CONSORT 2025 checklist of information to include when reporting a randomised trial*

Section / Topic	No	CONSORT 2025 checklist item description	Reported on page no.
Title and abstract			
Title and structured abstract	1a	Identification as a randomised trial	0
	1b	Structured summary of the trial design, methods, results, and conclusions	0
Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	12
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	Supplementary
Data sharing	4	Where and how the individual de-identified participant data (including data dictionary), statistical code and any other materials can be accessed	29
Funding and conflicts of interest	5a	Sources of funding and other support (e.g., supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	32-34
	5b	Financial and other conflicts of interest of the manuscript authors	32-34
Introduction			
Background and rationale	6	Scientific background and rationale	2-3
Objectives	7	Specific objectives related to benefits and harms	13
Methods			
Patient and public involvement	8	Details of patient or public involvement in the design, conduct and reporting of the trial	13
Trial design	9	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	12-13
Changes to trial protocol	10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	13
Trial setting	11	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial was conducted	12
Eligibility criteria	12a	Eligibility criteria for participants	13
	12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (e.g., surgeons, physiotherapists)	NA

Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	10
Outcomes	14	Pre-specified primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	13 and supplementary
Harms	15	How harms were defined and assessed (e.g., systematically, non-systematically)	13
Sample size	16a	How sample size was determined, including all assumptions supporting the sample size calculation	13
	16b	Explanation of any interim analyses and stopping guidelines	13
Randomisation:			13
Sequence generation	17a	Who generated the random allocation sequence and the method used	13
	17b	Type of randomisation and details of any restriction (e.g., stratification, blocking and block size)	13
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	13
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	13
Blinding	20a	Who was blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	13
	20b	If blinded, how blinding was achieved and description of the similarity of interventions	13
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	14-15
	21b	Definition of who is included in each analysis (e.g., all randomised participants), and in which group	14-15
	21c	How missing data were handled in the analysis	14-15
	21d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses), distinguishing prespecified from post-hoc	NA
Results			
Participant flow, including flow diagram	22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome	19
	22b	For each group, losses and exclusions after randomisation, together with reasons	5
Recruitment	23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	5
	23b	If relevant, why the trial ended or was stopped	NA

Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered (e.g., where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended [fidelity])	5
	24b	Concomitant care received during the trial for each group	5
Baseline data	25	A table showing baseline demographic and clinical characteristics for each group	21
Numbers analysed, outcomes and estimation	26	For each primary and secondary outcome, by group: ● the number of participants included in the analysis ● the number of participants with available data at the outcome time point ● result for each group, and the estimated effect size and its precision (such as 95% confidence interval) ● for binary outcomes, presentation of both absolute and relative effect size	19, 20, 24-28
Harms	27	All harms or unintended events in each group	27-28
Ancillary analyses	28	Any other analyses performed, including subgroup and sensitivity analyses, distinguishing pre-specified from post-hoc	NA
Discussion			
Interpretation	29	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7-10
Limitations	30	Trial limitations, addressing sources of potential bias, imprecision, generalisability, and, if relevant, multiplicity of analyses	NA

*We strongly recommend reading this statement in conjunction with the CONSORT 2025 Explanation and Elaboration and/or the CONSORT 2025 Expanded Checklist for important clarifications on all the items. We also recommend reading relevant CONSORT extensions. See www.consort-spirit.org.

Citation: Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 Statement: updated guideline for reporting randomised trials. BMJ. 2025; 388:e081123. https://dx.doi.org/10.1136/bmj-2024-081123.

SUPPLEMENTARY DATA

Supplementary Table 1: Long-term physicochemical stability of INP20 clinical batches stored at 2–8 °C

Mean hydrodynamic diameter (nm), aggregation, zeta potential, and non-encapsulated Ara h2 allergen content in INP20 nanoparticles from three GMP-manufactured clinical batches measured over time during storage at 2-8 ºC.

Analysis parameters	Specifications	Shelf life (months) at 2 – 8 ºC								
		0	1	3	6	9	12	18	24	36
Batch 190001 – (0.15 mg)										
Mean hydrodynamic diameter (nm)	120 – 300 nm	175.3	182.5	178.2	180.5	183.6	184.8	186.1	277.8	198.7
Aggregation	≤ 0.3	0.191	0.232	0.189	0.280	0.275	0.224	0.265	0.390 (1)	0.291
Zeta potential (mV)	-70 - -35 mV	-44.3	-44.6	-48.2	-38.6	-46.4	-41.3	-46.8	-42.6	-43.4
Free Ara h2 (%)	≤ 38 %	18	(1)	(1)	6	(1)	(1)	(1)	9	6
Batch 190001 – (1.5 mg)										
Mean hydrodynamic diameter (nm)	120 – 300 nm	170.4	165.2	168.9	164.8	165.9	174.6	165.7	202.9	190.5
Aggregation	≤ 0.3	0.190	0.156	0.187	0.196	0.212	0.194	0.175	0.314	0.268
Zeta potential (mV)	-70 - -35 mV	-44.0	-46.7	-43.6	-44.1	-41.4	-44.2	-44.8	-39.4	-40.4
Free Ara h2 (%)	≤ 38 %	19	(2)	(2)	(2)	(2)	(2)	(2)	13	(3)
Batch 220001 – (5 mg)										
Mean hydrodynamic diameter (nm)	120 – 300 nm	212.2	---	---	226.6	199.9	202.8	284.7	231.5	213.5
Aggregation	≤ 0.3	0.299	---	---	0.299	0.205	0.254	0.437 (4)	0.307	0.260
Zeta potential (mV)	-70 - -35 mV	-46.1	---	---	-45.1	-41.5	-47.7	-43.4	-45.1	-44.7
Free Ara h2 (%)	≤ 38 %	21	---	---	14	11	10	8	24	25

(1) Out-of-specification value attributed to improper sample preparation. Subsequent measurements fell within specification limits. (2) Method under development and optimization. (3) Peak difficult to integrate. (4) Result out of specification caused by improper sample preparation.

Supplementary Table 2: Baseline demographic and clinical characteristics by cohort in active arms

Baseline demographic and clinical characteristics of treated participants, stratified by dose cohort (A–F). Variables include age, sex distribution, history of allergic diseases, total serum IgE, peanut-specific IgE, skin prick test (SPT) wheal diameter, and maximum tolerated dose during screening double-blind placebo-controlled food challenge (DBPCFC). Continuous variables are presented as mean ± SD or median (interquartile range) with minimum and maximum values, as indicated. Categorical variables are expressed as number (percentage). No formal statistical comparisons between cohorts were performed.

Characteristics	Cohort A – 0.15 mg INP20 (n=6)	Cohort B – 1.5 mg INP20 (n=6)	Cohort C – 5 mg INP20 (n=9)	Cohort D – 10 mg INP20 (n=6)	Cohort E – 20 mg INP20 (n=7)	Cohort F – 30 mg INP20 (n=6)
Age						
Median – years (min – max)	15.0 (14.6 – 35.1)	20.9 (12.1 – 37.5)	19.1 (13.3 – 37.3)	18.6 (12.1 – 23.4)	13.1 (12.2 – 26.3)	15.7 (12.5 – 26.1)
Sex – no.of patients (%)						
Male	2 (33)	4 (67)	5 (56)	3 (50)	3 (43)	3 (50)
Female	4 (67)	2 (33)	4 (44)	3 (50)	4 (57)	3 (50)
History of allergic disease – no. of patients (%) *						
Skin and subcutaneous tissue disorders	2 (33)	0 (0)	2 (22)	0 (0)	1 (14)	1 (17)
Respiratory, thoracic, and mediastinal disorders	3 (50)	2 (33)	5 (56)	0 (0)	3 (43)	1 (17)
Immune system disorders	1 (17)	4 (67)	7 (78)	2 (33)	4 (57)	4 (67)
Others	2 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunologic markers – median (Q1, Q3, [min-max])						
Total IgE (IU/mL)	199 (88, 379, [72 – 668])	595 (228, 1223, [212 – 1351])	1140 (190, 1737, [42 – 4300])	368 (136, 1259, [89 – 3140])	454 (271, 1240, [191 – 2140])	785 (210, 2687, [92 – 2738])
Peanut-specific IgE, KUA/L	24.0 (4.5, 49.8 [3.6 – 100.0])	4.3 (0.9, 41.0, [0.6 – 95.7])	12.3 (2.2, 71.1, [0.5 -100.0])	2.0 (0.8, 15.4, [0.7 – 19.1])	7.3 (3.0, 15.8, [0.4 – 79.1])	11.3 (1.6, 65.6, [0.7 – 100.0])
Peanut wheal, mm, mean (SD)	5.4 (1.1)	3.4 (2.3)	4.7 (1.7)	3.4 (1.4)	4.5 (0.6)	3.3 (2.7)
MTD peanut protein at screening						
DBPCFC – median mg (Q1, Q3, [min-max])	50 (4, 163, [2 – 500])	750 (50, 5000, [50 – 5000])	500 (5, 1250, [2 – 5000])	50 (50, 163, [50 – 500])	50 (2, 1000 [2 – 5000])	28 (2, 50, [2 – 50])

Note: DBPCFC denotes double-blind, placebo-controlled food challenge; IgE, immunoglobulin E; MTD, maximum tolerated dose; SPT, skin prick test. Abbreviation: n, number of participants.
*Participants may be included in more than 1 category.

Supplementary Table 3: Baseline demographic and clinical characteristics by cohort in placebo arms

Baseline demographic and clinical characteristics of treated participants, stratified by dose cohort (A–F). Variables include age, sex distribution, history of allergic diseases, total serum IgE, peanut-specific IgE, skin prick test (SPT) wheal diameter, and maximum tolerated dose during screening double-blind placebo-controlled food challenge (DBPCFC). Continuous variables are presented as mean ± SD or median with minimum and maximum values, as indicated. Categorical variables are expressed as number (percentage). No formal statistical comparisons between cohorts were performed.

Characteristics	Cohort A – 0.15 mg Placebo (n=2)	Cohort B – 1.5 mg Placebo (n=2)	Cohort C – 5 mg Placebo (n=2)	Cohort D – 10 mg Placebo (n=2)	Cohort E – 20 mg Placebo (n=2)	Cohort F – 30 mg Placebo (n=2)
Age						
Median – years (min – max)	24.8 (14.8 – 34.7)	22.6 (21.9 – 23.3)	23.9 (18.0 – 29.7)	17.9 (13.9 – 21.9)	13.2 (12.2 – 14.3)	23.3 (23.0 – 23.7)
Sex – no.of patients (%)						
Male	2 (100)	0 (0)	2 (100)	2 (100)	0 (0)	0 (0)
Female	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	2 (100)
History of allergic disease – no. of patients (%) *						
Skin and subcutaneous tissue disorders	1 (50)	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic, and mediastinal disorders	0 (0)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)
Immune system disorders	0 (0)	2 (100)	2 (100)	1 (50)	2 (100)	1 (50)
Others	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)
Immunologic markers – median (Q1, Q3, [min-max])						
Total IgE (IU/mL)	791 (293 – 1288)	178 (127 – 229)	3479 (38 – 6920)	1382 (133 – 2630)	395 (103 – 687)	209 (20 – 397)
Peanut-specific IgE, KUA/L	48.9 (0.9 – 96.9)	15.5 (0.8 – 30.3)	45.9 (0.9 – 90.9)	3.3 (2.4 – 4.3)	4.8 (2.0 – 7.6)	16.3 (0.6 – 32.0)
Peanut wheal, mm, mean (SD)	4.3 (1.7)	2.2 (3.1)	5.5 (---)	5.3 (1.0)	3.2 (0.3)	11.6 (---)
MTD peanut protein at screening						
DBPCFC – median mg (Q1, Q3, [min-max])	5000 (5000 – 5000)	525 (50 – 1000)	50 (50 – 50)	251 (2 – 500)	50 (50 – 50)	253 (5 – 500)

Note: DBPCFC denotes double-blind, placebo-controlled food challenge; IgE, immunoglobulin E; MTD, maximum tolerated dose; SPT, skin prick test. Abbreviation: n, number of participants.

*Participants may be included in more than 1 category

Clinical Study Protocol

Compound: INP20

Study Code: INP20-01

A multicenter double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients

Document type:	Clinical Trial Protocol
EUDRACT number:	2018-003665-34
Version number:	4.0
Development phase:	I/II
Document status:	Final
Release date:	07.10.2021

Protocol Approval and Responsibilities Approval Page

This Clinical Study Protocol is approved by:

Sponsor Representative:

Maite Agüeros, PhD InnoUp Farma, S.L.	Signature DocuSigned by: Nombre del firmante: Maite Agüeros Motivo de la firma: Apruebo este documento Hora de firma: 12/11/2021 | 06:24 PST 77CC5167C9D24924BCA68A0115BC44F7	Date

Coordinator investigators:

Marta Ferrer Puga, PhD Clinica Universitaria de Navarra	Signature DocuSigned by: Marta Ferrer Nombre del firmante: Marta Ferrer Motivo de la firma: Apruebo este documento Hora de firma: 12/11/2021 | 14:54 CET EBE4FF859E284FCC884FE685A5946B10	Date
Ana Isabel Tabar Purroy, PhD Hospital Universitario de Navarra	Signature DocuSigned by: Ana Tabar Nombre del firmante: Ana Tabar Motivo de la firma: He revisado este documento Hora de firma: 14/11/2021 | 23:15 CET BB8C44B131EA4A888574CAEC0BFE149D	Date

The undersigned hereby declare their consent to perform the clinical trial in accordance with this clinical study protocol and to adhere to the ethical and regulatory considerations

Document History

Version	Date	Changes
01	14.12.2018	No applicable.
01.1	20.02.2019	CEIm Clarifications: - Protocol summary: changes on study design, inclusion and exclusion criteria, safety assessments (12-lead ECG removed) - 1.2.1.1: Pharmacodynamic properties, Pharmacokinetic properties, Preclinical safety data and Characterization of INP20 have been removed. - 3. Objectives and endpoints: remove ECG and basophil activation on the BAT analysis - 4.1 Description of study design have been modified: DSMB replaced by DEC, remove changes of posology in case of lack of tolerance, description of additional patients enrolled depending on DLTs - 5.2 Inclusion criteria and 2.3 Exclusion criteria updated - 6.1.1 remove changes of posology in case of lack of tolerance - 6.2.2 remove changes of posology in case of lack of tolerance, description of additional patients enrolled depending on DLTs - 6.3.1 remove changes of posology in case of lack of tolerance - 7.1 Screening period changed from D-15 to D-28, Baseline changed from D0 to D1. - 7.2.2 ECG was removed; peak flow, coagulation, and immunologic test were added. - 7.2.2.5.7 ECG: paragraph removed - 8.5 Change DMC to DEC. - 8.6 Steerign Committee: paragraph removed - 10.4.2.2 and 14.4.2.2.4 ECGs were removed. - 10.5.2 Basophil activation on the BAT were removed - 10.5.3 Biomarkers: change from screening to 2 weeks added - 10.8. Sample size calculation: Number of patients fro part B was modified. - 13 References were added - Minor changes such as re-wording and typos correction.

01.1	20.02.2019 v9 18.07.2019	Protocol Amendment: - Protocol Approval and Responsibilities Approval Page: Project Leader and Statistician have been removed. - 7.1.3.1 Reference to Recerca Clinica was removed. - 8.1.1. CTCAE version was updated from 4.03 to 5.0. - 8.2.2 Reporting: Syntax for Science Safety department was added replacing Recerca Clinica. Details about reporting timelines were added. - 8.3. Pregnancies: Syntax for Science Safety department was added replacing Recerca Clinica
2.0	16/12/2019	Non-relevant protocol amendment: - Document History Page has been added - 7.1 Visits Schedules were updated in order to facilitate the understanding of the scheme. In addition, the following changes were done: -Part A: Addition of visit D7 was added in order to dispense medication. It is considered a non-relevant modification because there are no assessments in this visit, the patient just returns and collect medication. -Part A and B: inclusion and exclusion criteria are added prior to the randomization; physical examination and vital signs were added to End of Treatment visit; IgG4 added to follow-up visits to be consistent with the figure 4.1 (study design); BAT evaluations were changed from EoT visit to safety follow-up visits. These changes are considered a non-relevant modification because there are no new patient assessments.
3.0	13/02/2020	Non-relevant protocol amendment: - 3. Pharmacodynamics endpoint Part A has been updated according to safety follow-up changes. - 7.1. Schedule Part A: the safety follow-up has been modified. These changes are considered a non-relevant modification because there are no new patient assessments.

4.0	07/10/2021	Protocol Amendment: - Protocol summary: - 3. Objectives and endpoints: removed spirometry test as an endpoint for primary objective. Added lymphocyte challenge assay as an endpoint for potential efficacy objective. - 4.1 Description of study design: text has been modified for clarification. Challenge test period of validity has been increased. - 4.3: changed part A duration in line with other protocol changes. - 5.2: added inclusion criteria nº8, as it was specified on the protocol but was not present on the inclusion criteria list. - 6.2.2: text has been modified for clarification. - 6.3.1: dose modification escalation to be decided case-by-case by the DEC. - 6.4.2: added comments on permitted medication for clarification. - 6.4.3: added montelukast to the list of prohibited medication. - 6.5.1: patient number is maintained from part A to part B. - 6.6.3.1: study medication to be administered by study nurse only the first two days of treatment. - 7.1: paragraph removed for consistency. Table of assessments: screening period increased from 28 to 56 days, erased informed consent from screening period for consistency. Challenge test validity period is increased up to 6 months. - 7.1.3: clarification on reasons for withdrawal. - 7.1.3.1: clarification on replacement policy. - 7.2: Table of assessments: screening period increased from 28 to 56 days, erased informed consent from screening period for consistency. Challenge test validity period is increased up to 6 months. - 7.2.3.3: added biosample research and sample repository section. - 10.1: added a modified FAS and modified ITT set only for patients with evaluable samples. Pe-protocol set divided into part A and part B for consistency. - 14.2: text modified for clarification. Removed dose 8 (10mg) on table 14-2 as this dose is never reached on the challenge test.

		- Removed all references to “Recerca Clínica” and replaced by “the CRO” - Minor changes such as re-wording and typos correction - Changed site 02 name from Complejo Hospitalario de Navarra to Hospital Universitario de Navarra

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List of abbreviations

AE	Adverse Event
ALT/GPT	Alanine aminotransferase/glutamic pyruvic transaminase
AST/GOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
BAT	Basophil Activation Test
BP	Blood pressure
CRF/eCRF	Case Report/Record Form / electronic Case Record/Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-blind placebo-controlled food challenge
DLT	Dose Limiting Toxicity
DEC	Dose Escalation Committee
EAACI	European Academy of Allergy and Clinical Immunology
ECG	Electrocardiogram
ED	Eliciting dose
EDC	Electronic Data Capture
FIH	First-in-human
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational medicinal product
ICU	Intensive Care Unit
LDH	Lactate dehydrogenase
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NP	Nanoparticles
OFCs	Oral food challenges
OIT	Oral immunotherapy
Pat. No.	Patient Number

SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard deviation
SOP	Standard Operating Procedures
TGF	Transforming Growth Factor
WBC	White blood count
WHO	World Health Organization

Protocol summary

Title	A multicenter double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients
Brief title	INP20 in peanut-allergy
Sponsor and Clinical Phase	InnoUp Farma, S.L. Phase I/II. First-in-human (FIH)
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The main goal is to establish the recommended dose and administration schedule of INP20 to support further investigations of this agent in repeated-dose randomized clinical trials.
Primary Objective(s)	**Part A: Dose-ranging study** • To determine the maximum tolerated dose (MTD) and the recommended oral dose of INP20 in repeated-dose oral administration to patients with peanut allergy. The safety and tolerability of rising oral doses of INP20 will be assessed to identify a safe dose range for Phase II assay. **Part B: Extension study** • To evaluate the safety and tolerability of INP20 in repeated-dose oral administration at the recommended dose(s) in patients with peanut allergy throughout the treatment period of 6 months.
Secondary Objectives	**Part A: Dose-ranging study** • To investigate the pharmacodynamics effects of rising oral doses of INP20 on Serum IgG4 concentrations in patients allergic to peanuts. **Part B: Extension study** • To assess potential efficacy in an expanded treatment cohort using the recommended dose(s) / schedule of INP20 versus placebo group after 6 months of treatment. • To assess the change in immune parameters associated with the therapeutic process of INP20 in repeated-dose oral administration at the recommended dose(s) in patients with peanut allergy at baseline and Months 1, 3 and 6.
Study design	This is a multicenter double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients. The overall study design consists of two sequential periods of Part A and Part B. In **Part A** (double blind, randomized, placebo-controlled, dose-escalation first phase study) in patients from ≥ 12 years old with a history of immediate hypersensitive reaction to peanut protein, 6 consecutive repeated oral-dose of INP20 will be administered to 6 cohorts of patients with peanut allergy once daily for 2 weeks. The study will test groups of 8 different patients during 6 dosing periods (or panel). Consecutive oral INP20 administration at following ascending doses: Group A: 0.15 mg once daily for 2 weeks (w), Group B: 1.5 mg once daily for 2 w, Group C: 5 mg once daily for 2 w, Group D: 10 mg once daily for 2 w, Group E: 20 mg once daily for 2 w, and Group F: 30 mg once daily for 2 w. If any adverse reaction is observed with the first dose, a dose escalation with dilutions (as inpatient) may be done until the planned dose is reached. Then it is estimated that 48 patients will be assigned to one of 6 panels that match a dosing period. In each

	panel, the patients will be randomly assigned to receive INP20 (6 subjects), or placebo (2 subjects). Every patient will only receive one treatment in each panel. In **Part B** (6-month double-blind, placebo-controlled, randomized and parallel groups second phase study) in patients from ≥ 12 years old with a history of immediate hypersensitive reaction to peanut protein. Two (2) doses of peanut proteins (dose and administration schedules depending on the preceding Part A study) will be evaluated for the study. Following confirmation of peanut allergy at screening, patients will be randomized in a 1:1:1 ratio into three (3) different treatment groups, including placebo and the two doses of peanut protein selected from Part A based on observations of IgG4 levels and tolerance of the treatment.
Population	48 patients with peanut allergy is estimated to be included in Part A, from which 36 patients are expected to continue in Part B (expected 20% rate of lost of follow-up)
Inclusion criteria	Patients **must meet all** of the following criteria: • Age 12 years and above of either sex, any race, any ethnicity at the time of the initial visit. • The presence of specific IgE to peanuts (a positive skin prick test to peanuts (diameter of wheal > 3.0 mm) and a positive peanut IgEs [CAP-FEIA] > 0.35 kUA/L. • A history of significant clinical symptoms (urticaria, angioedema, rhinorrhea, nasal congestion, pruritus, sneezing, abdominal pain, emesis, diarrhea, wheezing, shortness of breath, lip/tongue swelling, throat itching, throat swelling or impending sense of doom) occurring within 60 minutes after ingesting peanuts or history of unknown tolerance to peanut due to consumption avoidance. • Have a positive double blind placebo-controlled food challenge (DBPCFC)* to peanut at a cumulative dose of less than 8.5565 grams of peanut protein. • Provide signed informed consent for the participation in the study. In males and females aged 12-17 years old the informed consent will be signed and dated by them, and also by the parent(s) or the subject's legally acceptable representative(s). • Have self-injectable epinephrine available at home and be trained on its proper use. • Potentially fertile women (defined as all women physiologically capable of becoming pregnant) must agree to be sexually inactive or to use appropriate contraceptive measures for the duration of the study and for 1 month afterward. • Patients rolling from part A to part B must have recovered their baseline levels of IgG4. ** The oral challenge test will be considered positive when the patient shows objective clinical symptoms after the administration of one of the doses, or in case of showing subjective clinical symptoms, they are of great intensity (severe abdominal pain) and they persist (untreated or after administration of placebo treatment) for at least 30 minutes after the ingestion of a dose, or subjective moderate clinical symptoms (visual analogue scale) > 2 after ingestion of three consecutive doses*.
Exclusion criteria	Patients **must not meet any** of the following criteria: • History of severe anaphylaxis to peanut as defined by respiratory distress with cyanosis, hypoxemia (O2 Sat <92%) or, in the absence of other clinical records, severe dyspnea; hypotension with or without loss of consciousness; or relaxation of sphincters.

	• Currently participating in another study using an investigational new drug. • Participation in any interventional study, specific oral or sublingual immunotherapy building up phase, for the treatment of food allergy in the past 12 months. Patients in treatment with specific oral maintenance phase of OIT will be considered individually, to investigator's discretion. • Use within the past year of any systemic immunomodulatory treatment (i.e. cyclosporine, omalizumab, etc.), including inhalants immunotherapy building up phase. It is allowed the use of immunotherapy in the maintenance dosing against pollens, mites, animal dander and/or alternaria. • Allergic to placebo ingredients or reacts to any dose of placebo during study entry double blind placebo-controlled food challenge (DBPCFC). • Patients allergic to corn food. • Poor control or persistent activation of severe atopic dermatitis. • Moderate to severe persistent asthma as defined using the Impairment or Risk Criteria of the current NHBLI Guidelines for the Diagnosis and Management of Asthma (https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma). • Currently being treated with greater than medium daily doses of inhaled corticosteroids (fluticasone >500 µg per day, ciclesonide >400 µg per day or budesonide >800 µg per day) or montelukast. Two or more systemic corticosteroid courses for asthma in the past year or 1 oral corticosteroid course for asthma within 3 months prior to the enrollment or between the enrollment and the beginning of treatment. • Poorly controlled Asthma as defined using the Control Criteria of the current NHBLI Guidelines for the Diagnosis and Management of Asthma (https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma). • Prior intubation/mechanical ventilation for asthma. • Chronic gastrointestinal diseases including Celiac Disease, Inflammatory Bowel Disease, Eosinophilic Gastrointestinal Disorders, Irritable Bowel Syndrome, gastric or intestinal cancer, diverticulitis and active peptic ulcer or recurrent gastrointestinal symptoms of undiagnosed etiology in the past year. • Primary or secondary immunodeficiency, including IgA deficiency; HIV positive, or immunopathology of any kind. • History of other chronic diseases (except asthma, rhinitis, atopic dermatitis) and severe requiring treatment (type I diabetes or uncontrolled type 2 diabetes, uncontrolled hypertension, heart disease, etc.); malignancies or serious psychological disorders. • Have a severe reaction at initial double-blind placebo-controlled food challenge, defined as either: - Life-threatening anaphylaxis (with severe hypotension and/or severe bronchospasm), or - Reaction requiring hospitalization. • Inability to discontinue antihistamines for 7 days before skin testing and oral food challenges (OFCs). • Patients diagnosed with other serious food allergies defined as those who have required intubation and/or ICU admission. • Chronic use of beta blockers, angiotensin converting enzyme inhibitors, or monoamine oxidase inhibitors, proton pump inhibitors, H2-bloquers, prokinetic drugs and laxatives.

	• Women of childbearing potential (defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 1 month after stopping medication) who are pregnant, planning to become pregnant, or breastfeeding. Highly effective contraception methods include: a) total abstinence (when this is in line with the preferred and usual lifestyle of the patient); b) total sterilization (bilateral oophorectomy with/without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment; c) male sterilization at least 6 months prior to screening; d) use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%) such as hormonal vaginal ring or transdermal hormone contraception. • Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study may also exclude a participant from the study. • Poor compliance expected by the patient.
Investigational and reference therapy	Investigational therapy: INP20 and matching placebo Reference therapy: None
Efficacy assessments	Challenge test scores.
Safety assessments	Incidence, severity (CTCAE Grade), and relationship to study drug of adverse events (AEs) and serious adverse events (SAEs), and AEs leading to discontinuation (events coded using MedDRA). Number of participants with Dose limiting toxicities (DLT). Allergic symptoms and relatedness to treatment. Physical examination, vital signs, peak flow measurement, laboratory tests (biochemistry, hematology, coagulation, urinalysis and immunologic tests).
Other assessments	Pharmacodynamics: change in immunoglobulin G subtype (IgG4) and basophil activation on the BAT. Immunogenicity: allergen-specific biomarkers associated with INP20 immunotherapy.
Data analysis	Descriptive analysis will be undertaken for all safety determination in Part A to allow Part B continuation. Safety variables will be analyzed in the Safety Population which must include the set of all participants taking at least one dose of the study treatment, including those who have not completed the study. Efficacy and Immunological variables will be analyzed in the Per-Protocol and Intention-To-Treat populations.
Key words	Phase I/II, INP20, peanut allergy, challenge test, safety, efficacy.

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Pathogenesis of peanut allergy

Peanut allergy is a hypersensitivity reaction to peanuts and peanut substances, which is one of the most common allergies in both, children and adults, leading to severe physical symptoms. Peanut allergy affects approximately 1% of children under the age of 5 years and in the past 15 years, increasing numbers of children have been diagnosed with the allergy (Burks, 2008).

Peanut allergy is likely to develop because of both genetic and environmental factors. The genetic mechanisms that play a role in the development of food allergy are heterogeneous and complex. A genetic study determined that peanut allergy is more common in siblings of people with peanut allergy than in the parents or the general population (Carter et al., 2018). Its apparently increasing prevalence may reflect a general increase of genetic predisposition, which is inherited more commonly from the mother. Peanut allergy is presenting earlier in life, possibly reflecting increased consumption of peanut by pregnant and nursing mothers (Carter et al., 2018). On the other hand, several environmental factors have been shown to contribute to the development of food allergies. Potential environmental etiologies include a reduced exposure to bacteria and infections (the hygiene hypothesis), a rise in consumption of omega-3 polyunsaturated fatty acids, a reduced consumption of dietary antioxidants, an excess or deficiency of vitamin D and possible cutaneous exposure (Sicherer et al., 2009).

The initial introduction of a food allergen generally occurs at the mucosal surface of the gastrointestinal tract. Food proteins are taken up by specialized epithelial cells, M cells, transferred to antigen-presenting cells such as dendritic cells, and processed into peptide fragments presented on the cell surface by class II MHC molecules. Peptides are then presented to naive T helper (Th) cells via MHC/T cell receptor interaction, resulting in Th cell priming and activation. In a normal setting the T cell differentiates into a Th1 cell, which in turn interacts with a B cell, releasing cytokines that promote the B cell to differentiate into a plasma cell, which will start producing IgG antibodies to help immobilize and destroy the allergens without causing an allergic response. However, if the T cell differentiates into a Th2 cell, the B cell will produce IgE antibodies. The IgE's will bind to the surface of mast cells, priming them to recognize the allergen the next time it enters the body, inducing sensitization (Burks, 2008).

1.1.2 Clinical manifestations and diagnosis of peanut allergy

The clinical expression of peanut allergy is predictable, and it has a tendency to be severe, although the severity may vary with different episodes of ingestion. Clinical symptoms develop within seconds and up to 2 h after ingestion of even a few milligrams of peanut protein. The mean age of diagnosis in children is 14 months, with symptoms occurring after the first known peanut ingestion in 75% of those children eating peanuts for the first time (Burks, 2008).

The symptoms of an IgE-mediated disorder are typically related to the skin, gastrointestinal tract, and respiratory tract and include (Burks, 2008):

- Skin symptoms: acute urticaria, angioedema, or a pruritic erythematous skin rash.

- Gastrointestinal symptoms: acute vomiting, and significant abdominal pain or diarrhea, or both.
- Respiratory symptoms: the upper and lower respiratory tract, although lower respiratory symptoms, including laryngeal edema, repetitive coughing, voice changes, and wheezing are the most important.

Anaphylaxis, a systemic allergic response, can include any of these symptoms, and additionally may include cardiovascular symptoms, such as hypotension and dysrhythmia (Burks, 2008).

Biphasic, or secondary late-phase allergic response up to 4 h later, has been noted in up to a third of patients with fatal or near fatal anaphylactic reactions. While these patients might seem to recover from their initial symptoms, secondary responses can be harder to treat. Individuals who have life-threatening or fatal reactions usually have asthma and frequently have a history of atopy, including food allergy in childhood, and are typically young adolescents or adults (Burks, 2008).

Evidence of peanut-specific IgE can be established by either allergy skin-prick testing or determination in vitro. Additionally, peanut-specific in-vitro IgE levels also indicate the likelihood of disease (Burks, 2008).

1.1.3 Current treatments in peanut allergy

The current available therapies for the treatment of peanut allergy are: 1) diagnosis and education of patients; 2) management of allergic responses and anaphylactic shock; 3) treatment with immunotherapy.

Several treatment strategies with the goal of curing or providing long-term remission from food allergy are under clinical investigation. Novel therapeutic approaches to food allergy can be classified as food allergen specific (e.g. immunotherapy with native or modified recombinant allergens, or oral desensitization) or food allergen nonspecific (e.g. anti-IgE, traditional Chinese medicine). However, some therapies in development appear to only temporarily desensitize or protect patients, requiring continued treatment to maintain efficacy. Before these new approaches are applied in clinical practice, they must be carefully evaluated for side effects, such as acute adverse reactions, toxicity, and overstimulation of Th1 immune responses that could prime for autoimmunity (Nowak-Wegrzyn, 2018a).

Oral immunotherapy (OIT) or subcutaneous immunotherapy to food are generating increasing interest as a potential approach to the treatment of food allergy. The primary goal is to induce permanent tolerance to the food, such that there can be periods of abstinence that do not lead to a recurrence of clinical reactivity upon reintroduction of the food.

Subcutaneous immunotherapy has been shown in numerous clinical trials, to be effective in reducing the clinical symptoms associated with peanut hypersensitivity among others. Its benefits may persist long after treatment discontinuation and include prevention of allergic disease progression. Overall, the therapy has proven to be safe and well tolerated. However, systemic allergic reactions may occur and these have the potential to be life threatening (Anagnostou et al., 2014).

A few randomized trials and uncontrolled studies of OIT for peanut allergy have demonstrated successful desensitization to peanut in most patients who are able to tolerate the therapy (See Effects in Humans, in section 5 of the current IB). Although few treated patients became tolerant, the rate of tolerance acquisition is higher than that seen in patients who completely avoid the allergen (Nowak-Wegrzyn, 2018b).

Patients on OIT are generally started on a very small daily dose of the food (e.g. 3 to 6 mg of food protein) and advanced periodically to a maintenance dose (e.g. 300 mg or, depending on the food and goals, 1 to 2 g of food protein daily) over several months (Kulis et al., 2018; Nowak-Wegrzyn, 2018b). The initial dose and dose increases are given under clinical supervision, whereas the remainder of the daily doses during the dose advancement phase and maintenance therapy are administered at home. The food included in OIT is usually otherwise strictly avoided in the diet during the duration of OIT. The frequency of dosing required to maintain desensitization is still unknown. Desensitization is defined as a state of temporary food allergen hyporesponsiveness and an increased threshold for reactions compared with the pre-OIT threshold. Desensitization provides protection from anaphylaxis to unintentional ingestion of small amounts of food allergen and is dependent upon a regular intake of the OIT dose. The desensitized state can be lost when OIT dosing is interrupted by illness or nonadherence. Sustained unresponsiveness or permanent tolerance is associated with lower pre-treatment levels of food-specific IgE and can be increased with longer duration of therapy (Nowak-Wegrzyn, 2018b).

Allergic reactions to OIT are common, particularly during the build-up phase of dosing, and occur at higher rates in patients on OIT than those avoiding the food. Although they are usually mild, allergic symptoms can lead to withdrawal from a study. Oral and gastrointestinal symptoms are the most common, followed by lower respiratory symptoms (eg, wheeze). Anaphylaxis is uncommon, but many small trials report at least one case. Cases of newly diagnosed eosinophilic esophagitis after undergoing OIT have also been reported (Nowak-Wegrzyn, 2018b). Therefore, although OIT has shown to be a promising treatment approach in peanut allergy, it still remains experimental and it has not yet been recommended for routine clinical practice because most OIT studies have been small and limited by various flaws that limit the impact of their findings.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of INP20

INP20, which is currently under pharmaceutical development, constitutes a novel pathway for the desensitisation in peanut allergy. In this case, the strategy is to achieve effectiveness with the administration of a fixed dose of peanut extract avoiding the need for a personalised treatment based on increasing doses as in OIT. Efficacy is fostered in INP20 by the presence of the nanoparticles, with function as carriers and adjuvants.

For further details, please refer to the [INP20 Investigator’s Brochure].

1.2.1.1 Non-clinical experience

For further details, please refer to the [INP20 Investigator’s Brochure].

1.2.1.2 Clinical experience

This is the first use of INP20 (First-in-human). Up to now, no clinical studies have been conducted with the IMP INP20. Nevertheless, the human exposure of the active ingredient, peanut extract, has extensively been studied in the clinical setting.

For further details, please refer to the [INP20 Investigator’s Brochure].

1.2.1.2.1 Clinical Pharmacology

Formal pharmacodynamic studies for immunotherapies and allergen products are considered equivalent as the immunological effect. Therefore, to show the effect of specific immunotherapy on the immune system immunological changes (e.g. changes in allergen-specific IgG levels, T-cell responses, and/or cytokine production) and/or modifications of the end-organ specific response (e.g. provocation tests) should be measured.

The treatment of peanut allergy is nowadays faced by researchers through OIT as a method to provide protection against accidental exposure to peanut. The OIT process consists of the ingestion of increasing amounts of the allergen over a period of months to achieve desensitization of the patient. The primary clinical objective of most OIT programs for food allergy is to induce a desensitized state in the individual, defined here as a temporary increase in the threshold reactivity to the allergen such that clinical protection from accidental ingestion may be achieved. This occurs through continuously stimulating the immune system with sub-threshold daily doses of allergen and then gradually escalating the dose level over time to reach a target maintenance dose. The oral route of administration may take advantage of the unique set of immune cells and pathways involved in the induction of oral tolerance. Protocols vary in their approaches to the initial dose escalation phase, but they consistently begin OIT with low doses (e.g. ≤5 mg of allergenic protein) and generally increase the doses by 25-100% at a periodic interval until the target maintenance dose is reached or a dose-limiting toxicity (DLT) occurs (Kulis et al., 2018).

Generally, the mechanism of action of OIT involve activation of gut mucosal dendritic cells, which affect the allergic response through immunomodulation of circulating effector cells. Other mechanisms have been shown to be important, including the increase in specific IgG4 and modulation of IgE responses (downregulation of Th2 responses) via suppression of basophils. As with other forms of immunotherapy, T regulatory cells (Treg) appear to have likely a pivotal role in various immunosuppressive pathways (Pajno et al., 2014).

1.2.1.2.2 Clinical Pharmacokinetics

INP20 is formulated in combination with zein nanoparticles. Furthermore, the main part of the extract is polypeptides and proteins, which are expected to be broken down to amino acids and small polypeptides.

There is no evidence to suggest that the allergens present in INP20 are absorbed into the vascular system. In addition, the absorption of INP20 is not expected from a physicochemical viewpoint since the particle size is higher than 100 nanometres and INP20 particles are positively charged, which impede mucin swelling and thereby increase viscosity to difficult its absorption. However, the Sponsor has performed biodistribution studies with radiolabelled non-loaded zein nanoparticles to confirm the absence of penetration through the gastrointestinal mucosa.

As this is a food-based product, typical metabolism and excretion studies are not applicable as the active substance is not metabolized by traditional drug metabolizing enzymes such as cytochromes but are degraded by natural enzymatic and metabolic pathways into natural components. Thus, peanut extracts and zein nanoparticles will be metabolized and degraded and the individual components recycled for further use and some eliminated as normal bodily waste.

1.2.1.2.3 Clinical Safety and Efficacy

OIT has proved high efficacy rates, improvement in quality of life, and a good safety profile in studies. However, the capacity of this therapy to induce long-term tolerance has not been demonstrated conclusively yet. Studies of OIT have shown that a high proportion of patients achieve desensitization in the short term (weeks–months), and a significant proportion of these achieve clinical tolerance in the long term (months–years) (Anagnostou et al., 2016).

INP20, which is currently under pharmaceutical development, constitutes a novel pathway for the desensitization in peanut allergy. In this case, the strategy is to achieve effectiveness with the administration of a fixed dose of peanut extract avoiding the need for a personalized treatment based on increasing doses as in OIT. Efficacy is fostered in INP20 by the presence of the nanoparticles, with function as carriers and adjuvants.

2 Rationale

2.1 Study rationale and purpose

Results obtained up to now from the non-clinical program currently conducted by the Sponsor with the developed formulated product INP20 peanut extract nanoparticles (NP), together with the expected results from the ongoing non-clinical studies are considered appropriate to support the First-in-human (FIH) trial.

The proposed FIH clinical trial is a Phase I/II randomized double-blind placebo-controlled study which includes two sequential periods:

- Part A consists on an early safety and tolerability assessment with the primary objective to determine the maximum tolerated dose (MTD), and to investigate the pharmacodynamics effects as secondary objective.
- Part B is an expanded cohort using the MTD with safety and tolerability as co-primary objectives, and potential efficacy and immunogenicity as secondary objectives.

2.2 Rationale for study design, dose and regimen selection

The design of this Phase I/II randomized double-blind placebo-controlled study was chosen to assess the efficacy (challenge test) and safety of INP20 in patients with peanut allergy.

The Product, INP20, has not been tested previously in humans and subsequently in the early stage of the clinical development, Phase I/II clinical trial, the primary endpoints must be safety and tolerability.

In Part A, 6 consecutive repeated oral-dose of INP20 will be administered to 6 cohorts of patients with peanut allergy: Group A: 0.15 mg once daily for 2 weeks (w), Group B: 1.5 mg once daily for 2 w, Group C: 5 mg once daily for 2 w, Group D: 10 mg once daily for 2 w, Group E: 20 mg once daily for 2 w, and Group F: 30 mg once daily for 2 w.

In Part B, three (3) groups will be evaluated for the study: two (2) doses of peanut proteins (dose and administration schedules depending on the preceding Part A study) or placebo.

The observations of IgG4 levels, as well as the basophils activation on the BAT analysis and tolerance of the treatment will determine the selected dose and posology.

2.3 Risks and benefits

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, and close clinical monitoring.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint*
Part A: Dose-ranging study (dose escalation)	
Primary	
• To determine the MTD and the recommended oral dose of INP20 in repeated-dose oral administration to patients with peanut allergy. The safety and tolerability of rising oral doses of INP20 will be assessed to identify a safe dose range for Phase II assay.	- Incidence of adverse events (AEs), serious adverse events (SAEs), treatment-related AEs/SAEs, and AEs/SAEs leading to discontinuation will be calculated and classified by body system and preferred term using MedDRA dictionary and EAACI guidelines criteria. - Systemic allergic symptoms and relatedness to treatment. - Physical examination and vital signs. - Peak flow. - Biological safety (laboratory): hematology, coagulation, biochemistry, urinalysis, and immunologic tests. - Number of participants with Dose-limiting toxicities (DLT).
Secondary	
• Pharmacodynamics	- The change in Immunoglobulin G subtype (IgG4) (as biomarkers of immunogenicity of allergen-specific immunotherapy) at the end of treatment and at month 1, month 2 and month 3.
Part B: Parallel Group Extension study	
Primary	
• To evaluate the safety and tolerability of INP20 in repeated-dose oral administration at the recommended dose(s) in patients with peanut allergy throughout the treatment period of 6 months.	- Incidence of adverse events (AEs), serious adverse events (SAEs), treatment-related AEs/SAEs, and AEs/SAEs leading to discontinuation will be calculated and classified by body system and preferred term using MedDRA dictionary and EAACI guidelines criteria. - Systemic allergic symptoms and relatedness to treatment. - Physical examination and vital signs. - Peak flow. - Biological safety (laboratory): hematology, coagulation, biochemistry, urinalysis, and immunologic tests.
Secondary	
• Potential efficacy	- To detect differences in increases in reaction thresholds (challenge scores) to peanut of treatment groups versus the placebo after 6 months of INP20 treatment. Challenges scores will be measured by the amount of cumulative peanut protein participants are able to ingest successfully without symptoms of an allergic reaction.
• Immunogenicity	- The change from baseline to 4 weeks, 3 and 6 months in allergen-specific biomarkers (or immune parameters) associated with INP20 immunotherapy in blood and

Objective	Endpoint*
	between-groups. Outcome variables of interest will include 1) peanut specific IgE, IgG, and IgG4 response against complete extract and some allergenic components of peanut; 2) specific basophil activation against NP, NP-peanut and peanut raw extract; 3) mast cell responses through skin prick testing and endpoint titration; and 4) specific T-cell cytokine responses (IL10, TGF-beta, IL4, IL5 and IL13) and T regulatory cell (Treg) activation (subpopulation Treg1 CD4+ CD25+).

* Refer to Sections 10.4 and 10.5 for details.

4 Study design

4.1 Description of study design

This is a multicentric double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients. The overall study design consists of two sequential periods of Part A and Part B (see Figure 4-1 and Figure 4-2, respectively).

In **Part A** (double blind, randomized, placebo-controlled, dose-escalation first phase study) in patients from ≥ 12 years old with a history of immediate hypersensitive reaction to peanut protein. Dose escalation at 6 different doses will be done, 8 patients to be treated at each dose once daily for 2 weeks. At each dose, 6 patients will receive INP20 and 2 placebo. The starting dose will be 0.15 mg. Dose escalation will only proceed after all 8 patients have completed the dose evaluation period (48h after administration of last dose). Patients who discontinue treatment for other reason than DLT will be replaced.

The starting dose (once daily dose) will be: Group A: 0.15 mg once daily for 2 weeks (w), Group B: 1.5 mg once daily for 2 w, Group C: 5 mg once daily for 2 w, Group D: 10 mg once daily for 2 w, Group E: 20 mg once daily for 2 w, and Group F: 30 mg once daily for 2 w. If any adverse reaction is observed with the first dose, the second dose might be reduced for this patient and the subsequent doses escalated until the initially planned dose is reached (doses to be decided case-by-case by the DEC). Then 48 patients are estimated to be assigned in consecutive order to one of 6 panels that match a dosing period. In each panel, the patients will be randomly assigned to receive INP20 (6 subjects), or placebo (2 subjects). Every patient will only receive one treatment in each panel.

The Maximum Tolerated Dose (MTD) is the highest dose at which a pre-specified percentage of patients experience a dose-limiting toxicity (DLT), with rates often ranging between 20-33% depending on the disease (Garrett-Mayer, 2006).

A Dose Escalation Committee (DEC) will evaluate the safety to proceed with Part B. Ultimately the DEC will the responsible to decide whether to increase the dose to the next level.

Eight (6 active and 2 placebo) patients are going to be treated at each dose level. The INP20 doses will be increased after a review of the data from the 8 patients at the lower dose of medication by the DEC. Dose escalation is allowed if none of the 8 patients in a dosing group experienced a dose limiting toxic effect as defined by a severe allergic reaction attributable to the study medication, such as anaphylaxis (defined as severe, life-threatening, generalized or systemic hypersensitivity reaction) according to the European Academy of Allergy and Clinical Immunology (EAACI) (Johansson et al., 2001). The escalation of dose will continue up to determine the MTD or the highest dose that is safe to administer to subjects and defines the upper limit of the usable dose range for further efficacy studies. The Part A study will stop at the dose at which a serious adverse event occurs in one (1) or two (2) patients depending on the severity of the event. The DEC will review in detail any DLT occurring during the study. In the presence of only one (1) DLT in a panel, and after exhaustively reviewing the case by the DEC, 8 more patients may be included in the same panel (6 active and 2 placebo), and dose escalation to the next panel will be allowed if none of this second group of 8 patients experience a DLT..

The DLT evaluation period will involve from the first dose of INP20 administered to the first patient in each panel until 48 hours after administration the last dose to the last patient in the panel.

In Part A the first two doses of study medication will be administered at hospital: the patient will stay at the hospital for 4 hours after the first dose of study medication, and 2 hours after

the second dose of study medication. If good tolerance is observed to the first and second doses, then the remaining doses could be taken at home (with daily monitoring for dose intake and tolerance through investigator's phone call) providing that the patient has easy access to healthcare services. Treatment will be interrupted in case of a DLT. In the event of non-severe reactions after the first dose, the DEC might decide whether treatment should be interrupted, reduced, and/or closely followed-up at the hospital. After minor reactions, such as oral pruritus, study treatment might be administered at home.

In **Part B** , both patients having and not having participated in Part A, might be included. Eligibility criteria will be reviewed for all patients, but after 12 months, the challenge test will be repeated only upon investigator criteria if the clinical situation of the patient has changed.for those patients rolling-over from Part A. Two (2) doses of peanut proteins (maintenance dose and administration schedules depending on the preceding Part A study) will be evaluated for the study. Following confirmation of peanut allergy at screening, patients will be randomized in a 1:1:1 ratio into three (3) different treatment groups, including D1b and D2b peanut protein and placebo. It is expected that 36 patients will continue in Part B (expected 20% rate of lost of follow-up).

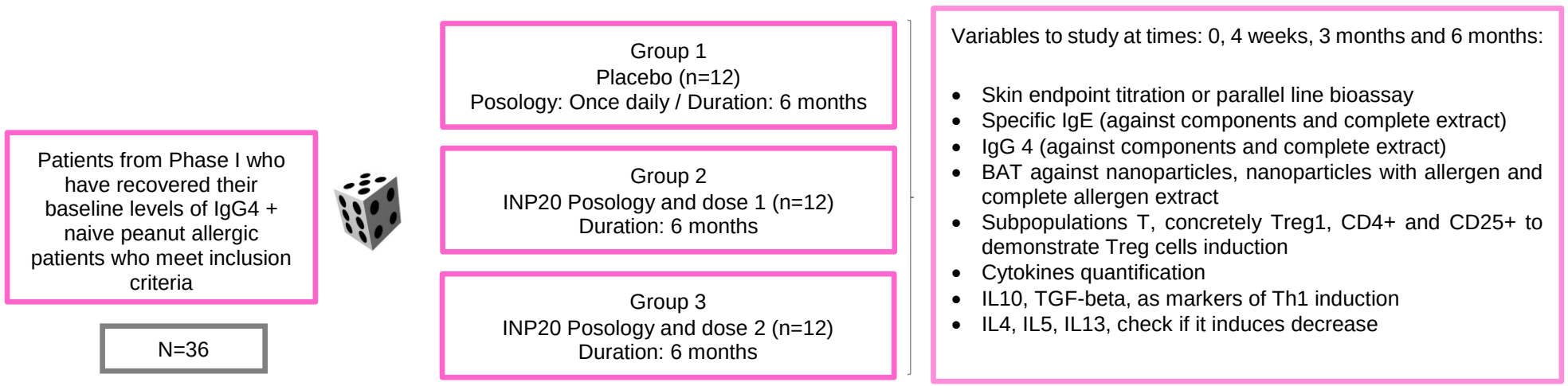
The treatment doses should be selected after the first phase study based on the IgG4 levels as well as BAT (basophils activation test) analyses and treatment tolerance. During Part B the patient will stay at the hospital for 2 hours after the first dose of study medication and the remaining doses will be taken at home. Refer to Section 7 for clinical assessments to be carried out at baseline, after 4 weeks, after 3 months and after 6 months (end of treatment).

Maximum duration of Part A should be 10 months to allow entry of patients in Part B without repeating the challenge test (the test should be repeated if more than 12 months are elapsed since the first test, and only upon investigation criteria if the clinical situation of the patient has changed for those patients rolling-over from part A). There will be, at least a 3-4 weeks washout period between Part A and Part B. Total duration of Part B will be of 9 months, 3 months for recruitment and 6 months of follow-up.

Overall, the **purpose** of the study will be to test the safety and tolerability of 6 rising repeated-dose oral administration of INP20 in patients with peanut allergy to establish the recommended dose and schedule for further phases of the study. In next Part B to assess potential efficacy, immunology and safety/tolerability of INP20 in the recommended orally two dose regimens previously evaluated in patients with peanut allergy.

Figure 4-1 Part A study design

Figure 4-2 Part B study design



4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned during this study. However, during the DEC meetings the course of the study will be discussed and analyzed, and any decisions taken will be documented.

4.3 Definition of end of the study

The study will end around 12 weeks (Part A) and 7 months (Part B) after LPFV (Last Patient First Visit). Study treatment will be provided until adverse events, unacceptable toxicities, physician's decision, patient decision, protocol deviation, study termination by the Sponsor, lost to follow-up, technical problems, pregnancy, patient withdrew consent or until the end of study, whichever event occurs first. Patients will be contacted for safety evaluations. All patients must have safety evaluations for 4 weeks, after the last dose of study treatment except if consent was withdrawn.

4.4 Early study termination

The study can be terminated at any time for any reason by the Sponsor, including a decision to suspend or discontinue the development of INP20. The coordinating/principal investigator may also terminate the study prematurely, including the discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study, or potential study patients.

The investigator will be responsible for informing the IEC and the Sponsor / the CRO will be responsible for informing the Health Authorities of the early study termination.

In case of early study terminations, the patients should be seen as soon as possible and the assessments for a discontinued or withdrawn patient should be performed. Patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during 4 weeks after the end of treatment. All patients must have safety evaluations for 4 weeks, after the last dose of study treatment except if consent was withdrawn.

5 Population

5.1 Patient population

This Phase I/II study will include individuals aged 12 to 65 years with a medical history of immediate hypersensitive reaction after peanut exposition, treatment-naïve, positive skin prick test to peanuts and positive by double-blind placebo-controlled food challenge (DBPCFC) at a cumulative dose of less than 8.5565 grams of peanut protein (refer to Appendix 14.2 for details on DBPCFC).

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Age 12 years and above of either sex, any race, any ethnicity at the time of the initial visit.
2. The presence of specific IgE to peanuts (a positive skin prick test to peanuts (diameter of wheal > 3.0 mm) and a positive peanut IgEs [CAP-FEIA] > 0.35 kUA/L.
3. A history of significant clinical symptoms (urticaria, angioedema, rhinorrhea, nasal congestion, pruritus, sneezing, abdominal pain, emesis, diarrhea, wheezing, shortness of breath, lip/tongue swelling, throat itching, throat swelling or impending sense of doom) occurring within 60 minutes after ingesting peanuts or history of unknown tolerance to peanut due to consumption avoidance.
4. Have a positive DBPCFC* to peanut at a cumulative dose of less than 8.5565 grams of peanut protein.
5. Provide signed informed consent for the participation in the study. In males and females aged 12-17 years old the informed consent will be signed and dated by them, and also by the parent(s) or the subject's legally acceptable representative(s).
6. Have self-injectable epinephrine available at home and be trained on its proper use.
7. Potentially fertile women (defined as all women physiologically capable of becoming pregnant) must agree to be sexually inactive or to use appropriate contraceptive measures for the duration of the study and for 1 month afterward.
8. Patients rolling from part A to part B must have recovered their baseline levels of IgG4.

** The oral challenge test will be considered positive when the patient shows objective clinical symptoms after the administration of one of the doses, or in case of showing subjective clinical symptoms, they are of great intensity (severe abdominal pain) and they persist (untreated or after administration of placebo treatment) for at least 30 minutes after the ingestion of a dose, or subjective moderate clinical symptoms (visual analogue scale) > 2 after ingestion of three consecutive doses*.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. History of severe anaphylaxis to peanut as defined by respiratory distress with cyanosis, hypoxemia (O2 Sat <92%) or, in the absence of other clinical records, severe dyspnea; hypotension with or without loss of consciousness; or relaxation of sphincters.
2. Currently participating in another study using an investigational new drug.

3. Participation in any interventional study, specific oral or sublingual immunotherapy building up phase for the treatment of food allergy in the past 12 months. Patients in treatment with specific oral maintenance phase of OIT will be considered individually, to investigator's discretion.
4. Use within the past year of any systemic immunomodulatory treatment (i.e. cyclosporine, omalizumab, etc.), including inhalants immunotherapy building up phase. It is allowed the use of immunotherapy in the maintenance dosing against pollens, mites, animal dander and/or alternaria.
5. Allergic to placebo ingredients or reacts to any dose of placebo during study entry double blind placebo-controlled food challenge (DBPCFC).
6. Patients allergic to corn food.
7. Poor control or persistent activation of severe atopic dermatitis.
8. Moderate to severe persistent asthma as defined using the Impairment or Risk Criteria of the current NHBLI Guidelines for the Diagnosis and Management of Asthma (https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma).
9. Currently being treated with greater than medium daily doses of inhaled corticosteroids (fluticasone >500 µg per day, ciclesonide >400 µg per day or budesonide >800 µg per day) or montelukast. Two or more systemic corticosteroid courses for asthma in the past year or 1 oral corticosteroid course for asthma within 3 months prior to the enrollment or between the enrollment and the beginning of treatment.
10. Poorly controlled Asthma as defined using the Control Criteria of the current NHBLI Guidelines for the Diagnosis and Management of Asthma (https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma).
11. Prior intubation/mechanical ventilation for asthma.
12. Chronic gastrointestinal diseases including Celiac Disease, Inflammatory Bowel Disease, Eosinophilic Gastrointestinal Disorders, Irritable Bowel Syndrome, gastric or intestinal cancer, diverticulitis and active peptic ulcer or recurrent gastrointestinal symptoms of undiagnosed etiology in the past year.
13. Primary or secondary immunodeficiency, including IgA deficiency; HIV positive, or immunopathology of any kind.
14. History of other chronic diseases (except asthma, rhinitis, atopic dermatitis) and severe requiring treatment (type I diabetes or uncontrolled type 2 diabetes, uncontrolled hypertension, heart disease, etc.); malignancies or serious psychological disorders.
15. Have a severe reaction at initial double-blind placebo-controlled food challenge, defined as either:
    - Life-threatening anaphylaxis (with severe hypotension and/or severe bronchospasm), or
    - Reaction requiring hospitalization.
16. Inability to discontinue antihistamines for 7 days before skin testing and oral food challenges (OFCs).
17. Patients diagnosed with other serious food allergies defined as those who have required intubation and/or ICU admission.

18. Chronic use of beta blockers, angiotensin converting enzyme inhibitors, or monoamine oxidase inhibitors, proton pump inhibitors, H2-bloquers, prokinetic drugs and laxatives.
19. Women of childbearing potential (defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 1 month after stopping medication) who are pregnant, planning to become pregnant, or breastfeeding.
20. Highly effective contraception methods include: a) total abstinence (when this is in line with the preferred and usual lifestyle of the patient); b) total sterilization (bilateral oophorectomy with/without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment; c) male sterilization at least 6 months prior to screening; d) use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%) such as hormonal vaginal ring or transdermal hormone contraception. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study may also exclude a participant from the study.
21. Poor compliance expected by the patient.

6 Treatment

6.1 Study treatment

The investigational drug to be used in this study is INP20 and the corresponding matching placebo.

6.1.1 Dosing regimen and treatment duration

In Part A (dose escalation study), consecutive oral INP20 will be administered at the following ascending doses:

Group A: 0.15 mg once daily for 2 weeks (w), Group B: 1.5 mg once daily for 2 w, Group C: 5 mg once daily for 2 w, Group D: 10 mg once daily for 2 w, Group E: 20 mg once daily for 2 w, Group F: 30 mg once daily for 2 w. If any adverse reaction is observed with the first dose, a dose escalation with dilutions (as inpatient) may be done until the planned dose is reached.

In Part B, oral INP20 at two (2) doses (maintenance dose and administration schedules depending on the preceding Part A study) or placebo will be randomly administered in a 1:1:1 ratio to an expanded cohort of patients with peanut allergy for a total duration of 6 months.

The patient will be given a daily diary to record the date and clock time of treatment intake.

Patients may receive treatment as outlined in Figure 4-1, Figure 4-2.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

The initial doses proposed in the Phase I/II study were fine-tuned based on the literature regarding similar approaches. Therefore, the initial doses to be administered in humans were derived from oral food challenges (OFC) studies from the literature that use graded, incremental doses administered at fixed interval (Wensing et al., 2002; Blom et al., 2013; Zurzolo et al., 2013; Allen et al., 2014; Ballmer-Weber et al., 2015; Klemans et al., 2015). Eliciting Dose (ED) is defined as the estimated dose likely to elicit reactions (Ballmer-Weber et al., 2015). The ED10, for example, is the estimated dose likely to induce a reaction in the 10% of European population with food allergy. The eliciting dose (ED) for a peanut allergic reaction in 5% of the peanut allergic population (ED05) has been estimated at 1.5 mg of peanut protein (Zurzolo et al., 2013). This ED05 estimate was derived from the statistical dose-distribution of incremental doses challenge trials of peanut allergic individuals (children and adult) and was validated in a multicenter single dose challenge study (Zurzolo et al., 2013).

6.2.2 Guidelines for dose escalation and determination of INP20

In **Part A, dose escalation at** 6 different doses of INP20 will be done, supervised by a DEC. At each dose cohort and for 2 weeks, 6 patients will receive INP20 and 2 patients placebo, no cross-over being permitted.

Consecutive oral INP20 administration at following ascending doses: Group A: 0.15 mg once daily for 2 weeks (w), Group B: 1.5 mg once daily for 2 w, Group C: 5 mg once daily for 2 w, Group D: 10 mg once daily for 2 w, Group E: 20 mg once daily for 2 w, and Group

F: 30 mg once daily for 2 w. If any adverse reaction is observed with the first dose, a dose escalation with dilutions (as inpatient) may be done until the planned dose is reached.

Eight (6 active and 2 placebo) patients are going to be treated at each dose level. The INP20 doses will be increased after a review of the data from the 8 patients at the lower dose of medication by the DEC. Dose escalation is allowed if none of the 8 patients in a dosing group experienced a dose limiting toxic effect. The escalation of dose will continue up to determine the MTD or the highest dose that is safe to administer to subjects and defines the upper limit of the usable dose range for further efficacy studies. The Part A study will stop at the dose at which a serious adverse event occurs in one (1) or two (2) patients depending on the severity of the event. The DEC will review in detail any DLT occurring during the study. In the presence of only one (1) DLT in a panel, and after exhaustively reviewing the case by the DEC, 8 more patients may be included in the same panel (6 active and 2 placebo), and dose escalation to the next panel will be allowed if none of this second group of 8 patients experience a DLT.

The DLT evaluation period will involve from the first dose of INP20 administered to the first patient in each panel until 48 hours after administration the last dose to the last patient in the panel.

6.2.3 Definitions of dose limiting toxicities (DLTs)

A dose limiting toxic effect is defined by a severe allergic reaction attributable to the study medication, such as anaphylaxis (defined as severe, life-threatening, generalized or systemic hypersensitivity reaction) according to the European Academy of Allergy and Clinical Immunology (EAACI) (Johansson et al., 2001).

6.3 Dose modifications

6.3.1 Dose modification, dose interruption and dose delay

In Part A, no INP20 dose modification within a treatment group is allowed. If any adverse reaction is observed with the first dose, the second dose might be reduced for this patient and the subsequent doses escalated until the initially planned dose is reached (doses to be decided case-by-case by the DEC). For patients who do not tolerate the dosing schedule due to drug related toxicities, the patient will be discontinued from study treatment.

In Part B, any clinically relevant, as determined by the investigator, Grade 4 AE related to INP20 should lead to treatment interruption. In case of Grade <4 AE related to INP20, the DEC will decide the corresponding modification on an individual basis.

Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Section 7.1.3.

These changes must be recorded in the CRF.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently according to the institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed

necessary. All patients must be followed up for adverse events and serious adverse events for 4 weeks following the last dose of INP20.

6.4 Concomitant medications

Conventional pharmacokinetic drug interaction studies are usually not relevant for food extracts as they are not metabolized by cytochromes nor subject to uptake by transporters. No studies of PK and/or PD interactions have been performed at this stage of the development.

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications taken after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications CRF.

6.4.2 Permitted concomitant therapy requiring caution and/or action

The following treatments are permitted with caution and/or action:

- Inhaled corticosteroid. It is prohibited to exceed following doses: fluticasone >500 µg per day, ciclesonide >400 µg per day or budesonide >800 µg per day.
- Following rescue drugs: oral or IV antihistamine, oral or systemic or corticoid, epinephrine.
- Beta 2 agonist used as rescue medication
- Subcutaneous immunotherapy with aeroallergens at maintenance dose. Patient in building-up phase within the 12 months before start of study treatment are excluded.
- Specific oral immunotherapy for any other food allergen at maintenance dose, if considered acceptable by the investigator. Patients in building-up phase within the 12 months before start of study treatment are excluded.

6.4.3 Prohibited concomitant therapy

During all the trial, at least the following treatments will be forbidden among others which might be added:

- Montelukast
- Beta-blockers
- ACE inhibitors
- MAO inhibitors
- Proton pump inhibitors: the dose frequency allowed is not higher than once per week
- H2-blockers

- Prokinetic drugs
- Macrolides
- Oral laxatives. Microenemas are allowed
- Peripherally acting anti-obesity drugs (lipase inhibitors) like orlistat
- Immunomodulatory and immunosuppressive
- NSAIDs. Acetaminophen (paracetamol) and COX2 inhibitors are allowed
- Any type of sublingual specific immunotherapy

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Pat. No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the study. The Pat. No. consists of the Center Number (Center No.) (assigned by the Sponsor / the CRO to the center) with a sequential subject number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Pat. No. provided to the investigator by the CRO. Patients having participated in Part A will retain the same Pat.No. in Part B.

Once assigned, the Pat. No. must not be reused for any other patient and must not be changed. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page.

6.5.2 Treatment assignment or randomization

Patients will be assigned to INP20 or placebo according to a randomization list. The randomization numbers will be generated by Syntax using a validated system to ensure that treatment assignment is unbiased, that automates the random assignment of patient numbers to randomization numbers.

6.5.3 Treatment blinding

This is a double-blind study. Patients, investigators, study team, or anyone involved in evaluating the drugs during the study conduct will remain blinded to the identity of the treatment from the time of randomization until database lock.

The identity of the treatments will be concealed by the use of investigational drugs (INP20 or INP20 matching placebo) that are identical in packaging, labeling and schedule of administration. The INP20 matching placebo for Part A will be mannitol, which is different in appearance, therefore the labels will be big enough to cover the vial. Furthermore, at hospital the preparation and administration of investigational drugs will be carried out by a different person (nurse) than the one evaluating the drugs (investigator). The study medication will be administered by the nurse at hospital and by the patient himself at home. The INP20 matching placebo for Part B will be administered at home by the patient himself (except the first dose).

Unblinding of study drug assignment will only occur for safety reasons in the case of patient emergencies (to be decided by the DEC), for regulatory reporting purposes and at the conclusion of the study.

6.6 Study drug preparation and dispensation

The Investigator or responsible site personnel must instruct the patient to take the study treatment as per protocol. Study treatment will be dispensed to the patient by authorized site personnel only (nurse). All dosages prescribed to the patient must be recorded on the Dosage Administration Record CRF. The patient will be given a daily diary to record the date and clock time of treatment intake.

INP20 and INP20 matching placebo will be supplied as powder for oral administration.

The INP20 matching placebo (administered at hospital) will be mannitol, which is clearly different in appearance, therefore preparation and administration of investigational drugs will be carried out by a different person (nurse) than the one evaluating the drugs (investigator). The nurse will dissolve either INP20 or INP20 matching placebo (mannitol) into water. Mannitol is easily dissolved while the nanoparticles are difficult to dissolve and present a milky yellowish appearance. The preparation will be administered immediately to the patient. The study medication will be administered by the nurse at hospital the first and second day of Part A when the patient will stay at the hospital for 4 hours after the first dose of study medication, and 2 hours after the second dose of study medication administration. For Part B, the patient will stay at the hospital for 2 hours after the first dose of study medication which will be administered by the nurse.

6.6.1 Study drug packaging and labeling

Medication labels will be in the local language and comply with the legal requirements. They will include storage conditions for the drug and study number but no information about the patient.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study medication should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the nurse/study personnel (other than the investigator) at each patient visit (Part A and Part B) and information provided by the patient daily diary (Part B) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. For Part A, the study medication will be administered by the study nurse the first two days and might be administered the following days by the patient. For Part B, the patient will be given a daily diary to record the date and clock time of study medication intake.

6.6.3.2 Study drug accountability

The study nurse or designee (other than the investigator) must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the nurse will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the study monitor.

6.6.4 Disposal and destruction

The study drug (used and unused) can only be destroyed by the Sponsor.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 list all of the assessments and indicate with an “X”, the visits when they are performed.

All data obtained from these assessments must be supported in the patient’s source documentation.

Table 7-1 Visit evaluation schedule – Part A (dose-ranging study)

	Screening Period	Study treatment (14 days)				Premature EOT	Safety FU [B]		
Day/Week	**D-56 to D-1**	**D1**	**D2**	**D7**	**D14 (+2) [A] EoT**	**< D14**	**D28 PT (±3)**	**D56 PT (±3)**	**D84 PT (±3)**
Patient history									
Demography	X								
Inclusion/exclusion criteria	X	X							
Randomization		X							
Medical History	X								
Diagnosis	X								
Prior and Concomitant Medications	X	Continuous X							
Physical examination	X	X			X	X	X		
Vital signs	X	X			X	X	X		
Spirometry	X								
Peak flow measurement	X	X			X	X			
Laboratory evaluations									
Hematology	X				X	X			
Biochemistry	X				X	X			
Coagulation	X				X	X			
Urinalysis	X				X	X			
Immunology tests	X								
Pregnancy test	X				X	X			
Safety evaluations									
ECG	X								
AEs/SAEs [C]	X	Continuous							
Allergic symptoms		Continuous							
Efficacy evaluations									
Challenge test [D]	X								
Other evaluations									
IgG4 [E]	X				X	X	X	X	X
BAT [E]	X						X		
Biomarkers [E]	X				X	X			
Study treatment									
INP20/placebo dispensation		X	X	X					
INP20/placebo administration		X (daily administration)							

AE = Adverse Event, BAT = Basophil Activation Test, D = Day, ECG = Electrocardiogram, EoT = End of Treatment, FU = Follow-up, PT = post dose, SAE = Serious Adverse Event, W = Week.

[A] Allergic symptoms must be evaluated 48 hours after last study treatment administration. If "End of treatment" visit is done before these 48 hours, the allergic symptoms must be evaluated by a phone call.

[B] Day count after last dose (post dose; PT) of study treatment. Safety FU visits will be performed on D14 PT, D28 PT and every 28 days (±3) until consent withdrawal, start of Part B or end of study, whichever occurs first.

[C] AEs and SAEs must be followed for 4 weeks after the last dose of INP20/placebo. Patients interrupting/permanently discontinuing treatment due to AE, must be followed-up at least once a week for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever occurs first (see Section **Error! Reference source not found.**).

[D] To be performed on two different days, as described in Appendix 2. Challenge test validity period is up to 6 months.

[E] To be performed before challenge test.

Table 7-2 Visit evaluation schedule – Part B (extension study)

	Screening Period	Study treatment (6 months)					Premature EoT	Safety FU
Day/Week/Month	**D-56 to D-1**	**D1**	**D14**	**D28±7 (W4)**	**D84±7 (W12)**	**D168±7 (W24) EoT**	**<D168 (W24)**	**D28 PT (±7) [A]**
Patient history								
Demography	X							
Inclusion/exclusion criteria	X	X						
Randomization		X						
Medical History	X							
Diagnosis	X							
Prior and Concomitant Medications	X	Continuous					X	X
Physical examination	X			X	X	X	X	X
Vital signs	X	X		X	X	X	X	X
Spirometry	X							
Peak flow measurement	X	X		X	X	X	X	
Laboratory evaluations								
Hematology	X					X	X	
Biochemistry	X					X	X	
Coagulation	X					X	X	
Urinalysis	X					X	X	
Immunology tests	X							
Pregnancy test	X					X	X	
Safety evaluations								
ECG	X							
AEs/SAEs [B]	X	Continuous [B]						
Allergic symptoms		Continuous						
Efficacy evaluations								
Challenge test [C]	X					X	X	
Other evaluations								
IgG4 [D]	X			X	X	X	X	
BAT [D]	X			X	X	X	X	X
Biomarkers [D]	X			X	X	X	X	X
Study treatment								
INP20/placebo dispensation		X		X	X			
INP20/placebo administration		X (daily administration)						

	AE = Adverse Event, BAT = Basophil Activation Test, D = Day, ECG = Electrocardiogram, EoT = End of Treatment, FU = Follow-up, PT = post dose, SAE = Serious Adverse Event, W = Week. [A] Day count after last dose (post dose; PT) of study treatment. [B] AEs and SAEs must be followed for 4 weeks after the last dose of INP20/placebo. Patients interrupting/permanently discontinuing treatment due to AE, must be followed-up at least once a week for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever occurs first (see Section **Error! Reference source not found.**). [C] To be performed on two different days, as described in Appendix 2. For patients rolling over from Part A, screening challenge test is only required if more than 12 months have elapsed since last test and only upon investigation criteria if the clinical situation of the patient has changed for those patients rolling-over from part A . Newly performed challenge test have a validity of 6 months. [D] To be performed before challenge test.

7.1.1 Screening

The informed consent form, approved by the corresponding IEC, must be signed and dated before any screening procedures are performed.

Patients must meet all inclusion and none of the exclusion criteria at screening to be eligible for the study.

7.1.1.1 Information to be collected on screen failures

Screen failures include any patient who signed the informed consent form but failed to start study treatment for any reason.

The following information must be collected for all screen failure patients: demographic information, informed consent, inclusion/exclusion criteria and, if applicable, SAEs, death and/or consent withdrawal. A screening failure log will be generated for these patients.

7.1.1.2

Data collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis, and any other assessments carried out to determine the eligibility for inclusion in the study.

7.1.2 Treatment period

Patients will undergo clinical assessments at scheduled visits as per Table 7-1. Refer to Section 4.1, Section 6.3.1, Figure 4-1 and Figure 4-2 for details.

Study treatment will be administered at the corresponding scheduled dose unless the patient experiences unacceptable toxicity, and/or treatment is discontinued at the discretion of the investigator or the patient. If a patient permanently discontinues study treatment, then the patient must follow an End of Study treatment visit with the appropriate follow-up assessments.

7.1.3 Discontinuation of Study Treatment

Patients are free to discontinue from the study treatment at any time and for any reason. In addition, the investigator and or the study Sponsor may also discontinue study treatment and assessments if deemed necessary.

Potential reasons for withdrawal of patients from study treatment are:

- Adverse events
- Death
- Lost to follow-up
- Physician’s decision
- Pregnancy
- Major Protocol deviation

- Study termination by the Sponsor
- Technical problems
- Unacceptable toxicities (including DLTs)
- Withdrawal of consent
- Requirement of a prohibited medication (except isolated use of NSAIDs)

The reason and date of patient discontinuation from the study treatment will be documented in the CRF (e.g. lost to follow-up, consent withdrawn, incorrect enrolment, AEs, etc.). In case of study treatment discontinuation, the investigator should attempt to continue all study assessment until the end of study or at least assessments as per end of study treatment visit.

Patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during 4 weeks after the end of treatment. All patients must have safety evaluations for 4 weeks, after the last dose of study treatment except if consent was withdrawn.

7.1.3.1 Replacement policy

On part A patients withdrawn for any reason except DLT and patients not evaluable due to low treatment adherence (<80%) will be replaced. Patients will not be replaced on part B. However, depending on the evolution, each case will be individually reviewed by the investigator together with the CRO / the Sponsor to decide if the patient should be replaced.

7.1.4 Withdrawal of Consent

Patients may withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact. Study treatment must be discontinued, and no further assessments will be conducted, however, all data that have already been collected before withdrawal of consent will be retained and used by the Sponsor.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.5 Follow up Period

All patients will be followed for safety evaluation for 4 weeks following the last dose of study treatment. The assessments to be performed are indicated in Table 7-1.

After this follow-up period, all patients will be managed/followed as per usual clinical practice.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy will be assessed with the challenge test.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, peak flow, laboratory results (hematology, coagulation, biochemistry, urinalysis and immunologic tests), number of participants with DLTs, allergic symptoms, as well as collection of the AEs. For details on AE collection and reporting, refer to Section 8. All safety assessments the first day of treatment have to be conducted prior to start of the first dose of study treatment, unless otherwise specified.

7.2.2.1 Physical examination

A physical examination will be performed at screening and as indicated in Table 7-1 (Part A) / Table 7-2 (Part B) and will include cardiopulmonary and skin exploration.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History CRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event CRF page.

7.2.2.2 Vital signs

Vital signs (sitting pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1 (Part A) / Table 7-2 (Part B).

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator if medically indicated and will be recorded as unscheduled assessment.

7.2.2.3 Spirometry

Spirometry will be measured as indicated in Table 7-1 (Part A) / Table 7-2 (Part B) as per institutional standards.

7.2.2.4 Peak flow measurement (PEF)

PEF measurement will be measured as indicated in Table 7-1 (Part A) / Table 7-2 (Part B) as per institutional standards.

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed will be evaluated as per Table 7-3 below and according to Table 7-1 (Part A) / Table 7-2 (Part B). More frequent evaluations may be performed at the investigator’s discretion if medically indicated; results should be recorded as unscheduled laboratory assessments.

Table 7-3 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, red blood cells, WBC with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Coagulation	Prothrombin rate, cephaline time
Biochemistry	Urea, creatinine, glucose, total protein, albumin, total and conjugated bilirubin, ALT, AST, alkaline phosphatase, LDH, GGT, sodium, potassium, chlorides, bicarbonates, calcium and phosphorus
Urinalysis	Macroscopic Panel (Dipstick) (pH, proteins, blood, glucose, ketone, bilirubin and urobilinogen)
Immunology	HIV1/2, HBs Ag, anti-HBc IgG Ab and anti-HCV Ab
Pregnancy Test	Serum or urine samples for women of childbearing potential

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B).

7.2.2.5.2 Coagulation

Coagulation outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B).

7.2.2.5.3 Clinical chemistry

Clinical chemistry panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B).

7.2.2.5.4 Urinalysis

Urinalysis panel outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B).

7.2.2.5.5 Immunology

Immunology tests outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B).

7.2.2.5.6 Pregnancy testing and assessments of fertility

Pregnancy tests will be performed for women of child bearing potential as outlined in Table 7-3 and as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B).

7.2.3 Other assessments

7.2.3.1 Pharmacodynamic

The pharmacodynamic effects will be performed as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B), and will be investigated through the change in Immunoglobulin G subtype (IgG4) (as biomarkers of immunogenicity of allergen-specific immunotherapy) and basophil activation on the BAT (basophil activation test) analysis.

7.2.3.2 Allergen-specific biomarkers

Allergen-specific biomarkers (or immune parameters) will be performed as per the assessment schedule in Table 7-1 (Part A) / Table 7-2 (Part B), and will include, among others:

1) specific IgE, IgG, and IgG4 against complete extract and some allergenic components of peanut;

2) specific basophil activation against NP, NP-peanut and peanut raw extract;

3) mast cell responses through skin prick testing and endpoint titration;

4) specific T-cell cytokine responses (IL10, TGF-beta, IL4, IL5 and IL13) and T regulatory cell (Treg) activation (subpopulation Treg1, CD4+ and CD25+);

7.2.3.3 Future biomarker research and sample repository

All residual samples after protocol-defined studies are completed will be stored in a central sample repository as a collection. The samples in the study repository might be used for future biomarker research to improve understanding of the study treatment, peanut allergy, related diseases, and adverse events, and/or for the development of potential, associated diagnostic assays. Samples will be stored up to 15 years or until they are exhausted, whatever occurs first, in accordance with applicable local regulations (Law 14/2007 on Biomedical Research and the Royal Decree 1716/2011).

A separate, specific signature will be required to document a patient's agreement to allow future biomarker research and storage in repository of any remaining samples. Labels of biological samples will not contain any clinical information of patients.

Samples from site 01 will be stored in the biorepository “BIOBANCO UNIVERSIDAD DE NAVARRA”. Responsible for the sample’s custody is “Universidad de Navarra - Clínica Universidad de Navarra – CUM”. The repository will be located in Avenida Pio XII 55 31008, Pamplona, Navarra. Contact details: biobanco@unav.es; phone: (+34)948194700.

Samples from site 02 will be stored in the biorepository “BIOBANCO NAVARRABIOMED”. Responsible for the sample’s custody is “FUNDACIÓN MIGUEL SERVET”. The repository will be located in Irunlarrea 3, 31008, Pamplona, Navarra. Contact details: Biobanco.navarrabiomed@navarra.es; phone: (+34) 848426000.

Samples will be stored as two separate collections and registered in the National Registry of Biobanks, in agreement with article 37 of the Royal Decree 1716/2011.

Results derived from the analysis of biological samples of a patient will not be provided to the investigators, unless patient explicitly requests this information, in compliance with local and national law. Patient must be informed that those results are for investigational use only and should not be used for treatment decision.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the CTCAE version 5.0.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe and life-threatening, and death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected on a Death eCRF form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met

If the event worsens, then the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an adverse event should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Results in death.
- Is life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition.

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 28 days after the patient has stopped study treatment must be reported to Optimapharm Safety Department / the Sponsor within 24 hours of learning of its occurrence at:

Optimapharm Safety Department

safety@optimapharm.eu

Fax: +34 932 75 43 96

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 28-day safety evaluation follow-up period (whichever is longer) should only be reported if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form within 24 hours to Syntax for Science Safety Department / the Sponsor. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the Sponsor study treatment, further information may urgently be required from the investigator for Health Authority reporting. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with the corresponding regulatory requirements, as soon as possible and in any event not later than seven days after the Sponsor became aware of the reaction, and no later than 15 days after the Sponsor became aware of the reaction for the rest of the cases.

8.3 Pregnancies

No pregnancy is expected for this study. However, if there is any pregnancy case, to ensure patient safety, each pregnancy occurring during the study when the patient is on study treatment must be reported to Syntax for Science Safety Department / the Sponsor within

24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pregnancy Report Form. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure (IB). Additional safety information collected between IB updates will be communicated to Investigators. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Dose Escalation Committee

There will be a Dose Escalation Committee (DEC) comprising one representative from InnoUp Farma), the Coordinator Investigators and one representative from the CRO. The DEC should meet on a regular basis (either physically or by teleconference) and will be responsible for decisions regarding increasing the dose and making recommendations on the conduct of the study.

9 Data collection and management

9.1 Data confidentiality

In order to maintain patient privacy, all data capture records, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The full patient name should never be used in any correspondence with the Sponsor or on the case record forms.

The investigator will grant monitor(s) and auditor(s) from the CRO and/or the Sponsor, and/or Regulatory Authority(ies) direct access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. Direct access includes examining, analyzing, verifying, and reproducing any recorded and reports that are important to the evaluation of the monitoring. The investigator is obliged to inform the patient that his/her study-related records will be viewed without violating their confidentiality and that the collected information will only be made publicly available to the extent permitted by the applicable laws and regulations. The Investigator and any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

If a subject revokes authorization to collect or use the study-related information (accepted by signing the corresponding ICF), only the information collected prior to the revocation of subject authorization will be used. However, the investigator should attempt to obtain permission to collect follow-up safety information at the end of the scheduled study period.

The data collection system for this study will use built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, the CRO / the Sponsor personnel will review the protocol, CRFs and Patients daily diaries with the investigators and their staff. During the study, the monitor will visit the study site on a regular basis (at least once a month) to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any study specific documents such as CRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained from all participants (a signed copy has been given to the patient)
- AEs have been reported as required
- Data are being accurately recorded in the CRFs
- IMP is being stored correctly and drug accountability is being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the study
- The Investigator and the site are receiving sufficient information and support throughout the study

All information recorded on CRFs must be traceable to source documents in the patient's file. Moreover, during monitoring visits the data recorded in the CRFs, source documents

and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the subject in the study i.e. source data verification. The patient daily diary is considered a source document.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs will have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

Data management and handling will be conducted according to the study specific Data Management Plan with ICH guidelines and the CRO Standard Operating Procedures (SOPs).

Data entry, validation, and data queries will be handled by the CRO Data Management Team via the EDC system. The data will be subjected to validation according to the CRO SOPs in order to ensure accuracy in the collected CRF data. Designated investigator staff will have to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Before database closure a reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets. Authorization will be required prior to making any database changes to locked data.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in a study specific Data Management Report.

10 Statistical methods and data analysis

A Statistical Plan will be defined by Syntax to conduct the clinical study. Syntax will perform all analyses. Data from all participating centers will be combined in the analyses. Final analyses will be performed at study termination.

Descriptive analysis will be undertaken for all safety determination in Part A to allow Part B continuation.

Safety variables will be analyzed in the Safety Population which must include the set of all participants taking at least one dose of the study treatment, including those who have not completed the study.

Efficacy and Immunological variables will be analyzed in the Per-Protocol and Intention-To-Treat populations.

Data will be summarized with regard to demographic and baseline characteristics, and safety observations and measurements.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented. Individual subject data will be listed. Tables and listings will also be presented globally, by treatment and by dose level.

10.1 Analysis sets

10.1.1 Full Analysis Set

All patients who received at least one dose of the study drug, including those who did not complete the study. Safety set and full analysis set (FAS) are the same in this study.

10.1.2 Modified Full Analysis Set

The modified FAS set will be FAS patients with evaluable samples for pharmacodynamic / biomarker evaluations. Part A and Part B will each have their own separated sets.

10.1.3 Safety Set

All patients who received at least one dose of the study drug, including those who did not complete the study. Safety set and FAS are the same in this study.

10.1.4 Per-protocol set

Part A:

The per-protocol set (PPS) will include the subset of the patients in the FAS without major protocol deviations, not discontinuing prematurely for reasons other than DLTs and with a study treatment compliance of at least 80%.

Part B:

The per-protocol set (PPS) will include the subset of the patients in the FAS without major protocol deviations.

10.1.5 Intention-to-treat set

The intention-to-treat set (ITT) will include all patients who were enrolled and randomly allocated to treatment. Part A and Part B will each have their own separated sets.

10.1.6 Modified intention-to-treat set

The modified ITT set will be ITT patients with evaluable samples for pharmacodynamic / biomarker evaluations. Part A and Part B will each have their own separated sets.

10.2 Patient demographics/other baseline characteristics

The safety set will be used.

Subject disposition, demographic and other baseline data will be presented using summary statistics.

Relevant medical history and current medication at baseline will be presented by system organ class and preferred term for all patients.

Tables and listings will also be presented globally, by arm and by dose level.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented. Individual subject data will be listed. Tables and listings will also be presented globally, by arm and by dose level.

Number of patients treated, number of doses administered, and duration of dosing (weeks), will be summarized and listed by dose level to describe the extent of exposure to INP20 in the all treated/safety population. Treatment interruption and re-administration will also be described (if any).

Concomitant medication and concomitant therapy will be summarized as number of subjects being treated with each type of medication/therapy classified according to the Anatomical Therapeutic Chemical (ATC) classification system and World Health Organization (WHO) Drug Dictionary preferred term for all patients.

Listing of previous medications stopped before the first INP20 administration will be produced.

10.4 Primary objective

Part A: Dose-ranging study

To determine the maximum tolerated dose (MTD) and the recommended oral dose of INP20 in repeated-dose oral administration to patients with peanut allergy. The safety and tolerability of rising oral doses of INP20 will be assessed to identify a safe dose range for Phase II assay.

Part B: Extension study

To evaluate the safety and tolerability of INP20 in repeated-dose oral administration at the recommended dose(s) in patients with peanut allergy throughout the treatment period of 6 months.

10.4.1 Variable

Safety:

Proportion of patients with AEs, CTCAE Grade AEs, SAEs, AEs leading to discontinuation (withdrawal rate), and deaths.

Changes between baseline and post-baseline laboratory parameter and vital signs.

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 Dose-Limiting Toxicities

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 5.0 and type of adverse event.

10.4.2.2 Other safety endpoints

10.4.2.2.1 Analysis set and grouping for the analyses

The safety set will be used for all analyses.

10.4.2.2.2 Adverse events (AEs)

All safety analyses will be performed on the Safety Set. All AEs will be graded according to the CTCAE v.5.0.

Overview of AEs summarizing the number (percentage) of patients with any AE, any grade 3-4 AE, any serious AE, any AE leading to death, any AE leading to dose reduction, any AE leading to dose delay, and any AE leading to permanent treatment discontinuation (withdrawal rate).

The number (percentage) of patients who die by study period (on-study, on-treatment) and the cause of death (disease progression, AEs, other) will be tabulated.

The clinical laboratory data (including hematology, coagulation, serum biochemistry, immunology and urinalysis) will be graded according to the CTCAE v.5.0 scale, when applicable. When the CTCAE scale is not applicable, the out-of-normal laboratory range value analysis will be performed. Clinical laboratory values will be analyzed after conversion into standard international units.

Appropriate summary statistics will be provided for the analyses of vital signs.

10.4.2.2.3 Laboratory abnormalities

For laboratory data, summary statistics will be produced for observed values and for changes from baseline to each visit. In addition, the number of abnormal and clinically significant observations will be tabulated by visit. Abnormal values will be flagged in listings.

Shift tables will show the number of subjects who changed from below, within or above the reference range at baseline to below, within or above the reference range at each time of assessment.

10.4.2.2.4 Other safety data

Other safety data will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Physical examination

Physical examination data will be summarized in tables.

Vital signs

Vital signs will be summarized together with changes from baseline, and clinical significance. Data on vital signs will be tabulated and listed, notable values will be flagged.

10.4.2.3 Tolerability

Tolerability will be summarized in terms of dose reductions or drug interruption due to an AE by treatment cohort.

10.4.2.4 Supportive analyses

Any analyses performed in support of the primary analysis will be defined in the SAP prior to clinical database lock.

10.5 Secondary objectives

Part A: Dose-ranging study

To investigate the pharmacodynamics effects of rising oral doses of INP20 on Serum IgG4 concentrations in patients allergic to peanuts.

Part B: Extension study

To assess potential efficacy in an expanded treatment cohort using the recommended dose(s) / schedule of INP20 versus placebo group after 6 months of treatment.

To assess the change in immune parameters associated with the therapeutic process of INP20 in repeated-dose oral administration at the recommended dose(s) in patients with peanut allergy at baseline and Months 1, 3 and 6.

10.5.1 Secondary Efficacy objectives

Differences in increases in reaction thresholds (challenge scores) to peanut of treatment groups versus the placebo after 6 months of INP20 treatment. Challenges scores will be measured by the amount of cumulative peanut protein participants are able to ingest successfully without symptoms of an allergic reaction.

In order to analyze at a molecular level the potential changes that the treatment with INP20 could cause on the patients participating in this clinical trial, their blood lymphocytes will be challenged to evaluate the performance of these cells before and after 14 days of treatment with INP20.

Lymphocytes will be challenged with different doses of the peanut extract and their behavior and release of cytokines related to the Th1, Th2 or Treg immune response will be assessed.

This information will be useful to evaluate potential indications of surrogate efficacy since with such a short treatment (14 days) the clinical answer will be likely to be meaningless, even though there are changes at the molecular level.

10.5.2 Pharmacodynamics

The change in Immunoglobulin G subtype (IgG4) (as biomarkers of immunogenicity of allergen-specific immunotherapy)

10.5.3 Biomarkers

The change from screening to 2 weeks for Part A and for Part B from screening to 4 weeks, 3 and 6 months in allergen-specific biomarkers (or immune parameters) associated with INP20 immunotherapy in blood and between-groups.

Outcome variables of interest will include, among others:

1) peanut specific IgE, IgG, and IgG4 response against complete extract and some allergenic components of peanut;

2) specific basophil activation against NP, NP-peanut and peanut raw extract;

3) mast cell responses through skin prick testing and endpoint titration;

4) specific T-cell cytokine responses (IL10, TGF-beta, IL4, IL5 and IL13) and T regulatory cell (Treg) activation (subpopulation Treg1 CD4+ CD25+);

10.6 Other measurements

10.6.1 Immunogenicity

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented to describe actual standardized scores and absolute changes from baseline.

10.7 Interim analysis

No formal interim analysis is planned during this study. However, during the DEC meetings the course of the study will be discussed and analyzed, and any decisions taken will be documented.

10.8 Sample size calculation

The sample size for this Phase I/II study follows empirical considerations and no formal sample size estimation will be considered.

In part A of the study, for each dose level, eligible patients with an immediate hypersensitivity reaction after peanut ingestion, positive skin prick test to peanuts, and positive by double-blind placebo-controlled food challenge (DBPCFC), will be randomly allocated to receive either the study drug or placebo (6+2), respectively.

It is estimated that 48 patients with peanut allergy of either sex will be included in six (6) dose level groups of 8 subjects (six receiving active, two receiving placebo). Two (2) back-up patients will be screened for each dose level (or panel). Patients from Part A plus an extra group of treatment-naïve patients (if required) with peanut allergy after checking they meet eligibility criteria will be re-randomized to be included in the 'Parallel Group Extension Study' (Part B). **Part B** assay will consist of 3 arms, placebo plus two (2) dosing schedules to be selected after the first phase of the study. The planned sample size for this part will be 12 patients each dose level. It is expected a lost of follow-up percentage of about 20%, thus a total of 36 patients are expected to continue in Part B.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study must be conducted in accordance with the protocol, with the regulatory requirements, with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), and with the ethical principles laid down in the Declaration of Helsinki and all applicable amendments as adopted by the World Medical Association.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the informed consent form(s) (ICFs) must be submitted to a properly constituted Independent Ethics Committee (ICE) for review and approval before study start. Approval/favorable opinion must be obtained in writing before the first subject can be recruited.

Prior to study start, the investigator is required to sign the protocol signature page confirming his/her agreement to conduct the study in accordance with the protocol/ICFs and all the instructions and procedures found in this protocol and to give access to all relevant data and record to monitors, auditors, IECs, and regulatory authorities as required.

11.3 Informed consent procedures

Eligible subjects may only be included in the study after receiving written and verbal information regarding the study and after providing written IEC-approved informed consent. The signed informed consent (including parental consent for patients < 18 years) must be obtained before any study-related procedures, and the date of signature should be documented in the source documents and CRFs.

A copy of the signed and dated written Informed Consent Form will be provided to the subject.

11.4 Discontinuation of the study

The study is planned to be terminated after completion of the last follow-up. However, the study may be prematurely terminated by the Investigator or the Sponsor under the conditions specified in the study agreement.

11.5 Publication of study protocol and results

After completion of the study, a clinical study report (CSR) will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) by the CRO in close collaboration with the Investigator and the Sponsor.

All publications and presentations must be based upon the CSR. All information supplied by the Sponsor in connection with this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IMP and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences.

The Sponsor may choose to publish or present data from this study. If an Investigator is offered authorship, he/she will be asked to critically review the article for important intellectual content and approve the version to be published. The Sponsor has the right to use the results for registration and internal presentation and for promotion of the Sponsor's commercial interests.

11.6 Study documentation, record keeping and retention of documents

It is the responsibility of the principal investigator at the study center to keep all essential documents relating to the trial for at least 25 years after the completion or premature termination of the clinical study. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and show whether the institution complied with the principles and guidelines of GCP.

The medical files of subjects enrolled into the study must be kept in accordance with the corresponding legislation and for the maximum period of time permitted by the institution. The Sponsor is required to keep all other documentation for the life of the product studied. The archived data can be kept in electronic form, provided that a back-up copy is kept and that a paper copy can be provided if necessary.

The protocol, ethical and government approvals, together with all other documents concerning the study, including any audit and inspection certificates are all to be kept as part of the study master reference file. All data about serious adverse events also need to be kept in this study master file. Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

All data should be available for inspection by the appropriate authorities on demand.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the CRO / the Sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Audits or inspections, including source data verification, may be performed by representatives of the CRO, the Sponsor, the Health Authorities and/or an IEC.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators will apply due diligence to avoid protocol deviations. However, any deviation to the study protocol will be documented in a Protocol Deviation Log. The classification of subjects into protocol violators will be made during a meeting before database lock. The classification will be mutually agreed between the Sponsor and the CRO. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol and/or ICF can only be made in a written protocol/ICF amendment that must be approved by the CRO, the Sponsor, the Health Authorities, and the IEC. Only amendments that are required for patient safety may be implemented prior to IEC approval. In such cases, the Sponsor should be notified of this action and the IEC at the study site should be informed according to the corresponding regulations but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: Clinical Study Protocol Agreement Form

I have read the clinical study protocol entitled “A multicenter double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients” and verified that it contains all necessary information for conducting the study.

I hereby confirm that:

- I have carefully read and understood this clinical study protocol
- My staff and I will conduct the study according to the study protocol and will comply with its requirements, including ethical and safety considerations.

I understand that, should the Sponsor decide to prematurely terminate or suspend the study for whatever reason, such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the study I will immediately communicate such a decision to the Sponsor.

I agree not to publish any part of the results of the study carried out under this clinical study protocol without consulting the Sponsor.

Principal Investigator:

_____	_____	_____
Name	Signature	Date

14.2 Appendix 2: Challenge testing: DBPCFC

The oral peanut challenge will be performed when patient is diagnosed and included in the study and, in Part B, also after the end of study treatment. A positive DBPCFC to peanut at a cumulative dose of less than 10 grams of peanut protein will be one criterion for entry into this study. Following the "Guideline on the Clinical Development of Products for specific Immunotherapy for the treatment of Allergic Diseases" (CHMP/EWP/18504/2006, 2008) for specific immunotherapy trials patients should have a well-documented history of their allergic condition before study entry. Sometimes, even after performing skin tests and blood tests, an allergist is unable to arrive at a definitive diagnosis. According to PRACTALL Consensus ("Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology–European Academy of Allergy and Clinical Immunology) (Sampson et al., 2012), the DBPCFC has become known as the gold standard to accurately diagnose food allergy.

The challenge will be double-blind and placebo-controlled and will be performed with peanut flour. The active meal and placebo will be administered randomly on separate days. The dose increases will be done each 30 minutes and as shown in Table 14-2 (expressed in peanut proteins quantity) derived from oral food challenges (OFC) studies from the available literature that use graded, incremental doses administered at fixed interval (Wensing et al., 2002; Blom et al., 2013; Zurzolo et al., 2013; Allen et al., 2014; Ballmer-Weber et al., 2015; Klemans et al., 2015).

Table 14-2 Estimation of the threshold dose for allergic reaction to peanut in peanut allergic subjects

Dose	Proteins quantity (mg/g)	Prevalence (%) of clinical reactivity in peanut allergic children and adults receiving the ED dose.
1	1.5 mg (ED05)	5
2	5 mg (ED10)	10
3	50 mg	38
4	500 mg	76
5	1 g	86
6	2 g	90
7	5 g	96

Abbreviations: ED: eliciting dose

The oral challenge will be done according to the established protocol and, once completed, the patient will remain under observation for two hours. The maximum nominal total dose administered will be 5 g of peanut protein (8.5565 g maximum cumulative dose) unless the challenge is interrupted before because of the presence of symptoms. Once the end of the challenge test is reached, the patient should stay under observation for two hours if he has not shown symptoms before.

Once the challenge test has been completed (both administration days, including the 2 hours symptoms observation period), the blind will be opened to evaluate the outcome of the test and the patient's eligibility. The oral challenge test will be considered positive when the patient shows objective clinical symptoms after the administration of one of the doses, or in case of showing subjective clinical symptoms, they are of great intensity (severe abdominal pain) and they persist (untreated or after administration of placebo treatment) for at least 30 minutes after the ingestion of a dose, or subjective moderate clinical symptoms (visual analogue scale) > 2 after ingestion of three consecutive doses.

Study INP20

"A multicenter double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients"

Statistical Analysis Plan Final Part A
Version 1.0,
31 October 2025

Sponsor: InnoUp Farma, S.L.

Study code: INP20-01

Prepared by: Mª Dolores Pérez Rodríguez
Biostatistician Lead
Evidenze Health España, S.L.U.

Approved by: Sara Gómez Martínez
Chief Technology Officer
Innoup Farma SL

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Version 1.0, 31 October 2025

Study title: A multicenter double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients.

Study code: INP20-01

	SIGNATURE	DATE
SPONSOR: Sara Gómez Martínez Chief Technology Officer Innoup Farma SL	Sara Gómez 31/10/2025 17:37:00 +01:00 I hereby confirm the document approval	
CRO: Mª Dolores Pérez Rodríguez Biostatistician Lead Evidenze Health España, S.L.U.	Mª Dolores Pérez Rodríguez 31/10/2025 22:38:06 +01:00 I am the author of the document	

TABLE OF CONTENTS

1 GLOSSARY

AE	Adverse Event
ALT/GPT	Alanine aminotransferase/glutamic pyruvic transaminase
AST/GOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
BAT	Basophil Activation Test
CRF/eCRF	Case Report/Record Form / electronic Case Record/Report Form
DBPCFC	Double-blind placebo-controlled food challenge
FEV1	Forced Expiratory Volume
FVC	Forced Vital Capacity
GGT	Gamma-glutamyl transferase
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
IL	Interleukin
INR	International Normalized Ratio
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NP	Nanoparticles
PEF	Peak Flow Measurement
PT	Preferred Term
PTT	Partial thromboplastin time
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SPSS	Statistical Package for the Social Sciences
SET	Skin Endpoint Titration
SD	Standard deviation
SOC	System Organ Class
SPT	Skin Prick Test
TGF	Transforming Growth Factor

2 INTRODUCTION

This document refers to Part A of clinical trial INP20. Its purpose is to provide a summary of the data collected for Part A of the study.

3 PROTOCOL AND CRF VERSION

Protocol version: 4.0, 07.10.2021

CRF version: Final, 09.03.2020

4 OBJECTIVE AND DESIGN

4.1 OBJECTIVES OF THE ANALYSIS PLAN

The analysis plan proposed below describes the aspects needed to know about the study and the statistical analysis methods to be used to apply them to the data collected and respond to the study objectives.

4.2 PRIMARY STUDY OBJECTIVE

The main objective of the protocol study in this part A is to determine the MTD. This objective is achieved by the DEC (Dose Escalation Committee).
The main objective of the analysis proposed in this document is to perform the descriptive analysis of part A of the INP20 project, focused on safety.

4.3 SECONDARY STUDY OBJECTIVE

The secondary objective is the descriptive analysis of part A of the INP20 project, focused on pharmacodynamics.

4.4 STUDY DESIGN

This is a multicenter double-blind, randomized, placebo-controlled phase I/II study to determine the safety, tolerability, potential efficacy and dose finding of INP20, an oral formulation for treatment of immunotherapy in peanut-allergic patients. The overall study design consists of two sequential periods of Part A and Part B.
In **Part A** (double blind, randomized, placebo-controlled, dose-escalation first phase study) in patients from ≥ 12 years old with a history of immediate hypersensitive reaction to peanut protein, 6 consecutive repeated oral-dose of INP20 will be administered to 6 cohorts of patients with peanut allergy once daily for 2 weeks. The study will test groups of 8 different patients during 6 dosing periods (or panel).

Consecutive oral INP20 administration at following ascending doses: Group A: 0.15 mg once daily for 2 weeks (w), Group B: 1.5 mg once daily for 2 w, Group C: 5 mg once daily for 2 w, Group D: 10 mg once daily for 2 w, Group E: 20 mg once daily for 2 w, and Group F: 30 mg once daily for 2 w. If any adverse reaction is observed with the first dose, a dose escalation with dilutions (as inpatient) may be done until the planned dose is reached. Then it is estimated that 48 patients will be assigned to one of 6 panels that match a dosing period. In each panel, the patients will be randomly assigned to receive INP20 (6 subjects), or placebo (2 subjects). Every patient will only receive one treatment in each panel.

The closure of the study in its part A is planned for September 2025.

4.4.1 Blinding and unblinding part A

This is a double-blind study. There is not an unblinding plan described in the protocol. By sponsor indication when the study Part A is completed, may unblind patients to study treatment assignment.

The blind will be opened after the closing of the database for Part A and before starting the statistical analyses, following the methodology described in this document.

Final analyses Part A for safety and efficacy will be conducted, using unblinded data.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age 12 years and above of either sex, any race, any ethnicity at the time of the initial visit.
2. The presence of specific IgE to peanut (a positive skin prick test to peanuts (diameter of wheal > 3.0 mm) and a positive peanut IgEs [CAP-FEIA] > 0.35 kUA/L.
3. A history of significant clinical symptoms (urticaria, angioedema, rhinorrhea, nasal congestion, pruritus, sneezing, abdominal pain, emesis, diarrhea, wheezing, shortness of breath, lip/tongue swelling, throat itching, throat swelling or impending sense of doom) occurring within 60 minutes after ingesting peanuts or history of unknown tolerance to peanut due to consumption avoidance.
4. Have a positive double blind placebo-controlled food challenge (DBPCFC)* to peanut at a cumulative dose of less than 10 grams of peanut protein.
   **The oral challenge test will be considered positive when the patient shows objective clinical symptoms after the administration of one of the doses, or in case of showing subjective clinical symptoms, they are of great intensity (severe abdominal pain) and they persist (untreated or after administration of placebo treatment) for at least 30 minutes after the ingestion of a dose, or subjective moderate clinical symptoms (visual analogue scale) > 2 after ingestion of three consecutive doses.*
5. Provide signed informed consent for the participation in the study. In males and females aged 12-17 years old the informed consent will be signed and dated by them, and also by the parent(s) or the subject's legal acceptable representative(s).
6. Have self-injectable epinephrine available at home and be trained on its proper use.
7. Potentially fertile women (defined as all women physiologically capable of becoming pregnant) must agree to be sexually inactive or to use appropriate contraceptive measures for the duration of the study and for 1 month afterward.

5.2 EXCLUSION CRITERIA

1. History of severe anaphylaxis to peanut as defined by respiratory distress with cyanosis, hypoxemia (O2 Sat <92%) or, in the absence of other clinical records, severe dyspnea; hypotension with or without loss of consciousness; or relaxation of sphincters.
2. Currently participating in another study using an investigational new drug.
3. Participation in any interventional study, specific oral or sublingual immunotherapy building up phase for the treatment of food allergy in the past 12 months. Patients in treatment with specific oral maintenance phase of OIT will be considered individually, to investigator's discretion.

4. Use within the past year of any systemic immunomodulatory treatment (i.e. cyclosporine, omalizumab, etc.), including inhalants immunotherapy building up phase. It is allowed the use of immunotherapy in the maintenance dosing against pollens, mites, animal dander and/or alternaria.
5. Allergic to placebo ingredients or reacts to any dose of placebo during study entry DBPCFC.
6. Patients allergic to corn food.
7. Poor control or persistent activation of severe atopic dermatitis.
8. Moderate to severe persistent asthma as defined using the Impairment or Risk Criteria of the current NHBLI Guidelines for the Diagnosis and Management of Asthma (https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma)
9. Currently being treated with greater than medium daily doses of inhaled corticosteroids (fluticasone >500 µg per day, ciclesonide >400 µg per day or budesonide >800 µg per day) or montelukast. Two or more systemic corticosteroid courses for asthma in the past year or 1 oral corticosteroid course for asthma within 3 months prior to the enrollment or between the enrollment and the beginning of treatment.
10. Poorly controlled Asthma as defined using the Control Criteria of the current NHBLI Guidelines for the Diagnosis and Management of Asthma (https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma).
11. Prior intubation/mechanical ventilation for asthma.
12. Chronic gastrointestinal diseases including Celiac Disease, Inflammatory Bowel Disease, Eosinophilic Gastrointestinal Disorders, Irritable Bowel Syndrome, gastric or intestinal cancer, diverticulitis and active peptic ulcer or recurrent gastrointestinal symptoms of undiagnosed etiology in the past year.
13. Primary or secondary immunodeficiency, including IgA deficiency; HIV positive, or immunopathology of any kind.
14. History of other chronic diseases (except asthma, rhinitis, atopic dermatitis) and severe requiring treatment (type I diabetes or uncontrolled type 2 diabetes, uncontrolled hypertension, heart disease, etc.); malignancies or serious psychological disorders.
15. Have a severe reaction at initial double-blind placebo-controlled food challenge, defined as either:

- Life-threatening anaphylaxis (with severe hypotension and/or severe bronchospasm), or
- Reaction requiring hospitalization.

16. Inability to discontinue antihistamines for 7 days before skin testing and oral food challenges (OFCs).
17. Patients diagnosed with other serious food allergies defined as those who have required intubation and/or ICU admission.
18. Chronic use of beta blockers, angiotensin converting enzyme inhibitors, or monoamine oxidase inhibitors, proton pump inhibitors, H2-bloquers, prokinetic drugs and laxatives.

19. Women of childbearing potential (defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 1 month after stopping medication) who are pregnant, planning to become pregnant, or breastfeeding.
20. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study may also exclude a participant from the study.
21. Poor compliance expected by the patient.

6 ANALYSIS POPULATION

All analysis, Efficacy and Safety, will be based on the randomized and treated population (RT), defined as all randomized patients receiving at least 1 dose of blinded study drug.

No checks of the selection criteria will be made.

7 STATISTICAL ANALYSIS METHODS

For this Part A data analysis no methods are described in the protocol. Before sponsor unblinding of the database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan.

Continuous variables will be described through centralization and dispersion statistics: mean, standard deviation (SD), first (Q1) and third quartile (Q3), minimum and maximum.
Categorical variables will be described through absolute and relative frequencies (N and %).

Missing data will not be imputed and will be left as missing.

All analyses will be presented by group (A/B/C/D/E/F). Furthermore, within each group, the treatment arm (INP20/Placebo) will be differentiated. The analysis will be descriptive. No hypothesis tests will be performed (associated p values will not be displayed).

Data will be analyzed using SPSS (v30.0 or later) or SAS (version 9.4).

8 DATABASE LOCK AGREEMENT

If anomalous and/or inconsistent values are detected in any table of results, the database will not be reopened for modification, but instead the anomalous data and the manner in which it was processed will be highlighted (for example, by assigning non-existent data or eliminating the case depending on the statistical method to be used in the analysis in question).

Any modification to this table will be set out in writing in the report, along with the procedure followed (for example, assignment of non-existent data, interpolation, elimination of the case, etc.).

For the final statistical analysis, the database will only be reopened and the study data and tables that could be modified will be re-analysed if the sponsor deems it necessary due to the inconsistencies identified. If this occurs, the additional work required to complete this process should be assessed.

9 DESCRIPTIVE STATISTICAL ANALYSIS

For qualitative variables (•) frequencies (N, %) will be shown and for quantitative variables (❖) descriptive statistics will be shown (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N).

All analyses will be presented by group (A/B/C/D/E/F). Furthermore, within each group, the treatment arm (INP20/Placebo) will be differentiated. Associated p values will not be displayed (see table below).

	Group A		Group B		Group C		Group D		Group E		Group F	
	INP20	P (*)	INP20	P (*)	INP20	P (*)	INP20	P (*)	INP20	P (*)	INP20	P (*)
Variable 1												
Variable 2												
…												

(*) P = Placebo.

This will be the table model except in those sections where a different one is specified.

9.1 PATIENT DISPOSITION

A schematic of patients included in the study will be shown.
In addition, it will be shown whether any patient doesn't meet at least one of the selection criteria and, if so, which criteria are not met.

9.2 RANDOMIZATION

- Has the patient been randomized? (No / Yes). If “yes”,
  - Study part A Group (Group A / Group B / Group C / Group D / Group E / Group F) (*).
  - Treatment arm (INP20/Placebo). A contingency table between “Group” and “treatment arm” will be shown.

(*) Group A: 0.15 mg once daily for 2 weeks, Group B: 1.5 mg once daily for 2 weeks, Group C: 5 mg once daily for 2 weeks, Group D: 10 mg once daily for 2 weeks, Group E: 20 mg once daily for 2 weeks, Group F: 30 mg once daily for 2 weeks.

9.3 SCREENING (DAYS -56 TO -1)

9.3.1 DEMOGRAPHY

❖ Age, defined as the time elapsed, in years, between the date of birth until the date of signature.

- Sex (Male / Female)

9.3.2 MEDICAL HISTORY

- Number of total clinical significant disease registered and number of patients with at least one clinical significant disease.

A table will be displayed with the number of clinical significant disease (type) and the number of patients with at least one clinical significant disease (type). The percentage will be shown based on the total number of patients in the study. This analysis will be performed for each of the groups (A / B / C / D / E / F) separately, differentiating between INP20 and placebo.

9.3.3 PHYSICAL EXAMINATION

- Has been the physical examination performed? (No / Yes). If “yes”,
  - Cardiopulmonary exploration. A new variable will be created with the following categories:
    - Normal, when the investigator consider “cardiopulmonary exploration” = “Normal”.
    - Abnormal - Not clinically significant, when the investigator consider “cardiopulmonary exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
    - Abnormal - Clinically significant, when the investigator consider “cardiopulmonary exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
    - ND, when the investigator consider “cardiopulmonary exploration” = “ND”.
  - Skin exploration. A new variable will be created with the following categories:
    - Normal, when the investigator consider “skin exploration” = “Normal”.
    - Abnormal - Not clinically significant, when the investigator consider “skin exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
    - Abnormal - Clinically significant, when the investigator consider “skin exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
    - ND, when the investigator consider “skin exploration” = “ND”.

9.3.4 VITAL SIGNS

- Has been the vital signs evaluated? (No / Yes). If “yes”,
  - ❖ Sitting pule rate (beats/minute).
  - ❖ Systolic blood pressure (mmHg).
  - ❖ Diastolic blood pressure (mmHg).

9.3.5 SPIROMETRY

- Has been the spirometry evaluation performed? (No / Yes). If “yes”,
  - ❖ FVC (%).
  - ❖ FEV1 (L).
  - ❖ FEV1/FVC.
  - ❖ PEF (L/s).

9.3.6 LABORATORY

9.3.6.1 Hematology

- Has been the hematology performed? (No / Yes). If “yes”,
  - Hematocrit (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Hemoglobin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Red blood cells (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - White blood cells (total) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Neutrophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Lymphocytes (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Eosinophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Basophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Monocytes (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Platelet count (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.3.6.2 Biochemistry

- Has been the biochemistry performed? (No / Yes). If “yes”,
  - Total bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Conjugated bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Alkaline phosphatase (ALP) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

- SGOT (AST) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- SGPT (ALT) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- GGTP (GGT) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- LDH (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Urea (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Creatinine (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Albumin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Total protein (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Glucose (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Sodium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Calcium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Potassium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Chlorides (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Bicarbonates (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Phosphorus (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.3.6.3 Coagulation panel

- Has been the coagulation panel performed? (No / Yes). If “yes”,
  - INR (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - PTT (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.3.6.4 Urinalysis

- Has been the urinalysis performed? (No / Yes). If “yes”,
  - pH (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Proteins (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Blood (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Glucose (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Ketones (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Urobilinogen (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.3.6.5 Immunology

- Has been the immunology performed? (No / Yes). If “yes”,
  - HIV 1/2 (Positive/ Negative / ND).
  - HBs Ag (Positive/ Negative / ND).
  - Anti-HBc IgG Ab (Positive/ Negative / ND).
  - Anti-HCV Ab (Positive/ Negative / ND).
  - IgA levels (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.3.7 SAFETY EVALUATIONS

- Has been the ECG performed? (No / Yes). If “yes”,
  - ❖ PR (s).
  - ❖ QRS (s).
  - ❖ QT (s).
  - ❖ QTcF (s).
  - Overall interpretation (Normal / Abnormal, not clinically significant / Abnormal, clinically significant / ND)

9.3.8 DBPCFC

9.3.8.1 DAY 1

- Dose (1 (1,5 mg) / 2 (5 mg) / 3 (50 mg) / 4 (500 mg) / 5 (1 g) / 6 (2 g) / 7 (5 g) / 8 (10 g)).
- Information regarding the dosis for which the test has tested positive. A multiple response table will be shown with the following options:
  - OAS - itching and tingling sensation on lips, oral cavity, auditory canal, throat.
  - Bl - blisters of the oral mucosa.
  - U – urticaria.
  - AE – angioedema.
  - F – flush.
  - R – rhinitis.
  - C – conjunctivitis.
  - L - larynx-edema.
  - Co – cough.
  - D – dyspnea.
  - BS - (objective) bronchospasm: positive lung auscultation and/or significant decrease of basal FEV1 (>12%) or PEF (>20%).
  - Dph – dysphagia.

- G - gastric pain and/or burning, abdominal pain.
- N – nausea.
- E – emesis.
- Di – Diarrhoea.
- BP - drop of blood pressure (at least 20 mm Hg).
- S – shock.
- Gpru - generalised pruritus.
- Lpru - local pruritus.
- Other.

- Interval (from intake to start of symptom/s) (<1 min / 1-5 min / >5-10 min / >10-15 min / >15-20 min / >20)
- Whole dose ingested? (No / Yes).
- Stop criteria applied: In case that the challenge has been stopped before the last dose:
  - Occurrence of objective symptoms (No / Yes / NA).
  - Occurrence of severe persistent (45 min) subjective symptoms (No / Yes / NA).
  - Occurrence or moderate (EVA>2) subjective symptoms in three consecutive dosis (No / Yes / NA).
  - Others (No / Yes / NA).
- Outcome of day 1 challenge (Positive / Negative).
- Challenge day 1 (Active / Placebo).

9.3.8.2 DAY 2

- Dose (1 (1,5 mg) / 2 (5 mg) / 3 (50 mg) / 4 (500 mg) / 5 (1 g) / 6 (2 g) / 7 (5 g) / 8 (10 g)).
- Information regarding the dosis for which the test has tested positive. A multiple response table will be shown with the following options:
  - OAS - itching and tingling sensation on lips, oral cavity, auditory canal, throat.
  - Bl - blisters of the oral mucosa.
  - U – urticaria.
  - AE – angioedema.
  - F – flush.
  - R – rhinitis.
  - C – conjunctivitis.
  - L - larynx-edema.
  - Co – cough.
  - D – dyspnea.
  - BS - (objective) bronchospasm: positive lung auscultation and/or significant decrease of basal FEV1 (>12%) or PEF (>20%).
  - Dph – dysphagia.

- G - gastric pain and/or burning, abdominal pain.
- N – nausea.
- E – emesis.
- Di – Diarrhoea.
- BP - drop of blood pressure (at least 20 mm Hg).
- S – shock.
- Gpru - generalised pruritus.
- Lpru - local pruritus.
- Other.

- Interval (from intake to start of symptom/s) (<1 min / 1-5 min / >5-10 min / >10-15 min / >15-20 min / >20)
- Whole dose ingested? (No / Yes).
- Stop criteria applied: In case that the challenge has been stopped before the last dose:
  - Occurrence of objective symptoms (No / Yes / NA).
  - Occurrence of severe persistent (45 min) subjective symptoms (No / Yes / NA).
  - Occurrence or moderate (EVA>2) subjective symptoms in three consecutive dosis (No / Yes / NA).
  - Others (No / Yes / NA).
- Outcome of day 2 challenge (Positive / Negative).
- Challenge day 2 (Active / Placebo).

9.3.9 PHARMACODYNAMICS EVALUATIONS

9.3.9.1 Ig G4 evaluation

- Has been the Ig G4 evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig G4 levels (mg/dL).
  - ❖ Ig G4 levels against complete peanut extract (mg/dL).
  - ❖ Ig G4 levels against component Ara h 1 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 2 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 3 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 9 (mg/dL).

9.3.10 ALLERGEN-SPECIFIC BIOMARKERS

9.3.10.1 Ig E evaluation

- Has been the Ig E evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig E levels (mg/dL).
  - ❖ Ig E levels against complete peanut extract (mg/dL).
  - ❖ Ig E levels against component Ara h 1 (mg/dL).
  - ❖ Ig E levels against component Ara h 2 (mg/dL).
  - ❖ Ig E levels against component Ara h 3 (mg/dL).
  - ❖ Ig E levels against component Ara h 9 (mg/dL).

9.3.10.2 Ig G evaluation

- Has been the Ig G evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig G levels (mg/dL).
  - ❖ Ig G levels against complete peanut extract (mg/dL).
  - ❖ Ig G levels against component Ara h 1 (mg/dL).
  - ❖ Ig G levels against component Ara h 2 (mg/dL).
  - ❖ Ig G levels against component Ara h 3 (mg/dL).
  - ❖ Ig G levels against component Ara h 9 (mg/dL).

9.3.10.3 Skin Prick Test (SPT)

- Has been the Skin Prick Test (SPT) performed? (No / Yes). If “yes”,
  - Result against NP (Positive / Negative / ND).
  - Result against NP-peanut (Positive / Negative / ND).
  - Result against peanut raw extract (Positive / Negative / ND).

9.3.10.4 Skin Endpoint Titration (SET)

- Has been the Skin Endpoint Titration (SET) performed? (No / Yes). If “yes”,
  - Result against NP (Positive / Negative / ND).
  - Result against NP-peanut (Positive / Negative / ND).
  - Result against peanut raw extract (Positive / Negative / ND).

9.3.10.5 Treg-cell (subpopulation CD4+ CD25+)

- Has been the Treg-cell (subpopulation CD4+ CD25+) performed? (No / Yes). If “yes”,
  - ❖ Result (% of CD4+ and CD25+ T-cells of the total T-cell population).

9.4 TREATMENT PERIOD DAY 14

The number of patients who completed treatment period day 14 will be indicated and the analyses proposed in this section will be displayed for those patients.

9.4.1 VITAL SIGNS

- Has been the vital signs evaluated? (No / Yes). If “yes”,
  - ❖ Sitting pule rate (beats/minute).
  - ❖ Systolic blood pressure (mmHg).
  - ❖ Diastolic blood pressure (mmHg).

9.4.2 SPIROMETRY

- Has been the spirometry evaluation performed? (No / Yes). If “yes”,
  - ❖ PEF (L/s).

9.4.3 PHYSICAL EXAMINATION

- Has been the physical examination performed? (No / Yes). If “yes”,
  - Cardiopulmonary exploration. A new variable will be created with the following categories:
    - Normal, when the patient has indicated “cardiopulmonary exploration” = “Normal”.
    - Abnormal - Not clinically significant, when the patient has indicated “cardiopulmonary exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
    - Abnormal - Clinically significant, when the patient has indicated “cardiopulmonary exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
    - ND, when the patient has indicated “cardiopulmonary exploration” = “ND”.
  - Skin exploration. A new variable will be created with the following categories:
    - Normal, when the patient has indicated “skin exploration” = “Normal”.
    - Abnormal - Not clinically significant, when the patient has indicated “skin exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
    - Abnormal - Clinically significant, when the patient has indicated “skin exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
    - ND, when the patient has indicated “skin exploration” = “ND”.

9.4.4 LABORATORY

9.4.4.1 Hematology

- Has been the hematology performed? (No / Yes). If “yes”,
  - Hematocrit (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Hemoglobin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Red blood cells (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - White blood cells (total) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Neutrophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Lymphocytes (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Eosinophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Basophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Monocytes (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Platelet count (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.4.4.2 Biochemistry

- Has been the biochemistry performed? (No / Yes). If “yes”,
  - Total bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Conjugated bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Alkaline phosphatase (ALP) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - SGOT (AST) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - SGPT (ALT) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - GGTP (GGT) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - LDH (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Urea (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Creatinine (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Albumin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

- Total protein (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Glucose (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Sodium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Calcium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Potassium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Chlorides (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Bicarbonates (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Phosphorus (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.4.4.3 Coagulation panel

- Has been the coagulation panel performed? (No / Yes). If “yes”,
  - INR (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - PTT (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.4.4.4 Urinalysis

- Has been the urinalysis performed? (No / Yes). If “yes”,
  - pH (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Proteins (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Blood (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Glucose (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Ketones (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Urobilinogen (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.4.5 PHARMACODYNAMICS EVALUATIONS

9.4.5.1 Ig G4 evaluation

- Has been the Ig G4 evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig G4 levels (mg/dL).
  - ❖ Ig G4 levels against complete peanut extract (mg/dL).
  - ❖ Ig G4 levels against component Ara h 1 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 2 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 3 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 9 (mg/dL).

9.4.6 ALLERGEN-SPECIFIC BIOMARKERS

9.4.6.1 Ig E evaluation

- Has been the Ig E evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig E levels (mg/dL).
  - ❖ Ig E levels against complete peanut extract (mg/dL).
  - ❖ Ig E levels against component Ara h 1 (mg/dL).
  - ❖ Ig E levels against component Ara h 2 (mg/dL).
  - ❖ Ig E levels against component Ara h 3 (mg/dL).
  - ❖ Ig E levels against component Ara h 9 (mg/dL).

9.4.6.2 Ig G evaluation

- Has been the Ig G evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig G levels (mg/dL).
  - ❖ Ig G levels against complete peanut extract (mg/dL).
  - ❖ Ig G levels against component Ara h 1 (mg/dL).
  - ❖ Ig G levels against component Ara h 2 (mg/dL).
  - ❖ Ig G levels against component Ara h 3 (mg/dL).
  - ❖ Ig G levels against component Ara h 9 (mg/dL).

9.4.6.3 Skin Prick Test (SPT)

- Has been the Skin Prick Test (SPT) performed? (No / Yes). If “yes”,
  - Result against NP (Positive / Negative / ND).
  - Result against NP-peanut (Positive / Negative / ND).
  - Result against peanut raw extract (Positive / Negative / ND).

9.4.6.4 Skin Endpoint Titration (SET)

- Has been the Skin Endpoint Titration (SET) performed? (No / Yes). If “yes”,
  - Result against NP (Positive / Negative / ND).
  - Result against NP-peanut (Positive / Negative / ND).
  - Result against peanut raw extract (Positive / Negative / ND).

9.4.6.5 Treg-cell (subpopulation CD4+ CD25+)

- Has been the Treg-cell (subpopulation CD4+ CD25+) performed? (No / Yes). If “yes”,
  - ❖ Result (% of CD4+ and CD25+ T-cells of the total T-cell population).

9.5 END OF STUDY

The number of patients who completed end of study visit will be indicated and the analyses proposed in this section will be displayed for those patients.

- Has the patient completed the study according to the protocol? (No / Yes). If “No”,
  - Reasons for study treatment discontinuation (Adverse Event / Death / Lost of Follow-up / Physician´s decision / Pregnancy / Major protocol desviation / Study Termination by Sponsor / Technical problems / Unacceptable toxicities / Withdrawal of consent / Other).

9.5.1 PREMATURE END OF TREATMENT (IF < DAY 14)

This section will analyze the patients who have indicated "No" in variable "Has the patient completed the study according to the protocol?".

9.5.1.1 VITAL SIGNS

- Has been the vital signs evaluated? (No / Yes). If “yes”,
  - ❖ Sitting pule rate (beats/minute).
  - ❖ Systolic blood pressure (mmHg).
  - ❖ Diastolic blood pressure (mmHg).

9.5.1.2 SPIROMETRY

- Has been the spirometry evaluation performed? (No / Yes). If “yes”,
  - ❖ PEF (L/s).

9.5.1.3 PHYSICAL EXAMINATION

- Has been the physical examination performed? (No / Yes). If “yes”,
  - Cardiopulmonary exploration. A new variable will be created with the following categories:
    - Normal, when the patient has indicated “cardiopulmonary exploration” = “Normal”.
    - Abnormal - Not clinically significant, when the patient has indicated “cardiopulmonary exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
    - Abnormal - Clinically significant, when the patient has indicated “cardiopulmonary exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
    - ND, when the patient has indicated “cardiopulmonary exploration” = “ND”.

- Skin exploration. A new variable will be created with the following categories:
  - Normal, when the patient has indicated “skin exploration” = “Normal”.
  - Abnormal - Not clinically significant, when the patient has indicated “skin exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
  - Abnormal - Clinically significant, when the patient has indicated “skin exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
  - ND, when the patient has indicated “skin exploration” = “ND”.

9.5.1.4 LABORATORY

9.5.1.4.1 Hematology

- Has been the hematology performed? (No / Yes). If “yes”,
  - Hematocrit (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Hemoglobin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Red blood cells (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - White blood cells (total) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Neutrophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Lymphocytes (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Eosinophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Basophils (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Monocytes (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Platelet count (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.5.1.4.2 Biochemistry

- Has been the biochemistry performed? (No / Yes). If “yes”,
  - Total bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Conjugated bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Alkaline phosphatase (ALP) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - SGOT (AST) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

- SGPT (ALT) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- GGTP (GGT) (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- LDH (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Urea (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Creatinine (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Albumin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Total protein (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Glucose (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Sodium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Calcium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Potassium (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Chlorides (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Bicarbonates (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
- Phosphorus (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.5.1.4.3 Coagulation panel

- Has been the coagulation panel performed? (No / Yes). If “yes”,
  - INR (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - PTT (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.5.1.4.4 Urinalysis

- Has been the urinalysis performed? (No / Yes). If “yes”,
  - pH (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Proteins (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Blood (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Glucose (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Ketones (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Bilirubin (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).
  - Urobilinogen (Normal / Abnormal - Not clinically significant / Abnormal - Clinically significant).

9.5.1.5 PHARMACODYNAMICS EVALUATIONS

9.5.1.5.1 Ig G4 evaluation

- Has been the Ig G4 evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig G4 levels (mg/dL).
  - ❖ Ig G4 levels against complete peanut extract (mg/dL).
  - ❖ Ig G4 levels against component Ara h 1 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 2 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 3 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 9 (mg/dL).

9.5.1.6 ALLERGEN-SPECIFIC BIOMARKERS

9.5.1.6.1 Ig E evaluation

- Has been the Ig E evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig E levels (mg/dL).
  - ❖ Ig E levels against complete peanut extract (mg/dL).
  - ❖ Ig E levels against component Ara h 1 (mg/dL).
  - ❖ Ig E levels against component Ara h 2 (mg/dL).
  - ❖ Ig E levels against component Ara h 3 (mg/dL).
  - ❖ Ig E levels against component Ara h 9 (mg/dL).

9.5.1.6.2 Ig G evaluation

- Has been the Ig G evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig G levels (mg/dL).
  - ❖ Ig G levels against complete peanut extract (mg/dL).
  - ❖ Ig G levels against component Ara h 1 (mg/dL).
  - ❖ Ig G levels against component Ara h 2 (mg/dL).
  - ❖ Ig G levels against component Ara h 3 (mg/dL).
  - ❖ Ig G levels against component Ara h 9 (mg/dL).

9.5.1.6.3 Skin Prick Test (SPT)

- Has been the Skin Prick Test (SPT) performed? (No / Yes). If “yes”,
  - Result against NP (Positive / Negative / ND).
  - Result against NP-peanut (Positive / Negative / ND).
  - Result against peanut raw extract (Positive / Negative / ND).

9.5.1.6.4 Skin Endpoint Titration (SET)

- Has been the Skin Endpoint Titration (SET) performed? (No / Yes). If “yes”,
  - Result against NP (Positive / Negative / ND).
  - Result against NP-peanut (Positive / Negative / ND).
  - Result against peanut raw extract (Positive / Negative / ND).

9.5.1.6.5 Treg-cell (subpopulation CD4+ CD25+)

- Has been the Treg-cell (subpopulation CD4+ CD25+) performed? (No / Yes). If “yes”,
  - ❖ Result (% of CD4+ and CD25+ T-cells of the total T-cell population).

9.6 SAFETY FOLLOW-UP VISIT DAY 28 (+-3 DAYS)

The number of patients who completed safety follow-up visit day 28 will be indicated and the analyses proposed in this section will be displayed for those patients.

9.6.1 VITAL SIGNS

- Has been the vital signs evaluated? (No / Yes). If “yes”,
  - ❖ Sitting pule rate (beats/minute).
  - ❖ Systolic blood pressure (mmHg).
  - ❖ Diastolic blood pressure (mmHg).

9.6.2 PHYSICAL EXAMINATION

- Has been the physical examination performed? (No / Yes). If “yes”,
  - Cardiopulmonary exploration. A new variable will be created with the following categories:
    - Normal, when the patient has indicated “cardiopulmonary exploration” = “Normal”.
    - Abnormal - Not clinically significant, when the patient has indicated “cardiopulmonary exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
    - Abnormal - Clinically significant, when the patient has indicated “cardiopulmonary exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
    - ND, when the patient has indicated “cardiopulmonary exploration” = “ND”.
  - Skin exploration. A new variable will be created with the following categories:
    - Normal, when the patient has indicated “skin exploration” = “Normal”.
    - Abnormal - Not clinically significant, when the patient has indicated “skin exploration” = “Abnormal” and all abnormalities = “No clinically significant”.
    - Abnormal - Clinically significant, when the patient has indicated “skin exploration” = “Abnormal” and at least one abnormality = “Yes clinically significant”.
    - ND, when the patient has indicated “skin exploration” = “ND”.

9.6.3 PHARMACODYNAMICS EVALUATIONS

9.6.3.1 Ig G4 evaluation

- Has been the Ig G4 evaluation performed? (No / Yes). If “yes”,
  - Ig G4 levels (mg/dL).
  - Ig G4 levels against complete peanut extract (mg/dL).
  - Ig G4 levels against component Ara h 1 (mg/dL).
  - Ig G4 levels against component Ara h 2 (mg/dL).
  - Ig G4 levels against component Ara h 3 (mg/dL).
  - Ig G4 levels against component Ara h 9 (mg/dL).

9.7 SAFETY FOLLOW-UP VISIT DAY 56 (+-3 DAYS)

The number of patients who completed safety follow-up visit day 56 will be indicated and the analyses proposed in this section will be displayed for those patients.

9.7.1 PHARMACODYNAMICS EVALUATIONS

9.7.1.1 Ig G4 evaluation

- Has been the Ig G4 evaluation performed? (No / Yes). If “yes”,
  - Ig G4 levels (mg/dL).
  - Ig G4 levels against complete peanut extract (mg/dL).
  - Ig G4 levels against component Ara h 1 (mg/dL).
  - Ig G4 levels against component Ara h 2 (mg/dL).
  - Ig G4 levels against component Ara h 3 (mg/dL).
  - Ig G4 levels against component Ara h 9 (mg/dL).

9.8 SAFETY FOLLOW-UP VISIT DAY 84 (+-3 DAYS)

The number of patients who completed safety follow-up visit day 84 will be indicated and the analyses proposed in this section will be displayed for those patients.

9.8.1 PHARMACODYNAMICS EVALUATIONS

9.8.1.1 Ig G4 evaluation

- Has been the Ig G4 evaluation performed? (No / Yes). If “yes”,
  - ❖ Ig G4 levels (mg/dL).
  - ❖ Ig G4 levels against complete peanut extract (mg/dL).
  - ❖ Ig G4 levels against component Ara h 1 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 2 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 3 (mg/dL).
  - ❖ Ig G4 levels against component Ara h 9 (mg/dL).

9.9 CONCOMITANT MEDICATION

- Number of total concomitant medication registered and number of patients with at least one concomitant medication. For total concomitant medication (no patients):
  - Type of treatment (Drug treatment / Non-drug treatment).

Drug treatment will be coding by ATC (ATC4 name and code).

A table will be displayed with the number of drug treatment (name and code) and the number of patients with at least one drug treatment (name and code). The percentage will be shown based on the total number of patients in the study. This analysis will be performed for each of the groups (A / B / C / D / E / F) separately, differentiating between INP20 and placebo (see table below).

Group A							
ATC4 name	ATC4 code	INP20			Placebo		
		N drug treatment	N patients	%*	N drug treatment	N patients	%*
ATC4 name 1	ATC4 code 1						
ATC4 name 2	ATC4 code 2						
...	...						

* Percentage calculated on the total number of patients in this group.

9.10 ADVERSE EVENTS

Adverse events will be codified by MedDRA dictionary (SOC and PT).

- Number of total adverse events registered and number of patients with at least one adverse event.
- Number of total serious adverse events registered and number of patients with at least one serious adverse event (SAE).
- Number of total related adverse events registered and number of patients with at least one treatment related adverse event.

For total adverse events (no patients),

- SOC and PT terms. A table will be made showing the PT terms based on the SOC terms.
- Outcome (Recovered-resolved / Recovered-resolved with sequelae / Fatal-death / Not recovered-not resolved / Unknown). In case of “Recovered-resolved” or “Recovered-resolved with sequelae”, time to resolved will be described like “end date time” – “start date time”.
- Possibly related to study treatment? (No / Yes).
- Serious (No / Yes). If “yes”, a list with PT will be shown.
- Severity (Grade 1-mild / Grade 2-moderate / Grade 3-severe / Grade 4-life threatening / Grade 5-death related).
- Treatment for adverse event? (No / Yes). In affirmative case,
    - Type of treatment (Level 1: Antihistamines and/or analgesics / Level 2: Corticosteroids, antiemetics, and/or bronchodilators / Level 3: Adrenaline). The treatment is collected in an open field, so a list will be sent to the sponsor for grouping into these three levels.
- Changes to study treatment due to AE (None / Temporarily interrupted / Permanently discontinued / Event occur prior to first intake of study treatment)
- In case of SAE, a multiple response table will be shown with the following options:
    - Death
    - Immediately life-threatening
    - Persistent or significant disability/incapacity
    - Congenital anomaly/birth defect
    - Important medical event
    - Inpatient hospitalization/prolonged hospitalization

In case the adverse event related to the treatment are possibly caused by a hypersensitivity mechanism:

- Possibly caused by a hypersensitivity mechanism? (No / Yes).
- Onset after study treatment administration (Immediate (less than 30 minutes after daily administration / Delayed (more than 30 minutes, less than 4 hours) / Very delayed (more than 4 hours)).

- Reaction (Local reaction (no systemic reaction) / Systemic reaction (no local reaction)).
  - If “local reaction (no systemic reaction)”, a multiple response table will be shown with the following options:
    - Itching and/or tingling sensation on lips, oral cavity, auditory canal, throat.
    - Urticaria perioral
    - Dysphagia
    - Gastric pain
    - Gastric burning
    - Nausea
    - Emesis
    - Abdominal pain/cramps
    - Diarrhoea
  - If “systemic reaction (no local reaction)”,
    - Severity (No symptoms or nonspecific symptoms of systemic reaction / Mild systemic reactions / Moderate systemic reactions / Severe systemic reaction / Hypotension or loss of consciousness is present)
- The related-treatment AE was a dose limiting toxicity (No / Yes).

A table will be made showing the number of PT and the number of patients with at least one the PT terms based on the SOC terms and maximum severity (Grade 1 / Grade 2 / Grade 3 / Grade 4 / Grade 5). This analysis will be performed for each of the groups (A / B / C / D / E / F) separately, differentiating between INP20 and placebo (see table below).

Group A INP20											
AE SOC	AE PT	Grade 1			Grade 2			…	Total		
		N AEs	N patients	%*	N AEs	N patients	%*		N AEs	N patients	%*
SOC 1	PT 1										
SOC 2	PT 1										
	PT 2										
…	…										

* Percentage calculated on the total number of patients in this group.

Group A Placebo											
AE SOC	AE PT	Grade 1			Grade 2			…	Total		
		N AEs	N patients	%*	N AEs	N patients	%*		N AEs	N patients	%*
SOC 1	PT 1										
SOC 2	PT 1										
	PT 2										
…	…										

* Percentage calculated on the total number of patients in this group.

10 OBJECTIVE ANALYSIS

10.1 PRIMARY OBJECTIVE

The main objective is the descriptive analysis of part A of the INP20 project, focused on safety.

This objective has been resolved throughout the report, with the analysis of:

- Incidence of adverse events (AEs), serious adverse events (SAEs), treatment-related AEs/SAEs, and AEs/SAEs leading to discontinuation will be calculated and classified by body system and preferred term using MedDRA dictionary and EAACI guidelines criteria (see section 9.10).
- Systemic allergic symptoms and relatedness to treatment (see section 9.3.2).
- Physical examination and vital signs (see sections 9.3.3, 9.3.4, 9.4.1, 9.4.3, 9.5.1.1, 9.5.1.3, 9.6.1 and 9.6.2).
- Peak flow (see sections 9.3.5, 9.4.2 and 9.5.1.2).
- Biological safety (laboratory): hematology, coagulation, biochemistry, urinalysis, and immunologic tests (see sections 9.3.6, 9.4.4 and 9.5.1.4).

10.2 SECONDARY STUDY OBJECTIVE

The secondary objective is the descriptive analysis of part A of the INP20 project, focused on pharmacodynamics

To solve this objective, we will analyze the change in Immunoglobulin G subtype (IgG4) (as biomarkers of immunogenicity of allergen-specific immunotherapy) at the end of treatment and at month 1, month 2 and month 3.

The percentage change is used to express the change between two values as a percentage of the initial value. The formula is:

$$Percentage\ change = \left(\frac{(Final\ value - Initial\ value)}{Initial\ value}\right) \times 100$$

10.2.1 Screening visit vs. day 14

Percentage change will be calculated between screnning visit and day 14 visit in the following variables:

- Ig G4 levels (mg/dL).
- Ig G4 levels against complete peanut extract (mg/dL).
- Ig G4 levels against component Ara h 1 (mg/dL).
- Ig G4 levels against component Ara h 2 (mg/dL).
- Ig G4 levels against component Ara h 3 (mg/dL).
- Ig G4 levels against component Ara h 9 (mg/dL).

10.2.2 Screening visit vs. Premature end of treatment visit

Percentage change will be calculated between screnning visit and premature end treatment visit in the following variables:

- Ig G4 levels (mg/dL).
- Ig G4 levels against complete peanut extract (mg/dL).
- Ig G4 levels against component Ara h 1 (mg/dL).
- Ig G4 levels against component Ara h 2 (mg/dL).
- Ig G4 levels against component Ara h 3 (mg/dL).
- Ig G4 levels against component Ara h 9 (mg/dL).

10.2.3 Screening visit vs. Follow-up visit day 28

Percentage change will be calculated between screnning visit and follow-up visit day 28 in the following variables:

- Ig G4 levels (mg/dL).
- Ig G4 levels against complete peanut extract (mg/dL).
- Ig G4 levels against component Ara h 1 (mg/dL).
- Ig G4 levels against component Ara h 2 (mg/dL).
- Ig G4 levels against component Ara h 3 (mg/dL).
- Ig G4 levels against component Ara h 9 (mg/dL).

10.2.4 Screening visit vs. Follow-up visit day 56

Percentage change will be calculated between screnning visit and follow-up visit day 56 in the following variables:

- Ig G4 levels (mg/dL).
- Ig G4 levels against complete peanut extract (mg/dL).
- Ig G4 levels against component Ara h 1 (mg/dL).
- Ig G4 levels against component Ara h 2 (mg/dL).
- Ig G4 levels against component Ara h 3 (mg/dL).
- Ig G4 levels against component Ara h 9 (mg/dL).

10.2.5 Screening visit vs. Follow-up visit day 84

Percentage change will be calculated between screnning visit and follow-up visit day 84 in the following variables:

- Ig G4 levels (mg/dL).
- Ig G4 levels against complete peanut extract (mg/dL).
- Ig G4 levels against component Ara h 1 (mg/dL).
- Ig G4 levels against component Ara h 2 (mg/dL).
- Ig G4 levels against component Ara h 3 (mg/dL).
- Ig G4 levels against component Ara h 9 (mg/dL).