XIX Encuentro de Cooperación Farma-Biotech

12 de noviembre de 2020

INP20: oral vaccine for peanut allergy

Dra. Maite Agüeros

InnoUp Farma
Overview

2013 — Company foundation

2014 — Private funding

2015 — INP20 development starts

2016 — Public funding

2018 — INP20 Phase 1/2 Clinical trial starts

2018 — INP30 Public funding

April 2020 — INP20 & INP12tox studies completed

April 2020 — INP12 Phase 1 Clinical trial authorization

2Q 2021 — INP12 Phase 1 Clinical trial start

2015 — INP12 development starts

Management & Development Team

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nanoimmunotech
global solutions in nanobiotechnology

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Almirall

NOVARTIS

CICbiomaGUNE
CENTER FOR COOPERATIVE RESEARCH IN BIOMATERIALS

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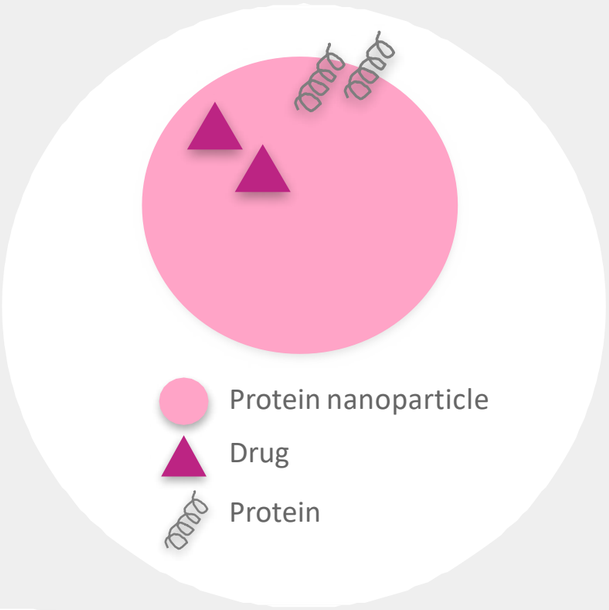
SANOFI

InnoUp Farma
Technology

Therapeutic Nanosystem:

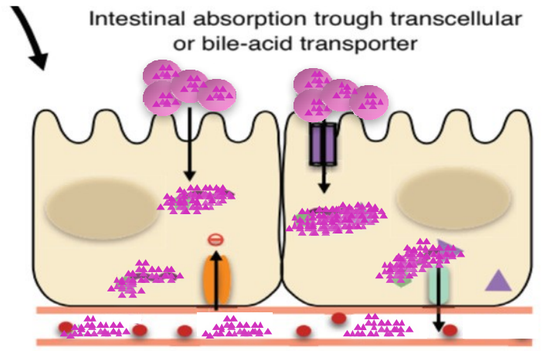
Colloidal dispersed solid particles with a size between 1 and 1000 nm, formed by at least two components, one being the active ingredient (drug or protein) developed to treat, prevent or diagnose diseases



InnoUp technology advantages:

- Oral administration
- Controlled release of drugs or proteins (such as peanut extract or other food allergens)
- Bioadhesion to the gut: high residence time which leads to the need of lower doses and lower toxicity of drugs
- Biocompatible
- Not absorbed to blood

Bioadhesion of the nanoparticles to the gut



Intellectual property

- Licensed composition of matter patent covering “Nanoparticles for the encapsulation of compounds, the obtaining and uses thereof” filed on 15/07/2011.

  - Filed in Europe, USA, Australia, Brasil, Canada, China, India, Japan, Korea, Mexico and Russia.

  - To date, granted in Europe (Germany, Belgium, Switzerland, Denmark, Spain, Finland, France, UK, Ireland, Italy, Luxemburg, Netherlands, Norway, Portugal and Sweden).

  - Protection up to July 2031 without extensions.

- Strategy to extend current patent and file new patents.

InnoUp Farma
Pipeline

Product	Indication	2018	2019	2020	2021	2022
INP20	Peanut allergy	Preclinical		Phase 1/2 Study	Phase 1 results	
INP12	Breast cancer	Preclinical		Phase 1/2 Study		
INP30	Oral SARS-CoV-2 vaccine			Preclinical	Phase 1 Study	

INP20

Oral vaccine for the treatment of peanut allergy

Peanut allergy
Commercial opportunity

- Most common food allergy with **incidence of 0.6 - 1%** of total population. **Prevalence** in children **increasing** globally and unlike many other food allergies, it usually persists through to adulthood.

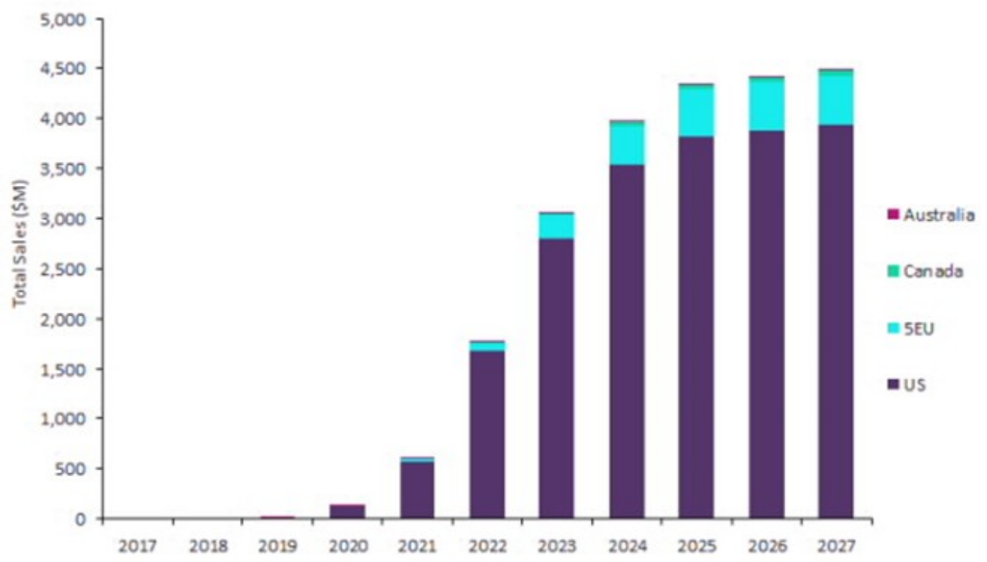
- To date, **no approved treatment for peanut allergy.**
  Main preventive measure (once diagnosed): education of patients and families to avoid ingestion, especially accidental, of peanuts.

- It can be **life-threatening** accounting for majority of deaths related to food allergy.
  It also impacts severely the **quality of life of patients,** especially of children and families.

- Patients who suffer **peanut-induced anaphylaxis** should be treated with intramuscular epinephrine, histamine H1-receptor and H2-receptor antagonists, oxygen,
  beta2-adrenergic receptor agonists and systemic corticosteroids.

- The economic cost of food allergies (28.7% to peanuts) in the United States is estimated at $24.8 billion per year, of which only $4.3 billion was direct medical costs. The remaining $20.5 billion represents costs borne by the families of affected children including out of pocket medical costs, the costs of special foods, and lost caregiver productivity.

- It is estimated that the peanut allergy market in major regions will grow at a CAGR of 111% and will reach **$4,5 billion in 2027.**



INP20
Value proposition

To address the significant unmet medical need in peanut allergic patients, InnoUp is developing **INP20, an oral vaccine in which the whole peanut extract is encapsulated within nanoparticles ensuring a safe and efficacious treatment** based on InnoUp´s proprietary technology:

Clean safety profile:

- Masking of the peanut allergen prevents adverse reactions.
- Safe nanoparticles composition (GRAS).
- No need for dose adjustment.

Long-term efficacy:

- Whole peanut extract used.
- Extract is controlled-released from nanoparticles.
- Adjuvant/immunomodulatory effects perse.

Peanut allergy
Competitive environment

- Prior to the arrival of new therapies, the only available treatment for peanut allergy is experimental oral immunotherapy (OIT). **The goal of peanut OIT is to desensitize patients to peanut by gradually exposing them to increasing doses of the food over time.** The therapy has grown in popularity in recent years, however, its use is fairly controversial because **it lacks regulatory approval.**

- Most new agents in development carry significant **drawbacks** since:

  - OIT therapies will only induce temporarily tolerance and require chronic dosing, thus if stopped, patients will no longer be protected.

  - Those containing part of the allergen extract are expected to show limited efficacy since not all of the allergic population will be covered.

  - Those containing full allergen extract are expected to be associated with safety concerns (if allergen not masked) which will be even more pronounced in parental therapies.

Peanut allergy
Pipeline

Product	Administration route	Description	Status	Advantages	Disadvantages
AR101 (Aimmune Therapeutics)	Oral	Oral peanut extract	Phase 3 completed	• First peanut extract manufactured under GMPs	• Risk of severe adverse effects • Moderate efficacy because it is OIT
Viaskin Peanut (DBV Technologies)	Epicutaneous	Epicutaneous immunotherapy	Phase 3 ongoing	• Low severe adverse effects	• Limited efficacy as it can be seen in last results
PPOIT (MCRI/Prota Therapeutics)	Oral	Mixture of peanut flour with a probiotic bacterium	Phase 2b ongoing	• Whole peanut extract • Long term results	• Risk of severe adverse effects • Moderate efficacy
HAL MPE-1 (Hal Allergy Group)	Subcutaneous	Modified peanut extract with aluminum hydroxide	Phase 1 completed	• Higher expected efficacy because of the administration route	• High risk of severe adverse due to administration route
PVX108 (Aravax)	Intradermal	Intradermal injection of peanut protein fragments	Phase 1 ongoing	• Safer - total protein not present in the product	• Only part of extract: limited efficacy
ASP0892 (Astellas Pharma)	Intradermal & intramuscular	Single Multivalent Peanut (Ara h1, h2, h3) Lysosomal Associated Membrane Protein DNA Plasmid Vaccine	Phase 1 ongoing	• Safer - total protein not present in the product	• Only part of extract: limited efficacy
SAR-439794 (Sanofi)	Sublingual	Combination of GLA (Glucopyranosyl Lipid A) with sublingual immunotherapy with peanut extract (SLIT PE)	Phase 1 ongoing	• Whole peanut extract used	• No efficacy demonstrated
INP20 (InnoUp Farma)	Oral	Oral vaccine of whole peanut extract loaded in nanoparticles	Phase 1/2 ongoing	• Safe and long-term efficacious treatment	

Product	Administration route	Description	Status	Advantages	Disadvantages
ASIT+™ (ASIT Biotech)	Oral	Oral administration of highly purified natural allergen fragments	Preclinical	• Safer - total protein not present in the product	• Only part of extract: limited efficacy
Polyvac® (Allergy Therapeutics)	Subcutaneous	Virus-like particles combined with recombinant peanut allergen	Preclinical	• Safer - total protein not present in the product	• Unknown safety implications of virus-like particles
VTC-064 (Virtici)	Oral	Recombinant protein composed of the reovirus head protein, ps1, fused to the peanut allergen Ara h 2	Preclinical	• Specific target to M cells	• Only AraH2: limited efficacy
SVP (Selecta Biosciences)		Peanut extract with immunomodulators	Preclinical	• Need of lower doses to obtain immune response	• Now evaluating strategic opportunities to continue advancing this non-core program.
Laboratorios LETI	Oral	Depigmented-Polymerized Peanut Allergenic Extract	Preclinical	• Hypoallergic peanut extract safe for immunotherapy treatment for toleration to peanuts	
Intrommune Therapeutics	Tooth paste	Peanut extract in tooth paste	Preclinical	• Low adverse effects	• No efficacy demonstrated
SCV-PHAV (Sementis)	Implant	Solid dose implant with a viral vector containing peanut allergens	Preclinical	• Lower administrations	• No efficacy demonstrated

INP20
Preclinical development

To date, the following studies have been completed:

Sensitization efficacy study in mice

Animals were sensitized with oral administration of peanut butter + cholera toxin and tape stripping with peanut extract until obtaining representative IgE levels.

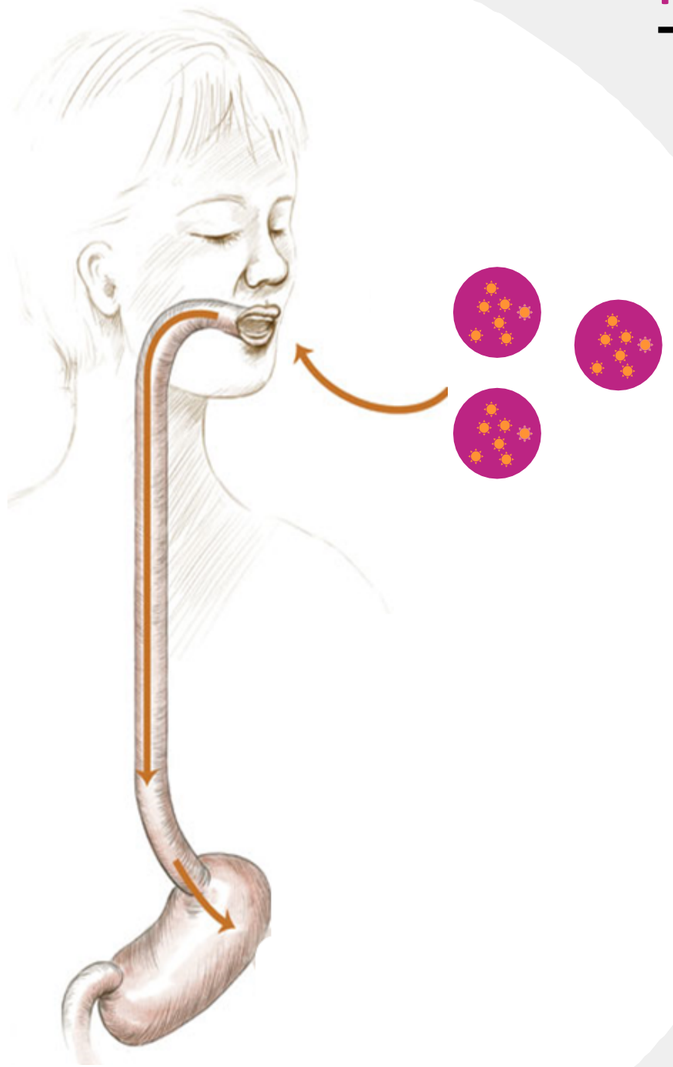
Then, free peanut extract and the same quantity of peanut protein encapsulated in INP20 were administered. A control group was also included.

At day 45, a challenge with intraperitoneal peanut extract was performed and survival rate was evaluated.

16-day toxicology GLP study in dogs

Repeated oral administration of INP20 or Empty INP20 or Vehicle (water) once daily during 16 consecutive days at the dose levels of 200, 1000 and 3000 mg protein / animal / day, corresponding to 2, 10 and 30 mg peanut protein extract / animal / day.

INP20
Dual mechanism of action



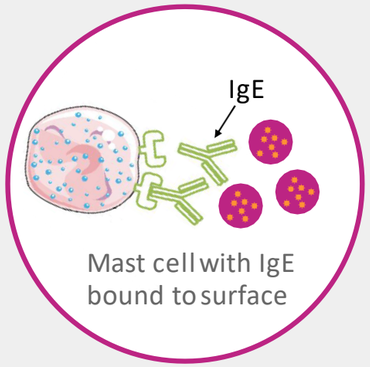
INP20: Peanut extract nanoparticles

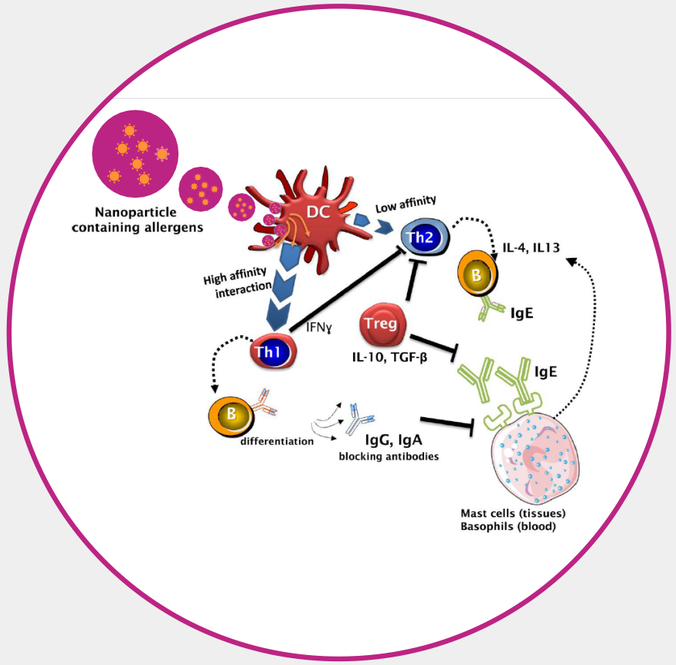
Nanoparticle

Peanut allergen

Allergen masking

The mastocytes of the GI tract are not able to “see” the allergen due to the nanoparticles masking effect and thus, no severe adverse events are expected.





Adjuvant effect

Nanoparticles imitate virus and bacterias and thus are more susceptible to be phagocyted by antigen presenting cells (APCs) as dendritic cells or macrophages.

INP20 is then easily captured and internalized by different APCs, which can enhance the delivery of the loaded allergen to the immune system, achieving immunomodulatory responses.

Moreover, INP20 protects peanut allergens from hydrolysis and/or enzymatic degradation and promotes a controlled and sustained release in the gut, which facilitates the interaction with immune cells.

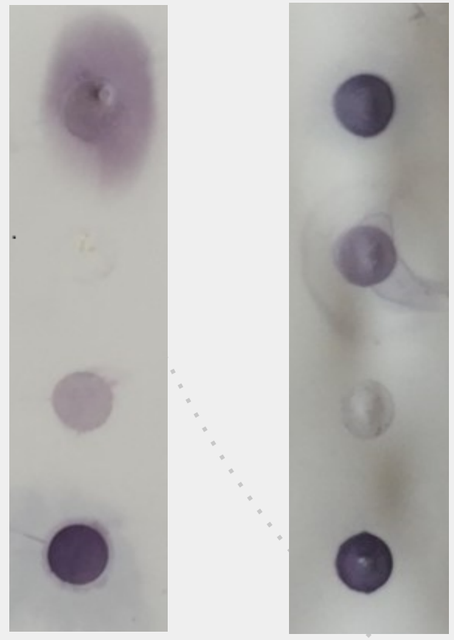
INP20
In vitro studies

Immunocap shows that gastrointestinal media destroys biological potency of free peanut extract and no inhibition is achieved in whole INP20 after being incubated in gastrointestinal tract:

	% Inhibition
Free peanut extract after 24h in gastrointestinal media	-25%
Free peanut extract after 24h in water	-69%
INP20 after 24h in gastrointestinal media	-18%
INP20 after 24h in water	-69%
Empty nanoparticles after 24h in gastrointestinal media	2%
Empty nanoparticles after 24h in water	-3%

Dot Blot shows that antibody is not able to recognize INP20 when peanut protein is inside but, when nanoparticles are digested, then the antibody is able to recognize the peanut protein that was inside the nanoparticles:

	Incubated directly	Incubated after digestion
INP20 after 24h in water		
INP20 after 24h in gastrointestinal media		
Free peanut extract after 24h in gastrointestinal media		
Free peanut extract after 24h in water		

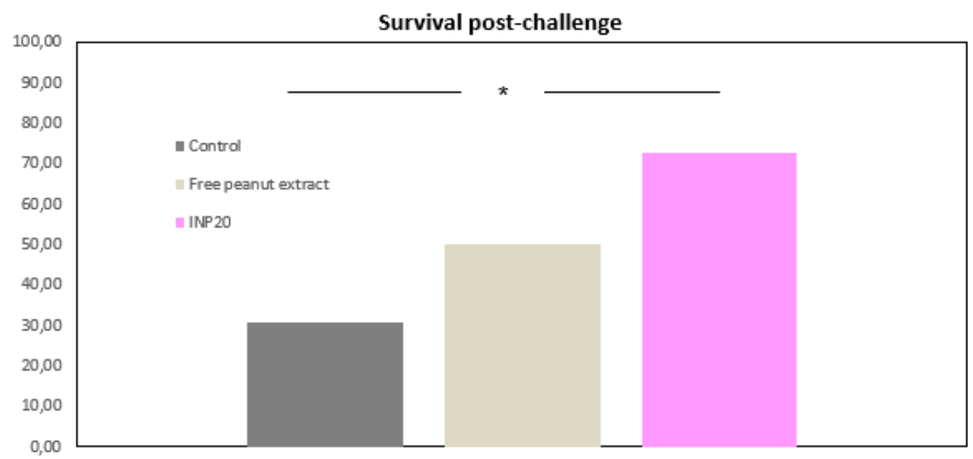


Efficacy study in sensitized mice

INP20 shows an adjuvant/immunomodulator effect

INP20 was able to protect mice from anaphylactic shock after challenge comparing its survival rate to the control group. This study confirmed the efficacy of INP20, showing that this formulation acts as an adjuvant.

- Animals were sensitized to peanut once a week, 3 weeks (4 doses).
- After 5 days, they received treatment 3 times (every 5 days).
- Finally: Intraperitoneal peanut challenge at Day 45.



Toxicology GLP study in Beagle dogs

- The repeated oral administration of **INP20 or Empty INP20 or vehicle (water) once daily during 16 consecutive days** at the dose levels of 200, 1000 and 3000 mg total protein/animal/day, corresponding to 2, 10 and 30 mg peanut protein extract/animal/day, respectively, **was well tolerated**.

- **No effects** of the treatment with INP20 at any **of the three dose levels tested were observed** on clinical signs, body weight, food consumption, clinical pathology parameters, ECG parameters, blood pressure, eye structures and absolute/relative organ weights.

- The dose of 3000 mg total protein/animal/day, corresponding to 30 mg peanut/protein extract/animal/day could be established as NOAEL for INP20.

- **The repeated oral administration of Empty INP20 once daily during 16 consecutive days was well tolerated.**

- **No effects of the treatment with Empty INP20** were observed on clinical signs, body weight, food consumption, clinical pathology parameters, ECG parameters, blood pressure, eye structures and absolute/relative organ weights.

INP20
CMC development

- INP20 is a powder for oral administration, after resuspension in water, which are nanoparticles encapsulating the roasted defatted peanut aqueous allergenic extract.

- INP20 has been manufactured under GMP as an intermediate bulk powder and subsequently filled in its primary packaging material. Several doses are planned to be tested in the clinic ranging from 0.15 to 30 mg of peanut extract, thus in order to allow this dosing scheme, three INP20 doses are being filled in vials at 0.15-1.5-5 mg of peanut extract per vial.

- Several batches have been manufactured during development for nonclinical and clinical use. Analytical methods used to control the drug product are suitably confirmed.

The production of nanoparticles is a challenging task in terms of reproducibility of size and polydispersity.

- INP20 scale up has been developed to be versatile and can be adapted to any scale as the process is continuous and it can be installed in any manufacturing site.
- Hydroalcoholic mixtures are required for the process instead of other organic solvents.
- It can be manufactured from a few grams of product to big amounts.
- The reproducibility of the process has been tested by manufacturing several batches. No differences among all of them were found and low polydispersion was achieved.
- Initial stability data indicate that long-term stability is achieved at least one year at 5ºC after the manufacturing of INP20. ICH stability studies are ongoing and 1 month data have already been analyzed and stability has been confirmed.

Phase 1/2 study

Clinical Trial Application was submitted to the Spanish Medicines Agency on December 2018 and has been approved in April 2019.

Phase 1/2 study design

Parallel, double-blind, randomized, placebo-controlled, safety and tolerability study in peanut allergic patients:

- **Part A (Phase 1):**
  INP20 ascending doses or placebo once daily during 2 weeks.

- **Part B (Phase 2):**
  two INP20 dose levels or placebo once daily during 6 months.

Timelines

- **Study start: 1**Q 2020
- **Part A top-line results: 2**Q 2021
- **Part B top-line results: 3**Q 2022

Phase 1/2 study
Part A

WEEK 1GroupA
0.15 mg INP20 (n=6) / Placebo (n=2)
Posology: Once daily for 2 weeks

WEEK 1GroupA
0.15 mg INP20 (n=6) / Placebo (n=2)
Posology: Once daily for 2 weeks

Peanut allergic patients who met inclusion criteria

WEEK 1GroupA
0.15 mg INP20 (n=6) / Placebo (n=2)
Posology: Once daily for 2 weeks

Safety and tolerability

WEEK 1GroupA
0.15 mg INP20 (n=6) / Placebo (n=2)
Posology: Once daily for 2 weeks

WEEK 1GroupA
0.15 mg INP20 (n=6) / Placebo (n=2)
Posology: Once daily for 2 weeks

WEEK 1GroupA
0.15 mg INP20 (n=6) / Placebo (n=2)
Posology: Once daily for 2 weeks

Phase 1/2 study
Part B

Patients from Phase I who have recovered their baseline levels of IgG4+naive peanut allergic patients who meet inclusion criteria

Group 1

Placebo (n=12)

Posology: Once daily / Duration: 6 months

Group 2

INP20 Posology and dose 1

(n=12) Duration: 6 months

Group 3

INP20 Posology and dose 2

(n=12) Duration: 6 months

Variables to study at times:

0, 4 weeks, 3 months and 6 months:

- Skin endpoint titration or parallel line bioassay
- Specific IgE (against components and complete extract)
- IgG 4 (against components and complete extract)
- BAT against nanoparticles, nanoparticles with allergen and complete allergen extract
- Subpopulations T, concretely Treg1, CD4+ and CD25+ to demonstrate Treg cells induction
- Intracellular cytokines quantification IL10, TGF-beta, as markers of Th1 induction IL4, IL5, IL13, check if it induces decrease

INP20
Summary

- Oral vaccine with great potential to address the significant unmet medical need and commercial opportunityin peanut allergy.

- InnoUp proprietary technology allows the development of a safe and long-term efficacious treatment for peanut allergic patients and represents a platform for the development of therapies to treat other food allergies.

- INP20 offers competitive advantages compared to OIT therapies and most agents in development in terms of efficacy, safety and posology.

- Phase 1/2 study ongoing.

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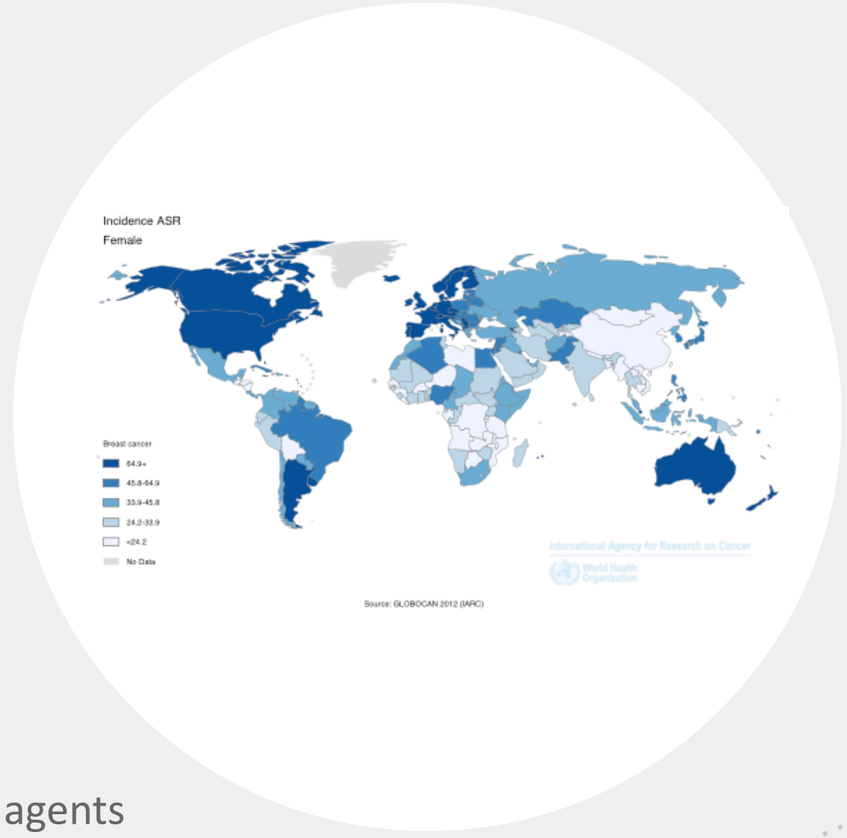
INP12

Oral paclitaxel for the treatment of breast cancer

Breast cancer
Commercial opportunity

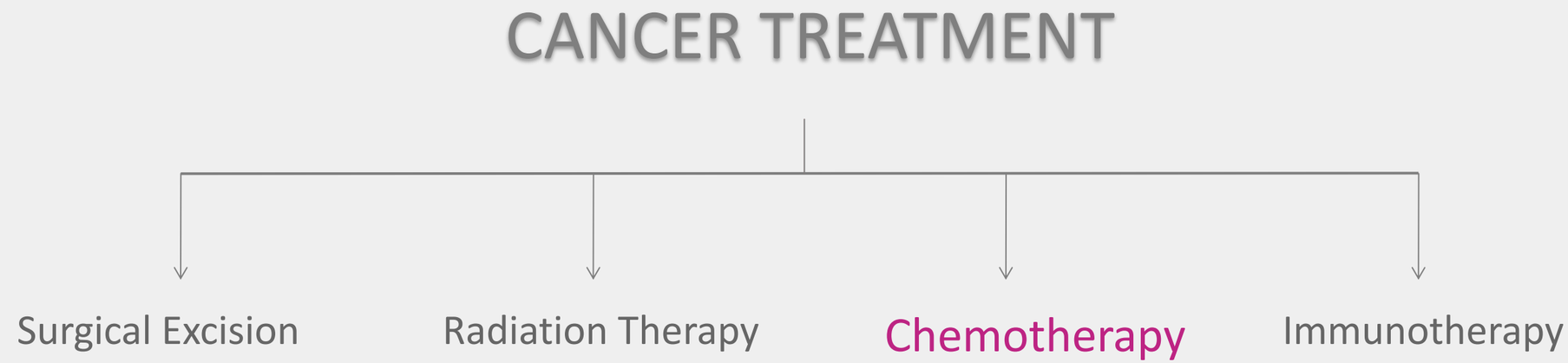


- **Breast cancer: first place in cancer mortality**
  1 in 8 women will develop breast cancer in their lifetime
  1.67 million new cases per year
  One of six women diagnosed with breast cancer die of the disease

- **Paclitaxel** is one of the three most widely used chemotherapeutic agents (https://www.ncbi.nlm.nih.gov/pubmed/28257998)

- **Abraxane case:**
  Albumin nanoparticles containing paclitaxel
  Only for i.v. administration, not feasible for oral administration
  2016 sales: $973 millions

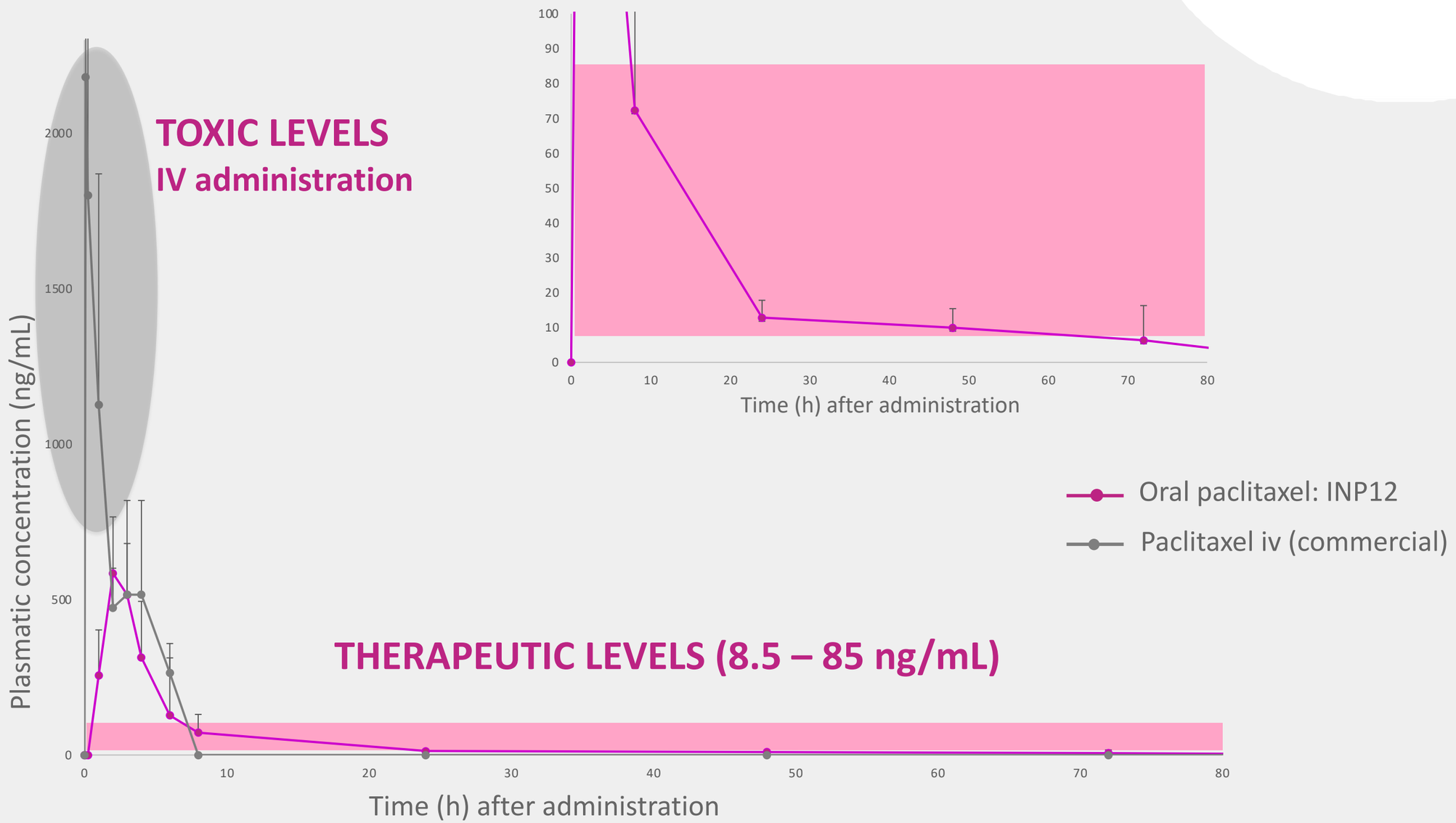
Cancer treatment
Facts



Low solubility & low permeability of anticancer drugs:
require intravenous administration

Pharmacokinetics
Oral administration

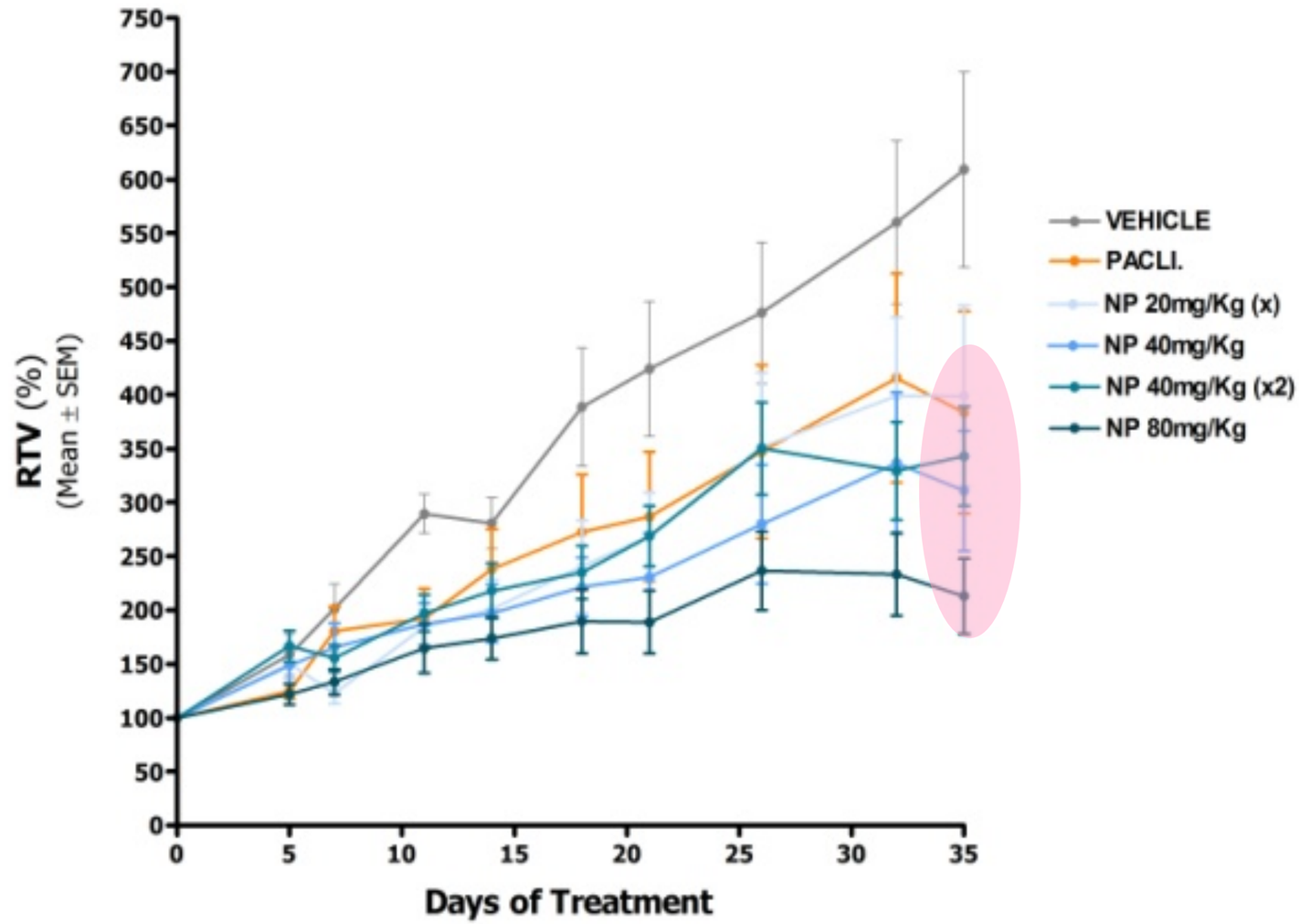
InnoUp Technology (INP12) increase the oral bioavailability of paclitaxel and maintains therapeutic levels for 60h (metronomic approach)



In vivo efficacy

InnoUp Technology allows to reduce 60% the tumor size, improving the efficacy of the commercial formulation up to 45%*

Conclusions of the "Efficacy study in Her2+ breast cancer orthotropic mice model" (Study number: AT17P2142-01) performed in Leitat Technological Center



In vivo toxicity
Conclusions of GLP study in mice

- After the repeated oral administration of 30, 60 and 120mg/kg of INP12 in mice, **no significant toxicological changes during the in-life phase of the study (mortality, severe clinical signs or significant reduction in body weights) were observed**.

- Some degenerative changes in testes and bone marrow, hypocellularity in sternum and femur were observed, but all of these changes were reversible.

CMC development

- INP12 is a lyophilized powder for oral administration, after resuspension in water, which are nanoparticles encapsulating paclitaxel.
- INP12 has been manufactured under GMP in vials containing 21mg of paclitaxel. The number of vials administered in the clinic trial will be estimated depending on the calculated dose according to the individual body surface.
- Several batches have been manufactured during development for nonclinical use. Analytical methods used to control the drug product are suitably confirmed.

- INP12 scale up has been developed to be versatile and can be adapted to any scale as the process is continuous and it can be installed in any manufacturing site.

- Hydroalcoholic mixtures are required for the process instead of other organic solvents. It can be manufactured from a few grams of product to big amounts.

- The reproducibility of the process has been tested by manufacturing several batches. No differences among all of them were found and low polydispersion was achieved.

- Initial stability data indicate that long-term stability is achieved at least six months at 25ºC after the manufacturing of INP12.

Phase 1 study

Clinical Trial Application has been approved in September 2020.

Phase 1 study design

Evaluation of the safety, tolerability, and pharmacokinetic profile of INP12 in patients with advanced solid tumors

- Part A (escalation pase):

INP12 will be administered orally once a week in patients with advance solid tumors.

MTD* or the highest protocol-defined dose and recommended part B dose of INP12 will be determined.

- Part B (expansion phase):

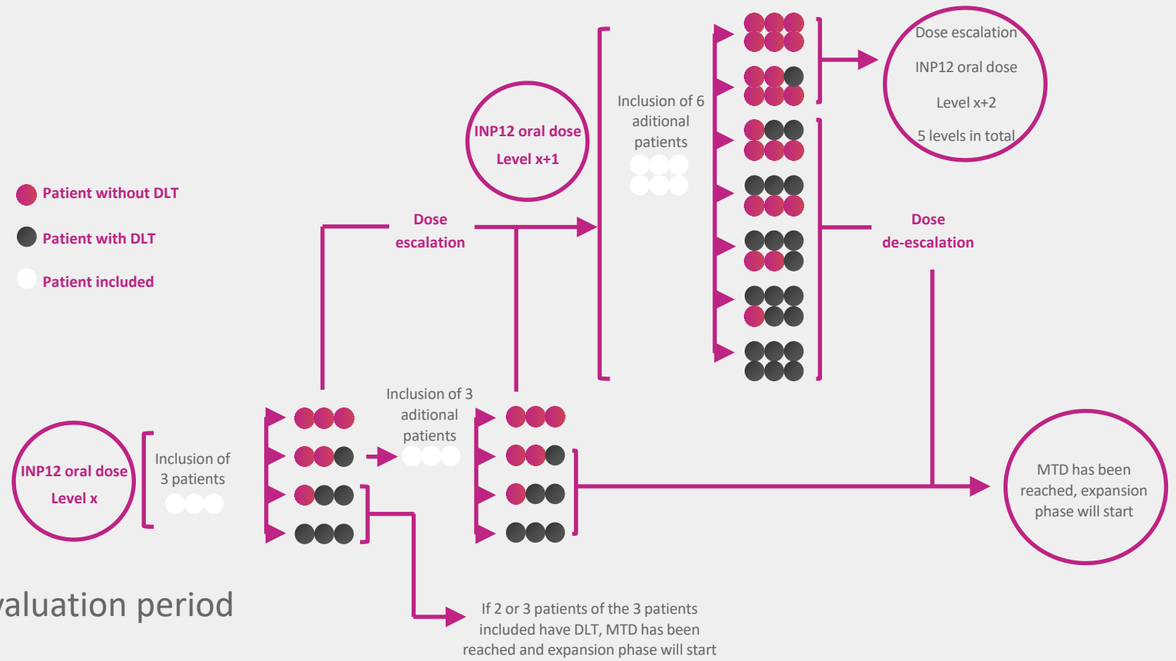
Safety and tolerability of INP12 in subjects with selected advanced solid tumors will be evaluated.

*MTD: Maximum Tolerated Dose

Timelines

- Study start: 1Q 2021
- Phase 1 top-line results: 1Q 2022

Phase 1 study
Escalation phase



- The MTD* will be determined based on the assessment of DLT** during the DLT evaluation period
- A minimum of 3 patients will be enrolled in each dose cohort.
- A 3+3 dose-escalation design will be followed as summarized below:
  - If 0 out of the 3 patients in a dose cohort experience a DLT during the evaluation period, dose escalation may proceed to the next planned cohort.
  - If 1 out of 3 patients experience DLT, enter up 3 patients more at the same dose level. If 0 of these additional patients experience a DLT making it a total of 1 out of 6 patients with a DLT at this dose level, continue doce escalation study and new 3 patients will be enrolled at the next dose level cohort.
  - If 2 or more patients in a dose cohort experience a DLT during the evaluation period, the MTD will have been exceeded and dose escalation is stopped. Then 3 additional patients will be enrolled at the next lowest dose level if only 3 patients were treated previously at that dose. Additionally, an intermediate dose cohort may be explored based on the recommendation of the scientific committee.
- At the discretion of the Dose Security Committee, dose escalation may be stopped before an MTD is reached. In this case, the dose chosen for expansion phase may be chosen based on an assessment of pharmacokinetics, pharmacodynamic, biomarker, safety, and response data. MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk.
- The complete assessment for MTD determination will take safety and pharmacokinetics data into consideration collected during 28 days of DLT evaluation period.

*MTD: Maximum Tolerated Dose
**DLT: Dose Limitng Toxicity

Phase 1 study
Expansion phase

Patients from escalation phase and new patients (at least 25 patients with breast cancer) will start expansion phase

Dose level of the MTD, or an intermediate one

INP12 administration once a week

(each cycle consists of administration for 3 weeks followed by 1-week rest period)

Study endpoints:

TOLERABILITY

Tolerability will be defined by the number of patients experiencing any DLT** during the first 28-day cycle of INP12.

SAFETY

Safety of INP12 will be assessed on the incidence rate, severity, and relationship to treatment of adverse events (AEs) and serious adverse events (SAEs) according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

Other assessments will include safety laboratory parameters, vital signs, and electrocardiograms (ECG) in each dose group and in the expansion phase.

EFFICACY

Efficacy will be assessed by the ORR, which is defined as the percentage of patients with a complete response (CR) or a partial response (PR) by investigator assessment as per RECIST v1.1.

*MTD: Maximum Tolerated Dose
**DLT: Dose Limitng Toxicity

INP12
Summary

- Oral paclitaxel with great potential to decrease significantly toxicity compared to intravenous formulations with the same or even better efficacy.

- InnoUp proprietary technology allows the development of a safe treatment and represents a platform for the development of therapies to encapsulate other anticancer agents.

- INP12 offers competitive advantages compared to intravenous paclitaxel in terms of efficacy, safety and quality of life.

- Phase 1 study planned to start 1Q 2021.

Company Strategy
Next steps

- Raise funds from strategic partner or venture capital to fund clinical development plan for INP20 and INP12.

- License-out development and commercialisation global rights on INP20 for the treatment of peanut allergy and INP12 for the treatment of breast cancer.

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Thank you

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