				0.1474[2]
NonReac	19 (37.3%)	4 (80.0%)	23 (41.1%)	
Reac	32 (62.7%)	1 (20.0%)	33 (58.9%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_final		Did the subjectexperience any Hypogammaglobulinaemia since last visit? N	Y	Total	P-value
NonReac		(N=19)	(N=4)	(N=23)	
	spike_final				[redacted]
	N	19	4	23	
	Mean (SD)	6749.4 (5533.21)	6949.5 (7311.51)	6784.2 (5687.32)	
	Median (IQR)	5368.0 (2269.0, 9287.0)	4180.0 (2608.5, 11290.5)	5302.0 (2269.0, 9287.0)	
	Range	582.0, 19264.0	1693.0, 17745.0	582.0, 19264.0	
	Missing	0	0	0	
Reac		(N=32)	(N=1)	(N=33)	
	spike_final				[redacted]
	N	32	1	33	
	Mean (SD)	23635.7 (20330.49)	31475.0 (.)	23873.2 (20056.79)	
	Median (IQR)	16044.0 (8955.0, 32492.5)	31475.0 (31475.0, 31475.0)	17866.0 (8967.0, 31475.0)	
	Range	117.0, 81334.0	31475.0, 31475.0	117.0, 81334.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response at baseline vs timing last dose

Baseline

	N months between last vaccination prior inclusion and date inclusion				
	a. <6 months (N=38)	b. 6 to 9 months (N=42)	c. >9 months (N=27)	Total (N=107)	P-value
spike_baseline					0.0765[1]
N	38	42	27	107	
Mean (SD)	13833.6 (21078.74)	22816.5 (27318.48)	16020.3 (17809.78)	17911.4 (23193.96)	
Median (IQR)	4320.5 (756.0, 16238.0)	13092.5 (3407.0, 29034.0)	9017.0 (3197.0, 26871.0)	9017.0 (2180.0, 26871.0)	
Range	5.5, 93273.0	105.0, 99800.0	246.0, 64506.0	5.5, 99800.0	
Missing	0	0	0	0	
nucleo_baseline, n (%)					0.0219[2]
NonReac	24 (63.2%)	13 (31.7%)	13 (48.1%)	50 (47.2%)	
Reac	14 (36.8%)	28 (68.3%)	14 (51.9%)	56 (52.8%)	
Missing	0	1	0	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

		N months between last vaccination prior inclusion and date inclusion				
nucleo_baseline		a. <6 months	b. 6 to 9 months	c. >9 months	Total	P-value
NonReac		(N=24)	(N=13)	(N=13)	(N=50)	
	spike_baseline					0.4507[1]
	N	24	13	13	50	
	Mean (SD)	3603.8 (4826.93)	6864.3 (11010.07)	3912.2 (3351.27)	4531.7 (6733.56)	
	Median (IQR)	2305.5 (183.0, 4770.0)	3310.0 (921.0, 6769.0)	3197.0 (933.0, 5618.0)	2864.5 (700.0, 5618.0)	
	Range	5.5, 21402.0	383.0, 38010.0	246.0, 9122.0	5.5, 38010.0	
	Missing	0	0	0	0	
Reac		(N=14)	(N=28)	(N=14)	(N=56)	
	spike_baseline					0.8824[1]
	N	14	28	14	56	
	Mean (SD)	31370.3 (26438.11)	30462.3 (29909.55)	27263.5 (18473.52)	29889.6 (26220.50)	
	Median (IQR)	23732.5 (11380.0, 54202.0)	19260.0 (9829.5, 38842.5)	24572.0 (12803.0, 33733.0)	20800.0 (10865.5, 41482.5)	
	Range	556.0, 93273.0	105.0, 99800.0	3785.0, 64506.0	105.0, 99800.0	
	Missing	0	0	0	0	

[1]Kruskal-Wallis p-value;

Immune response vs N prior vaccin doses

Baseline

	N prior doses class			
	2 or 3 (N=61)	4 or 5 (N=46)	Total (N=107)	P-value
spike_baseline				0.0013[1]
N	61	46	107	
Mean (SD)	14238.3 (22888.61)	22782.1 (22937.66)	17911.4 (23193.96)	
Median (IQR)	3785.0 (857.0, 15479.0)	15954.0 (7115.0, 29034.0)	9017.0 (2180.0, 26871.0)	
Range	5.5, 99800.0	105.0, 93273.0	5.5, 99800.0	
Missing	0	0	0	
nucleo_baseline, n (%)				0.0184[2]
NonReac	35 (57.4%)	15 (33.3%)	50 (47.2%)	
Reac	26 (42.6%)	30 (66.7%)	56 (52.8%)	
Missing	0	1	1	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_baseline		N prior doses class 2 or 3	4 or 5	Total	P-value
NonReac		(N=35)	(N=15)	(N=50)	
	spike_baseline				0.0047[1]
	N	35	15	50	
	Mean (SD)	2579.3 (2770.59)	9087.4 (10405.97)	4531.7 (6733.56)	
	Median (IQR)	1310.0 (481.0, 3462.0)	5618.0 (3054.0, 9915.0)	2864.5 (700.0, 5618.0)	
	Range	5.5, 9122.0	164.0, 38010.0	5.5, 38010.0	
	Missing	0	0	0	
Reac		(N=26)	(N=30)	(N=56)	
	spike_baseline				0.8566[1]
	N	26	30	56	
	Mean (SD)	29933.2 (28291.45)	29851.8 (24776.97)	29889.6 (26220.50)	
	Median (IQR)	20763.0 (9520.0, 40072.0)	20897.5 (12322.0, 45672.0)	20800.0 (10865.5, 41482.5)	
	Range	121.0, 99800.0	105.0, 93273.0	105.0, 99800.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Post-boost

	N prior doses class 2 or 3 (N=45)	4 or 5 (N=7)	Total (N=52)	P-value
spike_post_boosting				0.6389[1]
N	45	7	52	
Mean (SD)	39658.9 (40132.62)	44834.0 (57544.19)	40355.6 (42217.42)	
Median (IQR)	30473.0 (17591.0, 51403.0)	20444.0 (5572.0, 91697.0)	30079.0 (13668.5, 56337.0)	
Range	191.0, 225000.0	2583.0, 155332.0	191.0, 225000.0	
Missing	0	0	0	
nucleo_post_boosting, n (%)				1.0000[2]
NonReac	27 (62.8%)	4 (57.1%)	31 (62.0%)	
Reac	16 (37.2%)	3 (42.9%)	19 (38.0%)	
Missing	2	0	2	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_post_boosting		N prior doses class 2 or 3	4 or 5	Total	P-value
NonReac		(N=27)	(N=4)	(N=31)	
	spike_post_boosting				0.3458[1]
	N	27	4	31	
	Mean (SD)	25225.6 (19881.19)	15309.3 (12023.70)	23946.1 (19194.70)	
	Median (IQR)	21182.0 (6710.0, 35239.0)	14571.5 (5641.0, 24977.5)	20503.0 (6710.0, 33563.0)	
	Range	238.0, 69259.0	2583.0, 29511.0	238.0, 69259.0	
	Missing	0	0	0	
Reac		(N=16)	(N=3)	(N=19)	
	spike_post_boosting				0.3711[1]
	N	16	3	19	
	Mean (SD)	46403.6 (26565.26)	84200.3 (75160.92)	52371.5 (37633.54)	
	Median (IQR)	42034.0 (28790.0, 66700.0)	91697.0 (5572.0, 155332.0)	48396.0 (28179.0, 76371.0)	
	Range	191.0, 96425.0	5572.0, 155332.0	191.0, 155332.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

	N prior doses class 2 or 3 (N=34)	4 or 5 (N=22)	Total (N=56)	P-value
spike_final				0.5684[1]
N	34	22	56	
Mean (SD)	19206.1 (20888.39)	13220.3 (11265.66)	16854.5 (17859.31)	
Median (IQR)	10364.0 (4836.0, 29120.0)	8955.0 (5244.0, 18292.0)	10023.5 (5040.0, 25813.5)	
Range	117.0, 81334.0	1143.0, 42014.0	117.0, 81334.0	
Missing	0	0	0	
nucleo_final, n (%)				0.2824[2]
NonReac	16 (47.1%)	7 (31.8%)	23 (41.1%)	
Reac	18 (52.9%)	15 (68.2%)	33 (58.9%)	

[1]Kruskal-Wallis p-value; [2]Fisher Exact p-value;

nucleo_final		N prior doses class 2 or 3	4 or 5	Total	P-value
NonReac		(N=16)	(N=7)	(N=23)	
	spike_final				0.1606[1]
	N	16	7	23	
	Mean (SD)	5689.7 (4963.77)	9285.9 (6819.62)	6784.2 (5687.32)	
	Median (IQR)	5069.0 (1854.5, 7329.0)	5603.0 (3873.0, 18292.0)	5302.0 (2269.0, 9287.0)	
	Range	582.0, 17745.0	3541.0, 19264.0	582.0, 19264.0	
	Missing	0	0	0	
Reac		(N=18)	(N=15)	(N=33)	
	spike_final				0.0114[1]
	N	18	15	33	
	Mean (SD)	31220.6 (22370.89)	15056.3 (12613.06)	23873.2 (20056.79)	
	Median (IQR)	28422.5 (13238.0, 39630.0)	8967.0 (7253.0, 26999.0)	17866.0 (8967.0, 31475.0)	
	Range	117.0, 81334.0	1143.0, 42014.0	117.0, 81334.0	
	Missing	0	0	0	

[1]Kruskal-Wallis p-value;

Multivariate analysis

Outcome variable: spike at baseline (continuous variable)

Explanatory variables:

- Cohort (A1+A2 is reference)
- Nucleo caps at baseline (Reactive is reference)
- Sex (female is reference)
- Cancer_curren_status (non-metastatic is reference)
- Timing of last dose (<6 months is reference)
- N prior doses

If we perform robust regression (as there are outliers) with MM estimation, we obtain:

Parameter Estimates							
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	11388.67	5136.322	1321.667	21455.68	4.92	0.0266
A3	1	-2011.76	3009.709	-7910.68	3887.160	0.45	0.5039
B	1	-2716.31	4403.154	-11346.3	5913.708	0.38	0.5373
C	1	2086.058	2818.641	-3438.38	7610.492	0.55	0.4592
non_reactive	1	-13618.9	2330.632	-18186.9	-9050.97	34.15	<.0001
male	1	328.6366	3178.207	-5900.54	6557.808	0.01	0.9176
solidmeta	1	-1126.83	2480.741	-5989.00	3735.331	0.21	0.6497
interval6_9months	1	-1878.73	2609.965	-6994.17	3236.708	0.52	0.4716
interval9months	1	-25.9354	2773.601	-5462.09	5410.223	0.00	0.9925
Npriordoses	1	2420.153	1306.663	-140.860	4981.166	3.43	0.0640
Scale	0	13462.04					

If we perform backward variable selection, only the variables non_reactive and N prior doses remain:

Parameter Estimates							
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	8983.614	4076.964	992.9121	16974.32	4.86	0.0276
non_reactive	1	-12196.9	1926.879	-15973.5	-8420.24	40.07	<.0001
Npriordoses	1	2396.789	1072.748	294.2407	4499.338	4.99	0.0255
Scale	0	12289.75					

If we restrict to the baseline non-reactive cases and perform variable selection, we obtain:

Parameter Estimates							
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	-1485.62	1405.258	-4239.87	1268.638	1.12	0.2904
C	1	1819.709	871.0811	112.4217	3526.997	4.36	0.0367
male	1	-1776.98	884.8146	-3511.19	-42.7799	4.03	0.0446
Npriordoses	1	1523.544	451.6194	638.3862	2408.702	11.38	0.0007
Scale	0	3067.641					

6 ADVERSE EVENTS

No adverse events have been reported in the 152 included subjects.

7 ADDITIONAL INFORMATION

7.1 Global substantial modifications

BELGIUM

REFERENCE	TYPE	CA opinion	Date	CEC opinion	Date	INFORMATION
AMD-0129	AMENDT	N/A	02/01/1900	Approval	06/01/2022	
						New/amended other study documents
						New/amended patient information sheet / informed consent (including addendum)
						New/amended protocol
AMD-0136	AMENDT	Approval	04/04/2022	Approval	14/04/2022	
						New/amended patient information sheet / informed consent (including addendum)
						New/amended protocol
AMD-0141	AMENDT	N/A	02/01/1900	Approval	02/05/2022	
						New/amended patient information sheet / informed consent (including addendum)
						New/amended protocol
AMD-0144	AMENDT	N/A	02/01/1900	Approval	30/06/2022	
						Addition of at least a new site or a site whose LEC did not reply initially or moved site
AMD-0152	AMENDT	Approval	07/10/2022	Approval	06/10/2022	
						New/amended protocol
						New/amended documents or information related to IMP or IMPD
						New/amended patient information sheet / informed consent (including addendum)
AMD-0153	AMENDT	Approval	20/01/2023	Approval	02/02/2023	
						New/amended documents or information related to IMP or IMPD
						New/amended Reference Safety Information
						New/amended patient information sheet / informed consent (including addendum)
						New/amended protocol
AMD-0170	AMENDT	Approval	06/11/2023	Approval	16/11/2023	
						New/amended protocol
						New/amended patient information sheet / informed consent (including addendum)
						New/amended documents or information related to IMP or IMPD
						New/amended Reference Safety Information

7.2 Global interruptions and re-starts

There were no global interruptions to the trial.

7.3 Limitations, addressing sources of potential bias and imprecisions and caveats

The trial has been stopped prematurely due to slow accrual. Of the planned 100 evaluable subjects per cohort (400 evaluable subjects in total), we had

- 59 evaluable subjects in cohort A.1 + A.2
- 22 evaluable subjects in cohort A.3
- 9 evaluable subjects in cohort B
- 25 evaluable subjects in cohort 25.

⇨ 115 evaluable subjects in total.

All subjects had an immune response (anti-SARS-CoV-2 spike above the cut-off of 0.80 U/ml for each subject), resulting in an immune response rate of 100% in all four cohorts. Consequently, assessing differences in immune response rates according to subjects' characteristics was not possible.

8 REFERENCES

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