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Clinical Investigation Protocol

Protocol code: 0221

Double blind, randomized, parallel group, Phase 1 study comparing pharmacokinetics and safety of Bevacizumab

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CLINICAL INVESTIGATION PROTOCOL AGREEMENT

I have read this Clinical Investigation Protocol and I agree with its contents as presented herein. I shall conduct the study in accordance with the details contained in this document.

Principal Investigator

Name: Dr. Ethel C. Feleder
Position: Principal investigator

Signature:

Date:

Representative of the Sponsor

Name: Lic. Elvira Zini
Position: Legal agent (principal)

Signature:

Date:

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1. SUMMARY OF THE STUDY

1.1. General considerations

Study Sponsor: Laboratorios Richmond S.A.C.I.F.

Study title: Double blind, randomized, balanced, parallel group, Phase I Study comparing pharmacokinetics and safety of Bevacizumab.

Protocol code: 0221

Version of the clinical investigation protocol: 2

Date: 08 January 2019

1.2. Approvals, authorizations, records and notifications

- Clinical Investigation Ethics Committee (CEIC)
- Teaching and clinical investigation committee, CIAREC
- Medical director of CIAREC
- National Administration for Drugs, Food and Medical Technology
- Argentine Ministry of Health (Registro Nacional de Investigaciones en Salud- ReNIS)
- Central Ethics Committee of the City of Buenos Aires

1.3. Study responsible persons

1.3.1. Sponsor

Legal agent: Lic. Elvira Zini

1.3.2. Study coordination, development and organization

FP Clinical Pharma S.R.L.

1.3.3. Clinical stage

1.3.3.1. Clinical center

Unidad de investigación-clínica farmacocinética FP Clinical Pharma en Clínica CIAREC

1.3.3.2. Principal investigator

M.D.: Ethel C. Feleder

1.3.4. Statistical stage

FP Clinical Pharma S.R.L.
Dr. Ethel C. Feleder

1.4. Investigation hypothesis

The test formulation containing Bevacizumab - Bevacizumab Richmond Hetero- bulk product manufactured by Hetero Biopharma Limited, transported in bulk from India and dosed and packaged in Laboratorios Richmond S.A.C.I.F (Test Product 1) presents a bioavailability of bevacizumab measured in the amount and speed of the drug absorbed similar to that of product Avastin®- Bevacizumab from Productos Roche S.A.Q. e I. (Reference Product).

The test formulation containing bevacizumab - Cizumab®- Bevacizumab from Hetero Biopharma Limited manufactured and dosed in India (Test Product 2) presents a bioavailability of bevacizumab measured in the amount and speed of the drug absorbed similar to that of product Avastin®- Bevacizumab from Productos Roche S.A.Q. e I. (Reference Product).

The test formulation containing bevacizumab - Bevacizumab Richmond-Hetero- bulk product manufactured by Hetero Biopharma Limited, transported in bulk from India and dosed and packaged in Laboratorios Richmond S.A.C.I.F (Test Product 1) presents a bioavailability of bevacizumab measured in the amount and speed of the drug absorbed (since it is the same bulk used) similar to that of product Cizumab®- Bevacizumab from Hetero Biopharma Limited, manufactured and dosed in India (Test Product 2).

The process of transportation / local filling of the product Bevacizumab Richmond Hetero (Test Product 1) does not affect the pharmacokinetic profile or the safety profile of the molecule in comparison with Cizumab® (Test Product 2). Therefore, it is expected that the clinical response be similar in the three products under investigation.

1.5. Objectives

To evaluate the pharmacokinetics and safety profile of Bevacizumab after administering the following investigation products:

- A single IV dose of 1 mg/kg of the test product Bevacizumab-Richmond-Hetero [Test Product 1 local primary packaging]

- A single IV dose of 1 mg/kg of Avastin® [Local Reference Product]
- A single IV dose of 1 mg/kg of Cizumab® [Test Product 2 manufactured and packaged by Hetero in India]

The products are administered to male volunteer study subjects.

1.6. Design

The study to be conducted is a double blind, randomized, balanced, parallel group Phase I study comparing pharmacokinetics and safety with a single dose in healthy male volunteers.

1.7. Study type

This study is a clinical pharmacokinetics and safety comparison study belonging to the Phase 1 of the clinical studies.

1.8. Study duration

The duration of the participation of each subject in the study, in its clinical stage, is approximately 91 days.

1.9. Study schedule

- Visit 1: Screening and inclusion (Day -28 through -1)
- Visit 2: Dosing, blood draw, 24 hours confinement (Day 1)
- Visit 3: Outpatient blood draw- hour 48 post-infusion (Day 2)
- Visit 4: Outpatient blood draw- hour 72 post-infusion (Day 3)
- Visit 5: Outpatient blood draw- hour 96 post-infusion (Day 4)
- Visit 6: Outpatient blood draw- hour 120 post-infusion (Day 5)
- Visit 7: Outpatient blood draw- hour 168 post-infusion (Day 7)
- Visit 8: Outpatient blood draw- hour 336 post-infusion (Day 14)
- Visit 9: Outpatient blood draw- hour 504 post-infusion (Day 21)
- Visit 10: Outpatient blood draw- hour 672 post-infusion (Day 28)
- Visit 11: Outpatient blood draw- hour 840 post-infusion (Day 35)

- Visit 12: Outpatient blood draw- hour 1008 post-infusion (Day 42)
- Visit 13: Outpatient blood draw- hour 1176 post-infusion (Day 49)
- Visit 14: Outpatient blood draw- hour 1344 post-infusion (Day 56)
- Visit 15: Outpatient blood draw- hour 1512 post-infusion - End of study visit (Day 63)

The blood sampling times were as follows:

- Pre-infusion: 0.00 hours
- During the infusion: 0.33, 0.50, 1.00, 1.50 hours
- Post-infusion: 20 min, 40 min, 1.00, 2.00, 4.00, 8.00, 12.00, 24.00, 48.00, 72.00, 96.00, 120.00, 168.00, 336.00, 504.00, 672.00, 840.00, 1008.00, 1176.00, 1344.00 and 1512.00 hours.

1.10. Number of subjects

The study will be conducted with 90 volunteer subjects.

1.11. Main inclusion criteria

Volunteer healthy, adult, male subjects.

1.12. Products under investigation

- Test 1: Bevacizumab Richmond-Hetero, manufactured by Hetero Biopharma Limited, India, transported in bulk from India and dosed and packaged in Laboratorios Richmond S.A.C.I.F, Argentina.
- Reference: Avastin® Bevacizumab Productos Roche S.A.Q. e I.
- Test 2: Cizumab® Bevacizumab from Hetero Biopharma Limited, manufactured and dosed in India.

1.13. Pharmacokinetic parameters

Serum profiles shall be presented for bevacizumab using blood concentration-time curves.

The following main variables will be calculated: C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, λz, T1/2, systemic clearance, volume of distribution, individual and descriptive statistics.

1.14. Statistical analysis

Descriptive statistics of concentrations
Descriptive statistics of pharmacokinetic parameters
Statistical inference
Non-compartmental and/or compartmental analysis
Variance analysis
Calculation of point estimates and confidence intervals

1.15. Safety parameters

1.15.1. Safety

Anamnesis, general physical examination, vital signs, adverse event collection and electrocardiogram.

1.15.2. Immunogenicity

Serum anti-bevacizumab antibodies.

2. STYDY HYPOTHESIS

The test formulation containing Bevacizumab - Bevacizumab Richmond Hetero- bulk product manufactured by Hetero Biopharma Limited, transported in bulk from India and dosed and packaged in Laboratorios Richmond S.A.C.I.F (Test Product 1) presents a bioavailability of bevacizumab measured in the amount and speed of the drug absorbed similar to that of product Avastin®- Bevacizumab from Productos Roche S.A.Q. e I. (Reference Product).

The test formulation containing bevacizumab - Cizumab®- Bevacizumab from Hetero Biopharma Limited manufactured and dosed in India (Test Product 2) presents a bioavailability of bevacizumab measured in the amount and speed of the drug absorbed similar to that of product Avastin®- Bevacizumab from Productos Roche S.A.Q. e I. (Reference Product).

The test formulation containing bevacizumab - Bevacizumab Richmond-Hetero- bulk product manufactured by Hetero Biopharma Limited, transported in bulk from India and dosed and packaged in Laboratorios Richmond S.A.C.I.F (Test Product 1) presents a bioavailability of bevacizumab measured in the amount and speed of the drug absorbed (since it is the same bulk used) similar to that of product Cizumab®- Bevacizumab from Hetero Biopharma Limited, manufactured and dosed in India (Test Product 2).

The process of transportation / local filling of the product Bevacizumab Richmond Hetero (Test Product 1) does not affect the pharmacokinetic profile or the safety profile of the molecule in comparison with Cizumab® (Test Product 2). Therefore, it is expected that the clinical response be similar in the three products under investigation.

3. INTRODUCTION

3.1. Pharmacokinetics

Bevacizumab pharmacokinetic data stem from 10 clinical studies made on patients with solid malignancies who received bevacizumab as IV infusion. The infusion rate was established based on the tolerability, with a 90 minutes duration for the initial administration. Bevacizumab pharmacokinetics was linear in a dose interval of 1 to 10 mg/Kg *(Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017)*.

As observed with other antibodies, bevacizumab pharmacokinetic data are described by a two-compartment model. In general terms and in all clinical studies, bevacizumab clearance was characterized by a slow clearance, a distribution volume limited to the central compartment, and a long mean clearance half life. These parameters ensure the presence of stable bevacizumab therapeutic levels in plasma, with a wide range of administration schemes (such as once every 2 or 3 weeks) *(Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017).*

In the pharmacokinetic population meta analysis no significant differences were observed in bevacizumab pharmacokinetics with respect to race, when considering the body weight or based on the age (no correlation between bevacizumab clearance and the age of patients [the age median was 59 years and percentiles 5 and 95 of 37 and 76 years of age, respectively] was observed) *(Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017).*

3.1.1. Distribution

The mean value of the central volume was 2.73 liters in women and 3.28 liters in men, which are within the range described for IgG and other monoclonal antibodies. When bevacizumab was administered together with antineoplastic agents, the mean value of the peripheral volume was 1.69 liters in women and 2.35 liters in men. After the correction based on body weight, men showed a higher central volume (+20%) than women. *(Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017).*

3.1.2. Biotransformation

The evaluation of bevacizumab metabolism in rabbits after the administration of a single IV dose of ^{125}I-bevacizumab showed that the metabolic profile is similar to the profile expected for a native IgG not binding to the VEGF. Bevacizumab metabolism and clearance are similar to those of the endogenous IgG, namely, the catabolism is made mainly by proteolysis in all the organism, including endothelial cells and does not depend mainly on the elimination through the liver and kidneys. Binding to the FcRn receptor protects the IgG from the cell metabolism, which results in a long terminal clearance half life. *(Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017).*

3.1.3. Clearance

Bevacizumab pharmacokinetics is linear in doses ranging between 1.5 and 10 mg/kg/week. The clearance value is 0.188 and 0.220 l/day on average for women and men, respectively. After the correction based on the body weight, men showed a higher bevacizumab clearance (+17%) than women. According to the two-compartmental model, the average clearance half life is 18 days for an average female patient and 20 days for an average male patient. Low albumin levels and a high tumor load are general indicators of the disease gravity. Bevacizumab clearance was approximately 30% faster in patients with low serum albumin levels and 7% faster in those patients with a high tumor load when compared with a patient with average values of albumin and tumor load. *(Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017).*

3.2. Indications

- Metastatic carcinoma of the colon or rectum (CCRm)

Bevacizumab is indicated in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum.

- Metastatic breast cancer (CMm)

Bevacizumab is indicated with paclitaxel for first line treatment in adult patients with metastatic breast cancer.

Bevacizumab is indicated in combination with capecitabine as a first line treatment in adult patients with metastatic breast cancer, for which the treatment with other chemotherapy options including taxanes or anthracyclines are not considered appropriate. Patients with treatment regimens containing taxanes and anthracyclines in the adjuvant environment in the past 12 months shall be excluded from bevacizumab treatment in combination with capecitabine.

- Non-small cell lung cancer (NSCLC)

Bevacizumab associated with platinum-based chemotherapy is indicated as a first line treatment in adult patients with advanced unresectable metastatic or recurring non-microcytic lung cancer, with the exception of those having a histology type with squamous cells.

Bevacizumab is indicated in combination with erlotinib as the first line treatment in adult patients with advanced unresectable metastatic or recurring non-squamous non-microcytic lung cancer with mutations activating the receptor of the epidermal growth factor.

- Advanced and/or metastatic renal cell cancer (CRm)

Bevacizumab is indicated in combination with interferon Alpha-2a as a first line treatment of adult patients with advanced and/or metastatic renal cell cancer.

- Glioblastoma (Grade IV according to the WHO)

Bevacizumab is indicated as a monotherapy for the treatment of patients with relapse of glioblastoma (Grade IV according to the WHO) after a previous therapy with temozolomide.

- Epithelial ovarian cancer, Fallopian tube or primary peritoenal cancer

Bevacizumab is indicated in combination with carboplatin and paclitaxel as the first line treatment of adult patients with advanced (stages IIIB, IIIC and IV according to the International Federation of Gynecology and Obstetrics) epithelial ovarian cancer, Fallopian tube or primary peritoneal cancer.

Bevacizumab is indicated in combination with carboplatin and gemcitabine for the treatment of adult patients with epithelial ovarian cancer, Fallopian tube carcinoma or primary peritoneal carcinoma sensitive to platin after the first relapse, who have not received prior treatment with bevacizumab, other vascular endothelial growth factor (VEGF) inhibitors or agents targeting VEGF receptors.

Bevacizumab is indicated in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin for the treatment of adult patients with epithelial ovarian cancer, Fallopian tube carcinoma or primary recurring peritoneal carcinoma resistant to platinum, who have not received more than two prior chemotherapy regimens or prior treatment with bevacizumab, other vascular endothelial growth factor (VEGF) inhibitors or agents targeting VEGF receptors.

- Cervical cancer

Bevacizumab is indicated in combination with paclitaxel and cisplatin or carboplatin, or paclitaxel and topotecan for the treatment of adult patients with persistent, recurring or metastatic cervical cancer.

The information included in this section was extracted from *(Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017).*

3.3. Contraindications

Hypersensitivity to the active ingredient or to any of its excipients, hypersensitivity to products derived from Chinese hamster ovary (CHO) cells or other human or humanized recombinant antibodies, pregnancy and nursing.

3.4. Adverse reactions

Summary of the safety profile

Avastin's global safety profile is based on data of approximately 5,400 patients with various types of cancer, treated mostly with Avastin in combination with chemotherapy in clinical studies.

The most serious adverse events were:

- Gastrointestinal perforations
- Hemorrhage, including pulmonary hemorrhage/hemoptisis, more frequent in patients with non-microcytic lung cancer
- Arterial thromboembolism

In clinical studies the most frequent adverse reactions observed globally in patients treated with Avastin were: hypertension, fatigue or asthenia, diarrhea and abdominal pain.

The analysis of clinical safety data suggests that the incidence of hypertension and proteinuria during Avastin therapy may probably be dose dependent.

Table of adverse reactions

The adverse reactions listed in this section are classified according to the frequency in the following categories: Very Common (≥1/10); Frequent (≥1/100 and <1/10), Uncommon (≥1/1.000 and <1/100); rare (≥1/10.000 and <1/1.000); very rare (<1/10.000); and unknown frequency (estimation is not possible from the data available).

Tables 1 and 2 list the adverse reactions associated with the use of Avastin in combination with different chemotherapy regimes in multiple indications.

Table 1 shows adverse reactions classified according to frequency. It was determined that they had a causal relationship with Avastin through:

- Relative incidences observed among the treatment groups of the clinical study (at least with a 10% difference of reactions NCI-CTCAE Grades 1-5, or at least with a 2% difference of reactions NCI-CTCAE Grades 3–5).
- Post-authorization safety studies
- Spontaneous reporting
- Epidemiologic/non-interventional studies or observational studies
- The evaluation of the reporting of individual cases

Table 2 shows the frequency of the serious adverse reactions. They are defined as adverse events with at least a 2% difference in comparison with the control group in clinical studies for reactions NCI-CTCAE Grades 3-5. Table 2 also includes adverse reactions considered by Roche as clinically significant or serious.

Tables 1 and 2 include post-marketing adverse reactions, as appropriate. The detailed information regarding reporting post marketing is shown in Table 3.

The adverse reactions are included in the appropriate frequency category, in the following tables according to the highest incidence observed in any indication.

The adverse reactions are listed in decreasing order of severity within each frequency bracket. Some are frequently observed in the chemotherapy; however, Avastin may also exacerbate these manifestation when used in combination with chemotherapy agents. The examples include palmar plantar erythrodysesthesia with pegylated liposomal dosorubicin or capecitabine, sensory peripheral neuropathy with paclitaxel or oxaliplatin, alterations in nails or alopecia with paclitaxel and paronychia with erlotinib.

Table 1. Adverse reactions according to frequency

System Organ Class	Very Common	Frequent	Uncommon	Rare	Very Rare	Unknown Frequency
Infections and infestations	Paronychia	Sepsis Abscess[b,d,] Cellulite Infection Urinal tract infection		Necrotizing fascitiis[a]		
Blood and Lymphatic System Disorders	Febrile neutropenia Leukopenia Netropenia[b] Thrombocytopenia	Anemia Lynphocytopenia				
Immune System Disorders		Hypersensitivity Reactions to the infusion[a,b,d]				
Metabolism and Nutrition Disorders	Anorexia Hypomagnesemia Hyponatremia	Dehydration Hyponatremia				
Nervous System Disorders	Sensory peripheral neuropathy[b] Dysarthria Headache Dysgeusia	Stroke Syncope Drowsiness		Posterior Reversible Encephalopathy [a,b,d]	Hypertensive encephalopathy	
Eye disorders	Eye disorder Lachrimation increased					
Cardiac Disorders		Congestive heart failure[b,d] Supraventricular tachycardia				
Vascular Disorders	Hypertension[b,d] (venous) Thromboembolism[b,d,]	(arterial) Thromboembolism[b,d] Hemorrhage[b,d] Deep vein thrombosis				Renal thrombotic microangio-pathy[a,b]

Table 1. Adverse reactions classified according to frequency (Continued)

System Organ Class	Very Common	Frequent	Uncommon	Rare	Very Rare	Unknown Frequency
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea Rhynitis Cough	Pulmonary hemorrhage / homoptisis[b,d] Pulmonary embolism Hipoxia Epistaxis Dysphonia[a]				Pulmonay hypertension[a] Nasal septum perforation[a]
Gastrointestinal Disorders	Rectal hemorrhage Estomatitis Constipation Diarrhea Nausea Vomiting Abdominal pain	Gastrointestinal perforation[b,d] Intestinal perforation Ileus Intestinal obstruction Rectovaginal fistula[d,e] Gastrointestinal disorder Proctalgia				Gastrointestinal ulcer[a]
Hepatobiliary disorders						Perforation of the gallbladder[b,c]
Skin and subcutaenous tissue disorders	Complications in wound healing[b, d] Exfoliative dermatitis Dry skin Discoloration of the skin	Palmar plantar erythrodysesthesic syndrome				
Musculoskeletal and Connective Tissue Disorder	Arthralgia	Fistula[b,d] Myalgia Muscle weakness Back pain				Mandibular osteonecrosis[a,b] Non-mandibular osteonecrosis[a,f]

Table 1. Adverse reactions according to frequency (Continued)

System Organ Class	Very Common	Frequent	Uncommon	Rare	Very Rare	Unknown Frequency
Renal and Urinary Disorders	Proteinuria[b,d]					
Reproductive system and breast disorders	Ovarian insufficiency[b,c,d]	Pelvic pain				
Congenital, family and genetic disorders						Fetal anomalies[a,b]
General disorders and administration site conditions	Asthenia Fatigue Fever Pain Mucosa inflammation	Lethargy				
Complementary explorations	Weight loss					

When events were observed in clinical studies, be they as adverse reactions of all the Grades or belonging only to Grade 3-5, the highest frequency reported in patients was informed. The data are not adjusted according to the different treatment times.

a) For further information about adverse reactions reported in the post-marketing experience, refer to Table 3.
b) Terms representing a group of adverse events describing a medical concept instead of a single condition or MedDra (Medical Dictionary for Regulatory Activities) reference term. This set of medical terms may imply the same underlying physiopathology (for example, grouping of arterial thromboembolic reactions, including stroke, myocardial infarction, transient ischemic attack and other arterial thromboembolic reactions).
c) Based on a sub-study of study AVF3077s (NSABP C-08) with 295 patients.
d) For further details see "Description of selected serious adverse reactions".
e) Recto-vaginal fistulas are the most common fistulas in the category of GI-vaginal fistulas.
f) Observed only in pediatric population.

Table 2. Serious adverse reactions classified according to frequency

System Organ Class	Very Common	Frequent	Uncommon	Rare	Very Rare	Unknown Frequency
Infections and infestations		Sepsis Cellulite Abscess[a, b,] Infection Urinary tract infection				Necrotizing fascitiis[a]
Blood and Lymphatic System Disorders	Febrile neutropenia Leukopenia Netropenia[a] Thrombocytopenia	Anemia Lynphocytopenia				
Immune System Disorders						Hypersensitivity Reactions to the infusion
Metabolism and Nutrition Disorders		Dehydration				
Nervous System Disorders	Sensory peripheral neuropathy[b]	Stroke Syncope Drowsiness Headache			Hypertensive encephalopathy [a]	Posterior Reversible Encephalopathy [a,b,c] Hypertensive encephalopathy
Cardiac Disorders		Congestive heart failure[a,b] Supraventricular tachycardia				
Vascular Disorders	Hypertension[b,d]	(arterial) Thromboembolism[a,b] Hemorrhage[b,d] (venous) Thromboembolism[a,b] Deep vein thrombosis				Renal thrombotic microangiopathy[b,c]

Table 2. Serious adverse reactions classified according to frequency (Continued)

System Organ Class	Very Common	Frequent	Uncommon	Rare	Very Rare	Unknown Frequency
Respiratory, Thoracic and Mediastinal Disorders		Pulmonary hemorrhage / homoptisis[a,b] Pulmonary embolism Epistaxis Dyspnea Hypoxia				Pulmonay hypertension[c] Nasal septum perforation[a]
Gastrointestinal Disorders	Diarrhea Nausea Vomiting Abdominal pain	Intestinal perforation Ileus Intestinal obstruction Rectovaginal fistula[c,d] Gastrointestinal disorder Estomatitis Proctalgia				Gastrointestinal perforation[a,b] Gastrointestinal ulcer[c] Rectal hemorrhage
Hepatobiliary disorders						Perforation of the gallbladder[b,c]
Skin and subcutaenous tissue disorders		Complications in wound healing[a,b] Palmar plantar erythrodysesthesic syndrome				
Musculoskeletal and Connective Tissue Disorder		Fistula[b,d] Myalgia Arthralgia Muscle weakness Back pain				Mandibular osteonecrosis[b,c]
Renal and Urinary Disorders		Proteinuria[a,b]				

Table 2. Serious adverse reactions classified according to frequency (Continued)

System Organ Class	Very Common	Frequent	Uncommon	Rare	Very Rare	Unknown Frequency
Reproductive system and breast disorders		Pelvic pain				Ovarian insufficiency[a,b]
Congenital, family and genetic disorders						Fetal anomalies[a,b]
General disorders and administration site conditions	Asthenia Fatigue	Lethargy Mucosa inflammation				

Table 2 shows the frequency of the serious adverse reactions. These are defined as adverse events with a 2% difference in comparison with the control group in clinical studies for reactions NCI-CTCAE Grades 3-5. Table 2 also includes adverse reactions considered by Roche to be clinically significant or serious. These clinically significant adverse reactions were reported in the clinical studies, but those of Grades 3-5 did not reach the threshold of at least 2% of difference in comparison with the control group.

Table 2 also includes clinically significant adverse reactions observed only after the product was on the market, therefore, the frequency and the NCI-CTCAE grade is unknown. Consequently, these clinically significant reactions have been included in Table 2 in the column with heading "Unknown Frequency".

a) Terms representing a group of adverse events describing a medical concept instead of a single condition or MedDra (Medical Dictionary for Regulatory Activities) reference terms. This set of medical terms may imply the same underlying physiopathology (for example, grouping of arterial thromboembolic reactions, including stroke, myocardial infarction, transient ischemic attack and other arterial thromboembolic reactions).
b) For further details, see the "Description of selected serious adverse reactions".

c) For further details about adverse reactions reported in the post-marketing experience, refer to Table 3.
d) Recto-vaginal fistulas are the most common fistulas in the category of GI-vaginal fistulas.

Description of selected serious adverse reactions

Gastro-intestinal (GI) perforations and Fistulas (see Warnings and Precautions)

The use of Avastin was associated with serious cases of gastro-intestinal perforation.

Cases of gastro-intestinal perforations have been reported in clinical studies with an incidence of less than 1% in patients with non-microcytic lung cancer, of up to 1.3% in patients with metastatic breast cancer, of up to 2% in metastatic renal cell cancer, with a recent diagnosis of glioblastoma or with ovarian cancer, and of up to 2.7% in patients with metastatic colorectal cancer (including gastro-intestinal fistula and abscesses). Cases of gastrointestinal perforations were also observed in patients with relapsed glioblastoma.

In a clinical study of patients with persistent, recurring or metastatic cervical cancer (GOG-0240), gastrointestinal perforations (all the Grades) were observed in 3.2% of patients, all of whom had a history of prior pelvic radiation.

A difference in the type and severity of these reactions was observed, ranging from the presence of free air detected in a normal abdominal X-ray, which was resolved without the need of treatment up to the intestinal perforation with abdominal abscess and a fatal outcome. Some cases already presented an underlying intra-abdominal inflammation as a consequence of gastric ulcer, tumor necrosis, diverticulitis or chemotherapy associated colitis.

A fatal outcome was reported in approximately a third of the severe cases of gastrointestinal perforations, which accounts for between 0.2% and 1% of all patients treated with Avastin.

In clinical studies with Avastin, cases of gastrointestinal fistula (of all Grades) were informed, with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, and also (although with a lower frequency) in those patients with other types of cancer.

GI-Vaginal fistulas in study GOG-240

In a study with patients presenting persistent, recurring or metastatic cervical cancer, the incidence of GI-vaginas fistulas was 8.3% in patients treated with Avastin and 0.9% in control patients, all of whom had history of prior pelvic radiation. The frequency of GI-vaginal fistulas in the group treated with Avastin + chemotherapy was higher in patients with a recurrence of the disease within the previously radiated field (16.7%) in comparison with those with a recurrence of the disease outside the previously radiated field (3.6%). The frequencies corresponding to the control group who received only chemotherapy was 1.1% in comparison with 0.8% respectively. Those patients who

developed GI-vaginal fistulas may have intestinal obstructions and require surgical intervention, as well as ostomy.

Non-gastrointestinal (GI) fistulas (Refer to Warnings and Precautions)

The use of Avastin was associated with severe cases of fistulas, including reactions with fatal outcomes.

In a clinical study in patients with persistent, recurring or metastatic cervical cancer (GOG-0240), 1.8% of patients treated with Avastin and 1.4% of control patients reported having non-gastro intestinal fistulas: vaginal or vesical fistulas, or fistulas in the female genital tract.

Uncommon cases (≥0.1% and <1%) of fistulas with involvement of other parts of the body different from the gastro-intestinal tract (for example, bronchopleural and biliary fistulas) were observed in various indications. Fistulas were also reported during the post-marketing experience.

The reactions were reported at different moments of the treatment, ranging from the first week until past the first year since beginning the treatment with Avastin. Most of the cases were observed within the first six-month period of the treatment.

Wound Healing (Refer to Warnings and Precautions)

Because Avastin can have a negative impact in the healing of wounds, patients who had major surgery in the past 28 days were excluded from Phase III clinical studies.

In clinical studies in patients with metastatic carcinoma of the colon or rectum, patients who had undergone major surgery between the 28 and 60 day period before starting the therapy with Avastin did not show an increase in the risk of post-operative hemorrhage or complications in the healing of the wounds. It was observed that if patients were subject to treatment with Avastin at the moment of the surgery, they had a higher risk of post-operative hemorrhage or wound healing problems in the 60 days after the major surgery. The incidence ranged between 10% (4/40) and 20% (3/15).

Severe complications in the healing of wounds have been reported, including complications related to anastomosis, some of them with fatal outcomes.

In studies in patients with locally recurring and metastatic breast cancer, complications in wound healing (Grades 3-5) were observed in up to 1.1% of patients treated with Avastin compare to up to 0.9% in the control arms (NCI-CTCAE v.3).

In study AVF3708g in patients with relapsed glioblastoma, the incidence of post-operative wound healing complications (including wound dehiscence in the location of the craneotomy and loss of cerebrospinal fluid) was 3.6% in patients treated with Avastin as a single agent and 1.3% in patients receiving Avastin plus irinotecan.

In clinical studies in patients with ovarian cancer, wound healing complications (Grade 3-5) were observed in up to 1.2% of patients in the bevacizumab arm compared to 0.1% of the control arm (NCI-CTCAE v.3).

In study BO21990 in patients with recent diagnosis of glioblastoma, the incidence of post-operative wound healing complications Grade 3-5 (including those which presented themselves after the craneotomy) was 3.3% in patients treated with Avastin in combination with chemotherapy and radiotherapy, and 1.6% in those receiving only chemotherapy and radiotherapy.

Hypertension (Refer to Warnings and Precautions)

In clinical studies, with the exception of study JO25567, the global incidence of hypertension (all the Grades) was of up to 42.1% in patients treated with Avastin in comparison with up to 14% in patients receiving the comparator. The global incidence NCI-CTC of hypertension Grades 3 and 4 occurred in 0.4% through 17.9% of patients treated with Avastin. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with Avastin and chemotherapy in comparison with up to 0.2% of patients receiving the same single chemotherapy.

In study JO25567, all the Grades of hypertension were observed in 77.3% of patients who received bevacizumab in combination with erlotinib as first line of treatment for non-squamous CPNM with EGFR activating mutations, in comparison with 14.3% of patients treated with only erlotinib. Grade 3 hypertension occurred in 60.0% of patients treated with bevacizumab in combination with erlotinib in comparison with 11.7% of patients receiving only erlotinib. No Grade 4 or 5 hypertension events occurred.

In general, hypertension was adequately controlled with oral antihypertensive drugs, such as angiotensin-converting enzyme, diuretics and calcium channel blockers. Only rarely was it necessary to discontinue the treatment with Avastin or hospitalization.

Very rare cases of hypertensive encephalopathy have been reported, some of them were fatal.

There is no correlation between the risk of hypertension associated with Avastin treatment and the baseline characteristics of patients, the underlying disease or the concomitant therapy.

Posterior Reversible Ecephalopathy Syndrome (Refer to Warnings and Precautions)

Some rare cases have been reported of patients treated with Avastin who develop signs and symptoms coinciding with the Posterior Reversible Encephalopathy Syndrome (PRES), a rare case of neurological disorder. Its manifestation can include seizures, headache, altered mental status, visual alterations or cortical blindness, with or without associated hypertension. The clinical features of PRES are frequently unspecific and therefore the diagnosis requires confirmation using cerebral imaging techniques, preferably a magnetic resonance imaging (MRI).

In patients developing PRES, an early awareness of the symptoms is recommended, with a timely treatment of the specific symptoms, including control of the hypertension (if associated with uncontrolled severe hypertension), in addition to discontinuing bevacizumab administration. Symptoms generally resolve or improve in the days after the treatment discontinuation, although some patients have experienced some neurologic sequelae. The safety of resuming Avastin therapy in patients who had previously experienced PRES is unknown.

As a result of the clinical studies, 8 cases of PRES were reported. Two of the eight cases did not have a radiological confirmation using MRI.

Proteinuria (Refer to Warnings and Precautions)

In clinical studies, proteinuria cases were reported in a bracket ranging from 0.7% to 54.7% of patients treated with Avastin.

The proteinuria severity varied from the clinically asymptomatic, transitory, indication of proteinuria up to nephrotic syndrome, with most cases being Grade 1 (NCI-CTCAE v. 3) proteinuria. Grade 3 proteinuria was observed in up to 8.1% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was observed in up to 1.4% of treated patients.

Patients with known history of hypertension may have a higher risk of proteinuria during Avastin treatment. Some data suggest that Grade 1(NCI-CTCAE v. 3) may be related with the dose of Avastin. It is recommended to run proteinuria tests before starting with Avastin treatment. In most of the clinical studies where the protein levels in urine were ≥2 g/24 hours, the treatment with Avastin was discontinued until levels of <2 g/24 hours were recovered.

Hemorrhage (Refer to Warnings and Precautions)

In clinical studies in all indications, the overall incidence of hemorrhagic reactions Grade 3-5 according to scale NCI-CTCAE v.3, ranged from 0.4% to 6.9% in patients treated with Avastin, compared to up to 4.5% of the chemotherapy control group.

In clinical study (GOG-0240) in patients with persistent, recurring or metastatic carcinoma of the cervix, hemorrhagic reactions Grade 3-5 were reported in up to 8.3% of patients treated with

Avastin in combination with paclitaxel and topotecan, in comparison with up to 4.6% of patients receiving paclitaxel and topotecan.

The hemorrhagic reactions observed in the clinical studies were mostly hemorrhages associated with the tumor, and minor mucocutaneous hemorrhages (for example, epistaxis).

Tumor-associated hemorrhages (Refer to Warnings and Precautions)

Severe or massive pulmonary hemorrhage / hemoptisis was observed mainly in studies in patients with non-microcytic lung cancer. The possible risk factors include histology of squamous cells, treatment with anti-rheumatic/anti-inflammatory drugs or anticoagulant drugs, prior radiotherapy, treatment with Avastin, prior medical history of atherosclerosis, localization of the central tumor and cavitation of tumors before or during the treatment. The only variables that showed a statistically significant correlation with the hemorrhage were Avastin treatment and squamous cell histology. Patients with CPNM diagnosed with a histological type of squamous cells or with a histology of a mixed cell type with predominance of squamous cells were excluded from later Phase III studies, whereas patients with an unknown tumor histology were included.

In patients with non-microcytic lung cancer, excluding patients who had a histology with a predominance of squamous cells, reactions of all Grades were observed, with a frequency of up to 9.3% in patients treated with Avastin plus chemotherapy in comparison with up to 5% of patients receiving only chemotherapy. Grade 3-5 reactions were observed in up to 2.3% of patients treated with Avastin plus chemotherapy in comparison with <1% with chemotherapy alone (NCI-CTCAE v. 3). Severe or massive pulmonary hemorrhage / hemoptisis may occur suddenly and up to two thirds of serious pulmonary hemorrhages had a fatal outcome.

In patients with colorectal cancer, gastrointestinal hemorrhages were reported, including rectal hemorrhage and melena. They were evaluated as associated to the tumor.

Rare cases of hemorrhages linked to the tumor in other tumor types and locations were observed, including cases in the central nervous system (CNS) in patients with CNS metastasis (Refer to Warnings and Precautions) and in patients with glioblastoma.

No prospective evaluation in randomized clinical studies were conducted to assess the incidence of hemorrhage in the CNS in patients with untreated metastases located in the CNS who received bevacizumab. In a retrospective exploratory analysis of data from 13 randomized studies completed in patients with different types of tumors, 3 of 91 (3.3%) with brain metastasis experienced CNS hemorrhage (all Grade 4) when treated with bevacizumab versus 1 case (Grade 5) of 96 (1%) who did not receive bevacizumab. In two later studies in patients with treated brain metastases (including approximately 800 patients), when the interim safety analysis was conducted, one Grade 2 case was reported with hemorrhage in the CNS (1.2%) of the 83 patients administered with bevacizumab (NCI-CTCAE v.3).

Intracranial hemorrhage may occur in patients with relapsed glioblastoma. In study AVF3708g, CNS hemorrhage was reported in 2.4% (2/84) of Avastin only patients (Grade 1), and in 3.8% (3.79%) of patients treated with Avastin plus irinotecan (Grades 1, 2 and 4).

During the clinical studies, mucocutaneous hemorrhage was observed in up to 50% of patients treated with Avastin. The most frequent cases were Grade 1 epistaxis according to the scale (NCI-CTCAE v.3) lasting less than 5 minutes, and which resolved without the need of medical treatment and did not require any change in the regime with Avastin. Safety clinical data suggest that the incidence of minor mucocutaneous hemorrhages (for example, epistaxis) may be dose-dependent.

Likewise, but with a lesser frequency, cases of minor mucocutaneous hemorrhage were observed in other locations, such as gingival or vaginal hemorrhage.

Thromboembolism (Refer to Warnings and Precautions)

Arterial thromboembolism

An increase in the incidence of arterial thromboembolic reactions was observed in patients treated with Avastin in all the indications. These included stroke, myocardial infarction, transient ischemic attacks and other arterial thromboembolic reactions.

In clinical studies the overall incidence of arterial thromboembolic reactions was of up to 3.8% in the arms including Avastin in comparison with up to 2.1% in the control chemotherapy arms. Fatal outcomes were reported in 0.8% of patients treated with Avastin, compared with 0.5% of patients who were treated only with chemotherapy. Strokes were informed (including transient ischemic attacks) in up to 2.7% of patients treated with Avastin in combination with chemotherapy in comparison with up to 0.5% of patients who received only chemotherapy. Myocardial infarction was reported in up to 1.4% of patients treated with Avastin in combination with chemotherapy, versos up to 0.7% of patients receiving only chemotherapy.

In a clinical study to evaluate Avastin in combination with 5-fluorouracil/folinic acid, AVF2192g, patients with metastatic colorectal cancer who were not candidates for irinotecan treatment were included. In this study, arterial thrombo encephalic reactions were observed in 11% (11/100) of patients vs. 5.8% (6/104) in the control chemotherapy group. In non-controlled clinical study AVF3708g in patients with relapsing glioblastoma, arterial thromboembolic events were observed in up to 6.3% (5/79) of patients receiving Avastin in combination with irinotecan, versos up to 4.8% (4/84) who received only Avastin.

Venous thromboembolism

The incidence of venous thromboembolic reactions in clinical studies was similar in patients treated with Avastin in combination with chemotherapy versus patients receiving only control chemotherapy. Venous thromboembolic reactions include deep vein thrombosis, pulmonary embolism and thromboflebitis.

In clinical studies in all indications, the overall incidence of venous thromboembolic reactions ranged from 2.8% to 17.3% of patients treated with Avastin versus 3.2% to 15.6% in the control groups.

Grade 3-5 (NCI-CTCAE v.3) venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab in comparison with up to 4.9% in patients who received only chemotherapy (in all indications, excluding persistent, recurring or metastatic cervical cancer).

In a clinical study (GOG-0240) in patients with persistent, recurring or metastatic carcinoma of the cervix, Grade 3-5 venous thromboembolic events were reported in up to 15.6% of patients treated with Avastin in combination with paclitaxel and cisplatin compared to up to 7.0% of patients receiving paclitaxel and cisplatin.

Patients who suffered a venous thromboembolic reaction may have a higher risk of recurrence with Avastin in combination with chemotherapy, than with only chemotherapy.

In clinical study BO21990, Grade 3-5 venous thromboembolic events were observed in 7.6% of patients recently diagnosed with glioblastoma, treated with Avastin in combination with chemotherapy and radiotherapy, versus 8.0% of patients receiving only chemotherapy and radiotherapy.

Congestive heart failure

In Avastin clinical studies, congestive heart failure was observed in all the indications of cancer studied so far, although there was a preponderance in patients with metastatic breast cancer. In four Phase III studies in patients with metastatic breast cancer (AVF2119g, E2100, BO17708 and AVF3694g), up to 3.5% of patients treated with Avastin in combination with chemotherapy reported Grade 3 or higher (NCI-CTCAE v. 3) congestive heart failure versus up to 0.9% in the control arms. In the patients of study AVF3694g receiving anthracyclines concomitantly with bevacizumab, the incidences of Grade 3 or higher congestive heart failure in the control arms and with bevacizumab were similar to those of other metastatic breast cancer studies: 2.9% in the anthracycline plus bevacizumab arm and 0% in the anthracycline plus placebo arm. Additionally, in study AVF3694g the incidences of congestive heart failure of any grade were similar in the anthracycline plus Avastin arm (6.2%) and the anthracycline plus pacebo arm (6.0%).

After the adequate clinical therapy, an improvement in the symptoms and/or the left ventricular function was observed in most patients who developed congestive heart failure during the metastatic breast cancer studies.

In most of clinical studies with Avastin, patients with pre-existing congestive heart failure Grade II-V according to the NYHA (New York Heart Association) were excluded, therefore, no information is available related with the risk of worsening of the congestive heart failure in this population.

The previous exposure to anthracyclines and/or prior radiation on the chest wall may be a likely risk factor to develop congestive heart failure.

In a clinical study in patients with diffuse large B-cell lymphoma, an increase in the incidence of congestive heart failure was observed when patients received bevacizumab with a cumulative dose of doxorubicin in excess of 300 mg/m^2. This Phase III clinical study compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab with R-CHOP without bevacizumab. While the incidence of congestive heart failure was in both groups higher than the incidence observed previously for the doxorubicin therapy, the rate was higher in the R-CHOP group plus bevacizumab. These results suggest that a close clinical observation should be considered with adequate heart evaluations in patients exposed to cumulative doxorubicin doses in excess of 300 mg/m^2 when used in combination with bevacizumab.

Hypersensitivity reactions / reactions to the infusion (Refer to Warnings and Precautions, and Adverse Reactions, Post Marketing Experience)

In some clinical studies, anaphylactic reactions and anaphylactoid like reactions with higher frequency in patients who had received Avastin in combination with chemotherapy versus patients treated only with chemotherapy. The incidence of these reactions in some clinical studies with Avastin is frequent (up to 5% in patients receiving bevacizumab).

Infections

In clinical study (GOG-0240) in patients with persistent, recurring or metastatic carcinoma of the cervix, Grade 3-5 infections were reported in up to 24% of patients treated with Avastin in combination with paclitaxel and topotecan, versus up to 13% of patients who received paclitaxel and topotecan.

In randomized, double blind placebo controlled, multicenter Phase III clinical study BO21990 of Avastin in combination with chemotherapy plus radiotherapy for the treatment of patients with recent diagnosis of glioblastoma, the incidence of infections of all Grades was 54.4% and 12.8% for Grade 3-5 infections in the bevacizumab plus chemotherapy and radiotherapy arm, versus 39.1% and 7.8% in the chemotherapy plus radiotherapy only, respectively.

Ovarian insufficiency / Fertility (Refer to Warnings and Precautions)

In Phase III study NSABP C-08 of Avastin for the adjuvant treatment of patients with colon cancer, the incidence of new cases of ovarian insufficiency, defined as amenorrhea lasting 3 months or more, level FSH $\geq$ 30 MUI/ml and a negative value of β-HCG for the pregnancy test, was evaluated in 295 premenopausal women. New cases of ovarian insufficiency were reported in 2.6% of patients in the mFOLFOX-6 group compared to 39% of the Mfolfox-6 plus bevacizumab group. In 86.2% of the women evaluated, the ovarian function was recovered after discontinuing bevacizumab. The long term effect of bencizumab treatment on the fertility is unknown.

Abnormal laboratory findings

The decrease in the neutrophil count and white cells, and the presence of proteins in the urine may be associated with the treatment with Avastin.

As a result of clinical studies, patients treated with Avastin showed the following Grade 3 and 4 (NCI-CTCAE v.3) abnormal laboratory findings with at least 2% of difference in comparison with the corresponding control groups: hyperglycemia, decreased hemoglobin, hypokalemia, hyponatremia, decreased white cell count, and an increase in the International Normalized Ratio (INR).

The clinical tests showed that transitory increases in serum creatinine (ranging between 1.5 and 1.9 times the base line level), with and without proteinuria, are associated with Avastin use. The increase observed in serum creatinine was not linked with a higher incidence of clinical manifestation of renal insufficiency in patients treated with Avastin.

Other special populations

Elderly patients

In randomized clinical studies, an age or more than 65 years was associated with an increase of arterial thromboembolic reactions, including stroke, transient ischemic attacks and myocardial infactions. Other reactions during the Avastin treatment observed with a higher frequency in patients older than 65 years were leukopenia and thrombocytopenia Grades 3-4 (NCI-CTCAE v.3); and neutropenia, diarrhea, headache and fatigue of all Grades in comparison with patients younger than 65 years of age (Refer to Adverse reactions, and Warnings and Precautions, Thromboembolism). In a clinical study, the incidence of Grade ≥3 hypertension was twice higher in patients older than 65 years of age than in the younger group (less than 65 years of age).

In a study in patients with recurring platinum-resistant ovarian cancer cases of alopecia, inflammation of the mucous membranes, sensory peripheral neuropathy, proteinuria and

hypertension, which occurred with a rate of at least 5% higher in the QT + BV group in female patients of 65 years of age or older treated with bevacizumab in comparison with patients younger than 65 years of age equally treated.

No increase in the incidence of other reactions was observed, including gastrointestinal perforation, wound healing complications, congestive heart failure and hemorrhage in elderly patients (older than 65 years) treated with Avastin in comparison with patients younger than 65 years equally treated.

Pediatric population

The safety of Avastin in children and adolescents younger than 18 years of age has not been established. Avastin is not approved for use in patients younger than 18 years of age. Some publications indicate that some cases of non-mandibular osteonecrosis in patients younger than 18 years of age treated with Avastin were observed.

Post-marketing experience

Table 3. Adverse reactions reported during the post-marketing experience

System Organ Class	**Reactions (frequency*)**
Infections and infestations	Necrotizing fascitiis, in general, secondary to wounds resulting from complications in the wound healing, gastrointestinal perforations or formation of fistula (rare) (See Warnings and Precautions)
Immune system disorders	Hypersensitivity reactions and reactions to the infusion (unknown), with the following possible co-manifestations: dyspnea/breathing difficulty, flushing/redness/rash, hypotensionn or hypertension, oxygen desaturation, throacic pain, chills and nausea/vomiting (see Warnings and Precautions; Adverse Reactions, Hypersensitivity Reactions/reactions to the infusion).
Nervous system disorders	Hypertensive encephalopathy (very rare) (See Warnings and Precautions, and Adverse Reactions, hypertension). Posterior reversible encephalopathy syndrome (rare) (see Warnings and Precautions)
Vascular disorders	Renal thrombotic microangiopathy, which could present itself clinically as proteinuria (unknown) with and without the concomitant use of sunitinib (See Warnings and Precautions and Adverse reactions, proteinuria).

Table 3. Adverse reactions reported during the post-marketing experience (Continued)

System Organ Class	Reactions (frequency*)
Respiratory, Thoracic and Mediastinal Disorders	Perforation of the nasal septum (unknown) Pulmonary hypertension (unknown) Dysphonia (frequent)
Gastrointestinal disorders	Gastrointestinal ulcer (unknown)
Hepatobiliary disorders	Gallbladder perforation (unknown)
Musculoskeletal and Connective Tissue Disorder	Cases of maxilar osteonecrosis have been observed in patients treated with Avastin, most of which occurred in those which had risk factors identified in the maxilar osteonecrosis, concretely the intravenous exposure to bisphosphonate and/or history of dental disease which required invasive dental processes (see Warnings and Precautions). Cases of non-mandibular osteonecrosis have been observed in pediatric patients treated with Avastin (see Adverse Reactions, Pediatric Population).
Congenital, family and genetic disorders	Fetal anomanies were observed in women treated with bevacizumab alone or in combination with known embryotoxis chemotherapeutic agents (See Warnings and Precautions; Fertility, pregnancy and lactation).

* If indicated, the frequency was obtained from clinical study data.

The information described in this section was extracted from Avastin® Insert, Revision 2016, approved by ANMAT 17/02/2017.

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4. OBJECTIVES OF THE STUDY

4.1. Primary objectives

The primary objective of this Study was to evaluate the pharmacokinetics and safety profile of Bevacizumab after administering the following investigation products:

- A single IV dose of 1 mg/kg of the test product Bevacizumab-Richmond-Hetero [Test Product 1 local packaging]
- A single IV dose of 1 mg/kg of Avastin® [Local Reference Product]
- A single IV dose of 1 mg/kg of Cizumab® [Test Product 2 manufactured and packaged by Hetero in India]

The products will be administered to volunteer healthy male subjects.

4.2. Secondary objectives

Report the nature and the incidence of adverse events and the eventual discontinuation or drop out in the study or the participation of a subject in the study.

Evaluate the immunogenic potential of the products under investigation.

Evaluate if the transportation / local filling of the product Bevacizumab Richmond Hetero (Test Product 1) affects the pharmacokinetic profile and the safety profile of the molecule with respect to Cizumab® (Test Product 2).

5. ETHICAL CONSIDERATIONS

5.1. Good clinical practices

This Clinical Investigation Protocol will be carried out according to the "Guide for investigations in human beings" issued by the Ministry of Health (Ministry of Health resolution number 1480/11), the Good Clinical Practice Regime for clinical pharmacology studies of the National Administration for Drugs, Food and Medical Technology (ANMAT Provision number 6677/10), good clinical practices standards (as defined in the Guidelines for Good Clinical Practices of the ICH, and in keeping with the Helsinki Declaration " Ethical Principles for Medical Research Involving Human Subjects" of the World Medical Association.

The study will be carried out in compliance with the Clinical Investigation Protocol. The Clinical Investigation Protocol, its amendment(s) and the informed consent of the study subject will receive the approval/favorable opinion of the Independent Ethics Committee (CEI) before starting with the study.

5.2. Independent Ethics Committee

Before the study begins, the Investigator shall obtain the approval/favorable opinion by the CEI in writing of the Clinical Investigation Protocol, the consent form, the materials/process to include the subjects in the study (for example, announcements), and any other written information to be delivered to the study subjects. The Investigator or the sponsor shall provide the CEI with the necessary documents for the ethical evaluation of the Clinical Investigation Protocol, according to the descriptions included in their standard operating procedures.

The Investigator or the sponsor shall provide the CEI with reports, updates and any other information (for example, safety expedited reporting, amendments, administrative letters, study completion report, etc.) according to the local regulatory requirements and the standard operating procedures.

5.3. Informed consent

The Investigator shall ensure that the study subjects, or in the situations in which the consent cannot be given by the study subjects, their legally acceptable representative, have been informed clearly and comprehensively about the study purpose, potential risks and any other critical issues involving the Clinical Investigation Protocol in which the individual volunteers participate. The informed consent of each study subject shall be obtained in writing and shall be delivered willingly by said subject or by the legally acceptable representative if the subject is not in condition to do it, before their participation in the Clinical Investigation Protocol, including the informed consent to conduct any selection procedure to establish the eligibility condition of the study subject for the Clinical Investigation Protocol.

The study subject shall sign two (2) copies of the consent document (Section 2 - Signature Page), of which one copy shall be kept by the study subject and the remaining copy shall be filed in the investigator's file.

5.4. Approvals, notifications, authorizations and records

The following approvals, notifications, authorizations and records of the Clinical Investigation Protocol and the informed consent shall be processed:

• Clinical Investigation Ethics Committee (CEIC)

Larrea 1381 3º A – C1117ABK
C.A.B.A. – Bs. As. – Argentina
Telephone number: (54-11) 4826-3962

• Comité de Docencia e Investigación de Clínica (Teaching and Clinical Investigation Committee) CIAREC
Monroe 4770 – C1431CEF
C.A.B.A. – Bs. As. – Argentina
Telephone number: (54-11)
4541-5700

• Dirección Médica de Clínica (Medical Director's Office) CIAREC
Monroe 4770 – C1431CEF
C.A.B.A. – Bs. As. – Argentina
Telephone number: (54-11) 4541-5700

The following authorization shall be processed:

• Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) Av. de Mayo 869 – C1084AAD
C.A.B.A. – Bs. As. – Argentina
Telephone number: (54-11)
4340-0800

The following registration shall be processed:

• Ministerio de Salud de la Nación
Registro Nacional de Investigaciones en Salud (ReNIS)
Av. 9 de Julio 1925 – C1073ACA C.A.B.A. – Bs. As.
– Argentina, Telephone number: (54-11) 4379-9000

The following notification shall be processed:

• Comité de Ética Central de la C.A.B.A.
Monasterio 480 – C1284AEJ
C.A.B.A. – Bs. As. – Argentina
Telephone number: (54-11) 4123-3160/61/62/63

6. INVESTIGATION PLAN

6.1. Study design

A double blind, randomized, parallel group, balanced, Phase 1 study comparing pharmacokinetics and safety in healthy volunteer male subjects shall be conducted.

6.2. Study phases

For each study subject, the Clinical Investigation Protocol includes 15 visits with an IV perfusion administration regimen during 90 minutes once only according to the following detail:

Visit 1: Screening and inclusion (Day -28 a -1)

Visit 2: Dosing, blood draw, 24 hours confinement (Day 1)

Visit 3: Outpatient blood draw- hour 48 post-infusion (Day 2)

Visit 4: Outpatient blood draw- hour 72 post-infusion (Day 3)

Visit 5: Outpatient blood draw- hour 96 post-infusion (Day 4)

Visit 6: Outpatient blood draw- hour 120 post-infusion (Day 5)

Visit 7: Outpatient blood draw- hour 168 post-infusion (Day 7)

Visit 8: Outpatient blood draw- hour 336 post-infusion (Day 14)

Visit 9: Outpatient blood draw- hour 504 post-infusion (Day 21)

Visit 10: Outpatient blood draw- hour 672 post-infusion (Day 28)

Visit 11: Outpatient blood draw- hour 840 post-infusion (Day 35)

Visit 12: Outpatient blood draw- hour 1008 post-infusion (Day 42)

Visit 13: Outpatient blood draw- hour 1176 post-infusion (Day 49)

Visit 14: Outpatient blood draw- hour 1344 post-infusion (Day 56)

Visit 15: Outpatient blood draw- hour 1512 post-infusion - End of study visit (Day 63)

Table 6.2.1. Study phases

Visits	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Description	Screening / inclusion	Dosing	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	End of Study
Day	-28 to -1	1	2	3	4	5	7	14	21	28	35	42	49	56	63

6.3. Study duration

The estimated duration of the study, for each subject during the clinical stage from recruitment through Visit 15 - End of study- is expected to be approximately 91 days.

6.4. Centers

The screening, inclusion, control, clinical follow up, blood draws and confinement/hospitalization of the study subjects shall be carried out at Unidad de Investigation-clínica farmacocinética FP Clinical Pharma en Clínica CIAREC. The biological study samples shall be transferred to the Analytical center using a transportation system to conduct the quantification of bevacizumab and the determination of antibodies.

6.5. Study population

To be included in the Clinical Investigation Protocol, the following criteria must be met.

6.5.1. Inclusion criteria

1) Written and signed informed consent

- The subjects in the study were willing and able to provide their informed consent in writing

2) Target population

- Study subjects, volunteers, healthy, adults
- Study subjects whose laboratory test results for safety and complementary tests were within the normal values, or that at the discretion of the Investigator did not present a clinical significance: complete blood count, erythrocyte sedimentation rate, hepatogram, urea, creatinine, glucose, coagulogram, serology for HIV, hepatitis B, hepatitis C, urinalysis, detection of drugs of abuse in urine and electrocardiogram
- Body mass index between 19 and 27 kg/m^2 at the screening visit.
- Preferably non-smoker subjects.

3) Age and gender

- Men, 21 through 55 years of age.
- Men in a relationship with a child bearing age spouse agreed to having their spouse use an adequate contraceptive method before entering the study and during at least three months after the study completion. The participants understood that" adequate

contraceptive method" means any hormonal contraceptive or intra uterine device (placed before the beginning of the study) and the use of a spermicidal as a barrier method. The use of a barrier method alone or sexual abstinence was not considered adequate.

- Subjects agreed to not donate sperm during the study and for at four months after the treatment.

6.5.2. Exclusion criteria

1) Medical history and concurrent diseases

- History of the following diseases/conditions: pulmonary, gastrointestinal, hepatic, renal, hematologic, endocrine-metabolic, neurologic or psychiatric origin conditions (especially depressive disorder) at the moment of the anamnesis and the physical examination during the first visit of the Clinical Investigation Protocol.
- History of gastro-intestinal surgery (with the exception of uncomplicated appendectomy at least three months before the study)
- History of major surgery, surgical biopsy and/or history of significant trauma within one month of the screening visit.
- Specifically, preexisting gastrointestinal conditions such as abdominal fistulas, gastrointestinal perforation within the 6 months of the screening visit.
- Specifically, preexisting gastrointestinal conditions such as acute or sub-acute intestinal occlusion.
- Specifically, history of intestinal inflammatory disease.
- History of hemorrhagic diseases and/or coagulopathies and/or thromboembolic events.
- History of cardiac and vascular diseases: specifically, myocardial infarction, unstable angina, stroke, uncontrolled blood hypertension and cardiac arrhythmias.
- History or current occurrence or alcohol or drug abuse.
- Donating blood within the three months prior to screening.
- Administration of any drug under investigation or participation in a clinical investigation study within the three months prior to the scheduled participation in this Clinic Investigation Protocol.
- History or current occurrence of clinically significant diseases or disorders, which, at the discretion of the Investigator, may prevent the participation of the subject in the study due to safety reasons or because they may influence the study results, as well as the capacity of the study subject to participate in the Clinical Investigation Protocol.
- History of hypersensitivity to bevacizumab and/or any of the excipients.

2) Physical findings in laboratory test results

- Following diseases/conditions: cardiac, pulmonary, gastrointestinal, hepatic, renal, hematologic, endocrine-metabolic, neurological or conditions of a psychiatric origin (especially depressive disorders).
- Evidence of ulcers, unhealed wounds or bone fractures.
- Clinically significant abnormalities in any of the laboratory test results and electrocardiograms.
- Positive serology for HIV, hepatitis B, hepatitis C.
- Positive result in the immunogenicity test (anti-bevacizumab serum antibodies).

4) Allergies or adverse drug reactions

- Subjects of the study who presented contraindications to the therapy.

5) Prohibited treatments and/or therapies

- Subjects of the study who received (two weeks prior) or are currently receiving aspirin or clopidogrel.
- The study subjects must have discontinued possible pharmacological treatments at least two weeks prior to the beginning of this Clinical Investigation Protocol.

6) Other exclusion criteria

- Uncooperative subjects.
- Subjects of the study who are employees of the Investigator or the Clinical-Pharmacokinetic Investigation Unit, with a direct participation in the clinical protocol or other clinical protocols directed by the Investigator or the Clinical-Pharmacokinetic Investigation Unit.

The eligibility criteria for this Clinical Investigation Protocol have been considered to guarantee the safety of the study subjects and ensure that the results can be used.

6.5.3. Discontinuation of the treatment by the study subjects

The subjects MUST discontinue the product under investigation (and the non-experimental product, at the discretion of the Investigator) due to any of the following reasons:

- Withdrawal of the informed consent (the decision of the subject to withdraw for whatever reason).
- Any clinical adverse event, abnormal laboratory test results or intercurrent disease, which, at the discretion of the Investigator, indicates that the participation in the study is not the best option for the study subject.
- Medical contraindication to continue receiving the product under investigation.

The subjects of the study may have the therapy of the Clinical Investigation Protocol discontinued and/or removed from the Clinical Investigation Protocol due to the following reasons:

- Incapacity to comply with the Clinical Investigation Protocol.
- Significant lack of adherence by the study subject.
- Investigator's discretion.
- Need to take prohibited medications.
- Unavoidable administrative or scientific reasons.

Efforts must be made so that all the study subjects who discontinue the treatment of the Clinical Investigation Protocol comply with the end of study procedures specified in the Clinical Investigation Protocol described in Section 8.1.1.15.

The only exception to this pre-requisite is when the study subject withdraws his/her consent for all the procedures of the Clinical Investigation Protocol or loses his/her capacity to grant the consent freely.

6.5.4. Study subject substitution

Study subjects who dropped out cannot be substituted.

7. TREATMENTS

7.1. Treatments of the study

All the products under investigation and non experimental products included in the Clinical Investigation Protocol are considered products under investigation.

7.1.1. Product under investigation

A product under investigation is defined as follows:

A pharmaceutical form of an active ingredient or placebo that is being evaluated or used as a reference in a Clinical Investigation Protocol, including products that already have a free sale authorization but are used or presented (as to the formulation or the packaging) in a different form than the pharmaceutical form authorized, or used for an indication not approved, or when they are used to obtain more information about the approved pharmaceutical form.

In this Clinical Investigation Protocol the products under investigation are:

- Test Product 1: Bevacizumab Richmond-Hetero, manufactured by Hetero Biopharma Limited, India; transported in bulk and dosed and packaged in Laboratorios Richmond S.A.C.I.F., Argentina

- Reference product: Avastin® Bevacizumab Productos Roche S.A.Q. e I.

- Test Product 2: *Cizumab® Bevacizumab de Hetero Biopharma Limited, manufactured and packaged in India

* Product Cizumab® from Hetero Biopharma Limited is the same product in bulk that Richmond doses/fills in Argentina, Bevacizumab Richmond-Hetero. Cizumab® is approved to be sold in India since 13 May 2016. This approval is based on a series of comparability studies among which is found a Phase III study "Prospective, randomized, multi-dose, multicenter, parallel comparative study to evaluate the efficacy, safety and immunogenicity and pharmacokinetics of a Bevacizumab IV infusion (Test Product, Hetero) and the medicinal reference product (Reference product, Roche) administered in combination with standard chemotherapy in patients with metastatic colorectal cancer" (version in English and Spanish), registry number of the Clinical Trials Registry - India (CTRI): CTRI/2015/05/005757, non inferiority study which was completed as of the date in which a total of 137 patients with metastatic colorectal cancer were evaluated.

7.1.2. Non-experimental product

Other medications used in the Clinical Investigation Protocol as support medication or escape mediation as prevention, diagnosis medications or resulting from therapeutic reasons, as components of the standard treatment for a given diagnosis are considered non-experimental products.

Not applicable to this Clinical Investigation Protocol.

7.1.3. Identification

Table 7.1.3.1. Description of the products under investigation

API	Bevacizumab	Bevacizumab
Trade name	Bevacizumab Richmond-Hetero	Cizumab®
Treatment	Test 1	Test 2
Treatment code	T1	T2
Pharmaceutical form	Solution for IV infusion	Solution for IV infusion
Route of administration	IV- perfusion	IV- perfusion
Presentations	100 mg/4 ml	100 mg/4 ml

Dosing regime	1 mg/kg in 90 minutes	1 mg/kg in 90 minutes
Total dose	1 mg/kg	1 mg/kg
Frequency	Single dose	Single dose
Origin	Manufactured by Hetero Biopharma Limited, India; Transported in bulk from India and filled and packaged in Laboratorios Richmond S.A.C.I.F., Argentina	Hetero Biopharma Limited, manufactured and packaged in India

API	Bevacizumab
Trade name	Avastin®
Treatment	Reference
Treatment code	R
Pharmaceutical form	Solution for IV infusion
Route of administration	IV- perfusion
Presentation	100 mg/4 ml
Dosing regime	1 mg/kg in 90 minutes
Total dose	1 mg/kg
Frequency	Single dose
Origin	Productos Roche S.A.Q. e I.

7.1.4. Packaging and labeling

The packaging and labeling of the products under investigation is the responsibility of the Sponsor of the Clinical Investigation Protocol.

The containers shall have a label showing the name of the company, domicile, Clinical Investigation Protocol code, name of the drug, concentration, information about storage conditions and an investigation warning statement. Additional statements shall be added on the label(s) according to local regulations.

The reference products shall be provided by the Sponsor in the manufacturer's original packaging.

7.1.5. Handling and delivery

The drug of the Clinical Investigation Protocol shall be provided by the Sponsor to the Investigator and it shall be stored in a safe location according to the local regulations. The Investigator shall be responsible for ensuring that the products under investigation are delivered only to the study subjects. The products under investigation shall be distributed only in the clinical center of the Clinical Investigation Protocol by the authorized personnel, according to local regulations.

The investigator shall ensure that the products under investigation are stored in line with the established ambient conditions (temperature, light and humidity). Bevacizumab must be stored in accordance with the specifications which shall be provided by Laboratorios Richmond S.A.C.I.F. If doubts arise as to the quality or appearance of the experimental product, then the product shall not be administered and the Sponsor shall be advised.

See Section 11.2.2 for information about the conservation of the records of the product under investigation, and Section 11.3 for instructions to return and destroy the product under investigation.

7.1.6. Blinding and unblinding procedures

This Clinical Investigation Protocol is a double blind study.
The study subjects, the investigators, the sponsor, the monitor, the analytical center and the data analyst will not know the treatments assigned.
Each product in its original primary packaging shall be packaged in a blinding secondary package and labeled with the fantasy name "Product A", "Product B" or "Product C".
The link between "Product A, B or C" with Test Product 1, 2, or Reference Product, shall be kept in two independent copies in a sealed envelope. One copy shall remain in the possession of the Sponsor and the other envelope shall be delivered to the Principal Investigator. The envelope may only be opened if there is a medical emergency. The Investigator shall follow the study randomization procedures and shall make sure that the code is only broken according to the protocol. The Investigator shall document and give a brief explanation to the sponsor if the identity of the product under investigation is revealed (be it accidentally or due to a serious adverse event).

7.2. Method to assign treatments

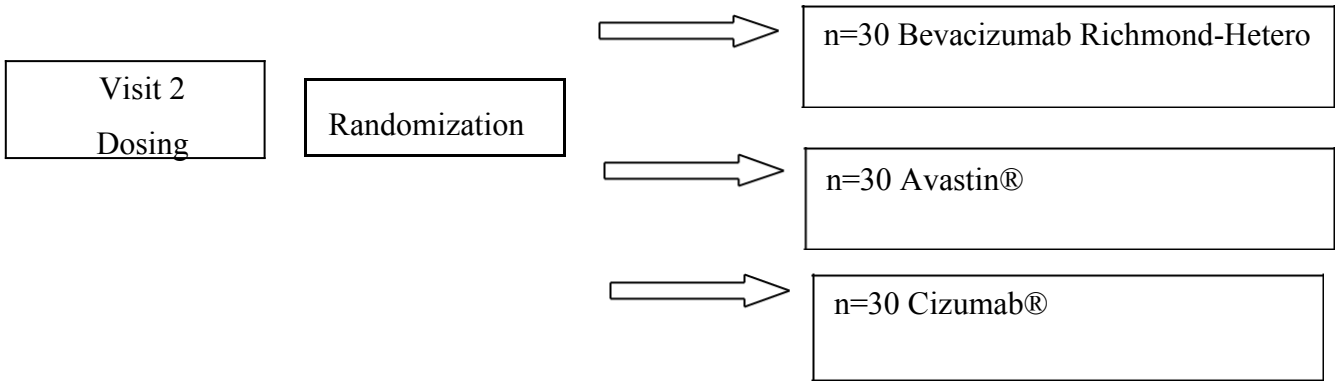
Each study subject included in the Clinical Investigation Protocol shall be assigned a ***randomization number*** at the moment the Investigator conducts the dosing visit. The ***randomization number*** is created using a specific software which generates a treatment assignment randomized list (randomization scheme), so that each randomization number is linked to a single treatment each study subject shall receive.

Table 7.2.1. Treatment assignment

Ninety (90) subjects shall be randomized to the three treatments under investigation in a 1:1:1 ratio. Then N=90 [total N], and n=30 [n per treatment]. The study subjects shall receive a number from 01 to 90 at random, each number corresponds to the assignment of a single treatment under investigation.

The investigator shall receive a randomization list which shall be kept filed in the investigator's file.

The treatment assignment scheme is included below:



7.3. Dose selection and schedule for each study subject

According to studies published involving bevacizumab in healthy volunteers a 30 minutes infusion at a dose of 1 mg/kg of body weight is considered safe for a healthy population *(Hettema W, 2017; Tajima N, 2017; Knight B, 2016)*.

7.4. Concomitant treatments

7.4.1. Prohibited treatments and/or restricted use

The study subjects are not allowed to receive any medication different from the medications of the Clinical Investigation Protocol during the study period.

Once the study subjects are included, they shall not start any treatment with any systemic therapy during the duration of this Clinical Investigation Protocol. The study subjects requiring a systemic therapy shall be analyzed by the Investigator before starting the therapy, whenever this is possible.

The study subjects shall abstain from consuming products containing caffeine, xanthines and alcohol starting 72 hours prior to the confinement/hospitalization visit and during the whole of the Clinical Investigation Protocol.

7.4.2. Other restrictions and precautions

The study subjects shall be warned that any new therapy with prescribed or over the counter medication, or herbs-based / nutritional medication must be discussed in detail with the Investigator before it is started, since the concomitant use may cause significant events interfering with the objectives of this Clinical Investigation Protocol.

The study subjects shall abstain from consuming drinks and foods containing xanthines, and foods which are difficult to digest within 72 hours prior to the confinement/hospitalization visit, and during said visit.

During the confinement/hospitalization visit, the study subjects shall only ingest the meals provided by the center. Subjects shall remain in a fasting condition for 10 hours prior to the administration of the medication under study and up to 4 hours after said administration. The study subject shall not consume any snack in-between the meals provided. Only water shall be allowed (with the exception of 1 hour prior and up to 2 hours after the administration of the treatments).

The study subjects shall avoid extenuating exercise, contact sports and sunbathing during the 72 hours prior to the confinement/hospitalization visit and during said visit.

7.5. Treatment adherence

The study subjects shall receive 1 single dose of the test 1, 2 or reference treatments. The treatments shall be administered by IV infusion as a 90 minutes perfusion.

To ensure treatment adherence, the Investigator (or the person appointed), shall verify the intravenous infusion.

The Investigator (or the person appointed) shall record the process in the source documents of the study.

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8. STUDY EVALUATIONS AND PROCEDURES

8.1. Schedule of events

Refer to **Table 8.1.1. Schedule of events** on the following page.

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Phase	*Screening & inclusion*	*Dosing*	*Follow up*												*End of Study*
Day	*-28 to -1*	*1*	*2*	*3*	*4*	*5*	*7*	*14*	*21*	*28*	*35*	*42*	*49*	*56*	*63*
Visit	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
Explaining the features and scope of the participation in the Clinical Protocol	X														
Obtaining the informed consent	X														
Reviewing and confirming eligibility	X														
Obtaining the comprehensive medical record	X														
Conducting physical check up	X														X
Vital signs (Including: blood pressure, heart rate Respiratory rate, axillary temperature)[1]	X	X			X			X		X		X			X
Other evaluations (Including: body weight, size and body mass index)	X														
History and review of concomitant medications	X														
(Blood) sample for initial safety laboratory test results[2]	X														
(Blood) sample for serological detection dashboard[3]	X														
(Blood) sample for immunogenicity[4]	X														X
Sample for urinalysis	X														X
Drugs of abuse in urine	X	X													
Electrocardiogram	X	X				X			X			X			X
Instructions with indications and restrictions for the subject of the study	X														
Study subject randomization		X													
24-hour confinement / hospitalization		X													
Measuring body weight		X (pre-dose)													
Administration of the product under investigation IV infusion during 90 minutes)		X													
Obtaining samples for PK[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
(Blood) sample for final safety laboratory test results[6]															X
Food		X													
Discharge		X													
Anamnesis about compliance with diet, fasting Concomitant medication, restrictions and contraception		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation and adverse event recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1= At the times and conditions described in Section 8.5.4.1 **2**= Including: CBC, erythrocyte sedimentation rate, hepatogram (alkaline phosphatase, TGO, TGP, direct and indirect total bilirubin), urea, creatinine, glucose, coagulogram (prothrombin time, KPTT) **3**= Including: HIV, hepatitis B (HBsAg) and C (Anti HCV) **4**= Immunogenicity (anti-bevacizumab antibodies) **5**= Pre-infusion: 0.00; During infusion: 0.33-0.50-1.00-1.50 hours; Post-infusion: 20 min, 40 min, 1.00, 2.00, 4.00, 8.00, 12.00, 24.00, 48.00, 72.00, 96.00, 120.00, 168.00, 336.00, 504.00, 672.00, 840.00, 1008.00, 1176.00, 1344.00 & 1512.00 hours **6**= Including: CBC, erythrocite sedimentation rate, hepatogram (alkaline phosphatase, TGO, TGP, direct and indirect total bilirubin), urea, creatinine, glucose

8.1.1. Procedures according to visit

The visits scheduled in the Clinical Investigation Protocol are as follows:

Visit 1: Screening and inclusion (Day -28 to -1)

Visit 2: Dosing, blood draw, 24 hours confinement (Day 1)

Visit 3: Outpatient blood draw- hour 48 post-infusion (Day 2)

Visit 4: Outpatient blood draw- hour 72 post-infusion (Day 3)

Visit 5: Outpatient blood draw- hour 96 post-infusion (Day 4)

Visit 6: Outpatient blood draw- hour 120 post-infusion (Day 5)

Visit 7: Outpatient blood draw- hour 168 post-infusion (Day 7)

Visit 8: Outpatient blood draw- hour 336 post-infusion (Day 14)

Visit 9: Outpatient blood draw- hour 504 post-infusion (Day 21)

Visit 10: Outpatient blood draw- hour 672 post-infusion (Day 28)

Visit 11: Outpatient blood draw- hour 840 post-infusion (Day 35)

Visit 12: Outpatient blood draw- hour 1008 post-infusion (Day 42)

Visit 13: Outpatient blood draw- hour 1176 post-infusion (Day 49)

Visit 14: Outpatient blood draw- hour 1344 post-infusion (Day 56)

Visit 15: Outpatient blood draw- hour 1512 post-infusion - End of Study Visit (Day 63)

8.1.1.1. Visit 1: Screening and inclusion (Day -28 to -1)

The study subjects shall be evaluated with respect to their participation in the Clinical Investigation Protocol, and the eligibility shall be determined by evaluating the inclusion and exclusion criteria listed in Sections 6.5.1 and 6.5.2.

The procedures to be performed during this visit include:

- Oral explanation to the subject of the features and scope of the subject's participation in the Clinical Investigation Protocol
- Obtaining the written informed consent before performing any procedure of the Clinical Investigation Protocol

- Review and confirmation of the subject eligibility, according to the inclusion and exclusion criteria listed in Sections 6.5.1 and 6.5.2.
- Obtaining the full medical record
- Physical examination
- Obtaining vital signs (blood pressure [sitting position after 5 minutes at rest] heart rate, respiratory rate, axillary temperature).
- Obtaining other safety evaluations (body weight, size and calculation of body mass index)
- Obtaining history and review of concomitant medications
- Obtaining (blood) sample for safety laboratory test results
- Obtaining (blood) sample for serologic detection dashboard
- Obtaining (blood) sample for immunogenicity
- Obtaining urine sample for full urinalysis
- Tests to determine drugs of abuse
- 12-channel electrocardiogram.
- Delivery of written instructions containing indications and restrictions to study subject

The study subject shall be considered included when the informed consent form is signed.

After the inclusion, the subject shall be contacted to inform them of their inclusion/exclusion in this Clinical Investigation Protocol. At the moment of confirming the inclusion of the study subject, the scheduling of the following visits included in this Clinical Investigation Protocol shall be performed.

The study medical team shall inform the study subject of their inclusion or not inclusion in this study.

If changes in the health status of the subject are detected impeding the subject's participation in this study, the medical team shall then inform the subject of this situation, shall provide advice as to the medical follow up and shall refer the subject to the clinician or hospital medical service, as appropriate.

The inclusion shall be made in a period of not more than 4 weeks after the signature of the informed consent.

8.1.1.2. Visit 2: Dosing, blood draw, 24 hours confinement (Day 1)

The procedures to be performed during this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)

- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining a (urine) sample to determine drugs of abuse
- Performing 12 channel electrocardiogram
- Measuring body weight [prior to the administration of the product under investigation]
- Obtaining vital signs (blood pressure, heart rate, respiratory rate, axillary temperature) prior to the administration of the product under investigation and at the times described in Section 8.5.4.3
- Randomization of the study subject
- Placing a peripheral line in a forearm vein, preferably
- IV administration of the product under investigation according to the randomization scheme of the Clinical Investigation Protocol
- Obtaining samples for PK according to the extraction schedule [Pre-infusion; during the infusion; post infusion (up to hour 24:00)]
- Evaluation and recording of adverse events
- Supervision of the intake of food and water provided during the confinement/hospitalization
- Reviewing with the study subject of the fasting requirements (at least 10 hours); indications and restrictions for follow up visits before the next scheduled follow up visit.
- Discharge of the subject at 24 hours post dose

8.1.1.3. Visit 3: Outpatient blood draw- hour 48 post-infusion (Day 2)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining sample for PK corresponding to hour 48 post infusion
- Evaluation and recording of adverse events
- Reviewing with the study subject of the fasting requirements (at least 10 hours); indications and restrictions for follow up visits before the next scheduled follow up visit.

8.1.1.4. Visit 4: Outpatient blood draw- hour 72 post-infusion (Day 3)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining sample for PK corresponding to hour 72 post infusion
- Evaluation and recording of adverse events

8.1.1.5. Visit 5: Outpatient blood draw- hour 96 post-infusion (Day 4)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining vital signs (blood pressure, heart rate, respiratory rate and axillary temperature)
- Obtaining sample for PK corresponding to hour 96 post infusion
- Evaluation and recording of adverse events

8.1.1.6. Visit 6: Outpatient blood draw- hour 120 post-infusion (Day 5)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Performing 12 channel electrocardiogram
- Obtaining sample for PK corresponding to hour 120 post infusion
- Evaluation and recording of adverse events

8.1.1.7. Visit 7: Outpatient blood draw- our 168 post-infusion (Day 7)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)

- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining sample for PK corresponding to hour 168 post infusion
- Evaluation and recording of adverse events

8.1.1.8. Visit 8: Outpatient blood draw- hour 336 post-infusion (Day 14)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining vital signs (blood pressure, heart rate, respiratory rate and axillary temperature)
- Obtaining sample for PK corresponding to hour 336 post infusion
- Evaluation and recording of adverse events

8.1.1.9. Visit 9: Outpatient blood draw- hour 504 post-infusion (Day 21)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Performing 12 channel electrocardiogram
- Obtaining sample for PK corresponding to hour 504 post infusion
- Evaluation and recording of adverse events

8.1.1.10. Visit 10: Outpatient blood draw- hour 672 post-infusion (Day 28)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception

- Obtaining vital signs (blood pressure, heart rate, respiratory rate and axillary temperature)
- Obtaining sample for PK corresponding to hour 672 post infusion
- Evaluation and recording of adverse events

8.1.1.11. Visit 11: Outpatient blood draw- hour 840 post-infusion (Day 35)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining sample for PK corresponding to hour 840 post infusion
- Evaluation and recording of adverse events

8.1.1.12. Visit 12: Outpatient blood draw- hour 1008 post-infusion (Day 42)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining vital signs (blood pressure, heart rate, respiratory rate and axillary temperature)
- Performing 12 channel electrocardiogram
- Obtaining sample for PK corresponding to hour 1008 post infusion
- Evaluation and recording of adverse events

8.1.1.13. Visit 13: Outpatient blood draw- hour 1176 post-infusion (Day 49)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception

- Obtaining sample for PK corresponding to hour 1176 post infusion
- Evaluation and recording of adverse events

8.1.1.14. Visit 14: Outpatient blood draw- hour 1344 post-infusion (Day 56)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Obtaining sample for PK corresponding to hour 1344 post infusion
- Evaluation and recording of adverse events

8.1.1.15. Visit 15: Outpatient blood draw- hour 1512 post-infusion – End of Study visit (Day 63)

The procedures to be performed in this visit include:

- Admission of the study subject to Unidad de investigación clínica-farmacocinética in a fasting condition (at least 10 hour fasting)
- Anamnesis about compliance with diet, fasting, concomitant medication, restrictions, adverse events and contraception
- Performing physical examination
- Obtaining vital signs (blood pressure, heart rate, respiratory rate and axillary temperature)
- Obtaining immunogenicity (blood) sample
- Obtaining a urine sample for full urinalysis
- Performing 12 channel electrocardiogram
- Obtaining sample for PK corresponding to hour 1512 post infusion
- Obtaining (blood) sample for final safety laboratory test results
- Evaluation and recording of adverse events

If an adverse event occurred, irrespective of the causal relationship with the product under investigation, this shall be notified according to Section 9.5. Adverse Event Reporting

If no adverse event occurred, Visit 15 shall be considered as End of Study Visit for each study subject.

8.1.2. Eating plan

This corresponds to the eating plan included for Visit 2. The remaining of the study visits were outpatient visits. The study subjects shall have a balanced diet.

Standardized meals and/or menus shall be provided. The hours the meals shall be served are as follows:

Breakfast

- No breakfast shall be provided. This clinical investigation protocol requires a fasting period of at least 10 hours.

Lunch

- Approximately 4 hours after the administration of the medication

Snack

- Approximately 8 hours after the administration of the medication

Dinner

- Approximately 12 hours after the administration of the medication

All meals shall be ingested in the space of 30 minutes. The subject shall try to ingest all the food. The starting and end time of food intake shall be recorded in the source documents, as well as the percentage of food consumed.

Regarding water drinking, the morning of the hospitalization visit subjects are not allowed to drink water during the previous half hour to the administration of the medication. Water drinking is allowed at request after two hours past the medication administration.

8.1.3. Blood samples

8.1.3.1. PK blood sampling schedule

In Visit 2 through Visit 15, a total of 26 venous blood samples shall be obtained from every subject according to the following schedule:

- Pre-infusion: 0.00 hours
- During the infusion: 0.33, 0.50, 1.00, 1.50 hours

- Post-infusion: 20 min, 40 min, 1.00, 2.00, 4.00, 8.00, 12.00, 24.00, 48.00, 72.00, 96.00, 120.00, 168.00, 336.00, 504.00, 672.00, 840.00, 1008.00, 1176.00, 1344.00 and 1512.00 hours

The exact hours of all blood draws shall be recorded in the source documents of the Clinical Investigation Protocol.

8.1.3.2. Extraction

With the subject lying down on the bed, at an angle of approximately 45 degrees, in a dorsal decubitus position, a line or Abbocath type catheter shall be placed in a permeable peripheral venous access. This line shall remain placed (if possible) until the completion of the confinement/hospitalization of each period, in order to avoid multiple punctures.

This line will be constantly purged with physiological saline solution. The total volume of the physiological saline solution the subject receives shall be recorded in the nurse's source documents.

If the line becomes non operational, it may be replaced with a new one on another vein of the same arm or the other arm.

If this inconvenience occurs near the hour in which the sample must be obtained, the sample may be obtained by direct puncture and then place a new line during the timeframe before the next extraction.

8.1.3.3. Labeling

The labeling of the tubes shall be agreed with the Analytical Laboratory.

8.1.3.4. Volume

During Visit 1 and after signing the informed consent, a first sample containing approximately 10 ml of blood shall be obtained as outpatient in order to run the initial safety and immunogenicity tests (pre-study).

From Visit 2 through Visit 15, twenty-six (26) samples will be obtained from each study subject containing approximately 10 ml of blood each. The total amount of blood to be drawn in these Visits will be approximately 260 ml [including final safety analysis and immunogenicity (post-study) corresponding to Visit 15].

For each sample, approximately 10 ml of blood shall be drawn, with a total of 270 ml of blood drawn along the study (including samples to run the initial safety and immunogenicity analysis

(pre-study of Visit 1 and post-study of Visit 15).

8.1.3.5. Storage and transportation

The samples obtained from each study subject, for each sampling time shall be stored according to the specifications of the analytical method of the Unidad de investigación clínica-farmacológica up to the moment they are transported to the Analytical Center.

The form "Biological Sample Shipment" shall be filled out each time the samples are transported from Unidad de investigación clínica-farmacocinética to the Analytical Center.

The original copy of the form shall be filed in the investigator's file.

The samples shall be packaged for transportation by skilled staff trained for that task, using adequate thermal containers fitted with refrigerating material to keep the cold chain at all times.

The transportation is the responsibility of the Analytical Center and it shall comply with Good Practices regarding transportation and storage of samples, according to current regulations.

8.1.3.6. Sample rejection

The criterion to reject samples shall be the one defined in the validation report of the analytical method.

8.2. Analytical method

Bevacizumab levels shall be determined using a validated ELISA method. Samples shall be quantified in Syngene International Ltd. Biocon Park, SEZ, Bommasandra Industrial Area - Phase-IV, Bommasandra-Jigani Link Road, Bangalore 560 099 India.

8.3. Efficacy evaluations

8.3.1. Main efficacy evaluation

Bioavailability shall be evaluated from the quantification of bevacizumab in the samples obtained from the study subjects.

The primary analysis shall consist in calculating the pharmacokinetic parameters from the individual concentrations at each sampling time using the non-compartmental and/or compartmental model.

The pharmacokinetic parameters calculated shall include, but are not limited to, the following:

- C_{max}: Peak serum concentration obtained directly from the serum concentration-time curve [Day 1 through Day 63]
- AUC_{0-t}: Area under the serum concentration-time curve from time 0 to the last experimental point, calculated using the trapezoidal rule [Day 1 through Day 63]
- AUC_{0-inf}: Area under the serum concentration-time curve from time zero to infinity
- T_{max}: Time to reach serum peak concentration, which is obtained directly from the serum concentration-time curve.
- λz: Elimination constant calculated using a linear regression analysis of the semi-logarithmic curve.
- T1/2 λz: Elimination half life
- Systemic clearance
- Volume of distribution

The pharmacokinetic parameters described shall be calculated for the test product and for the reference products.

The results shall be presented as follows:

- Individual data: Unit of measure, value at each time, sequence, treatment received.
- Concentration/time data: arithmetic mean, median, standard deviation, percent coefficient of variation, minimum value, maximum value.
- Serum concentration-time curves for every subject, with non-transformed data.
- Serum concentration-time curves compared for test and reference products with average values for each sampling time, for non-transformed data.
- Pharmacokinetic parameters: individual data and descriptive statistic including: arithmetic mean, median, geometric mean, standard deviation, percent coefficient of variation, minimum value, maximum value.

The analysis shall be made using Phoenix® WinNonlin® software, version 7.0 from Certara USA, Inc. The software is authorized by license granted to F.P. Clinical Pharma S.R.L.

8.4. Immunogenicity evaluation

The immunogenic potential shall be evaluated by the presence of anti-bevacizumab serum antibodies in the serum samples obtained from the study subjects.

The immunogenic potential shall be evaluated for each treatment, in Visits 1 and 15.

8.5. Safety evaluations

Anamnesis, physical examination, clinical laboratory tests (initial-final safety laboratory dashboard, serologic detection dashboard, immunogenicity) and electrocardiogram shall be performed. Blood pressure, heart rate, respiratory rate and axilliary temperature shall be measured.

8.5.1. Blood safety laboratory dashboard, serum detection dashboard and immunogenicity

All the clinical laboratory samples shall be retrieved in the morning after the study subject has fasted for at least 10 hours before the blood draw.

Additional blood and urine samples may be obtained at specific time points to run laboratory tests.

8.5.1.1. Blood safety laboratory dashboard for initial safety laboratory tests

The blood clinical laboratory tests to evaluate the initial safety of the study subjects shall be made at Visit 1.

8.5.1.1.1. Blood test

Complete Blood Count (CBC)

- Red cells, leukocytes, hemoglobin, hematocrit

Relative leukocyte formula

- Segmented neutrophils, eosinophils, basophils, lymphocytes, monocytes

Hematimetric indices

- MCV (Mean corpuscular volume), MCH (Mean corpuscular hemoglobin), MCHC (Mean corpuscular hemoglobin concentration)

Erythrocyte sedimentation rate

8.5.1.1.2. Serum chemistry

Uremia, creatinine, blood sugar level
Hepatogram

- Alkaline phosphatase - FAL, TGO/AST, TGP/ALT, total bilirubin, direct bilirubin, indirect bilirubin

8.5.1.1.3. Clotting time

Prothrombin time and concentration, KPTT

8.5.1.1.4. Serum detection dashboard

HIV, Hepatitis B (HBsAg), Hepatitis C (Anti HCV)

8.5.1.2. Blood safety laboratory dashboard for final safety laboratory tests

The blood clinical laboratory tests to evaluate the final safety of the study subjects shall be made at Visit 15.

8.5.1.2.1. Blood test

Complete blood count

- Red cells, leukocytes, hemoglobin, hematocrit

Relative leukocyte formula

- Segmented neutrophils, eosinophils, basophils, lymphocytes, monocytes

Hematimetric indices

- MCV (Mean corpuscular volume), MCH (Mean corpuscular hemoglobin), MCHC (Mean corpuscular hemoglobin concentration)

Erythrocyte sedimentation rate

8.5.1.2.2. Serum chemistry

Uremia, creatinine, blood sugar level
Hepatogram

- Alkaline phosphatase - FAL, TGO/AST, TGP/ALT, total bilirubin, direct bilirubin, indirect bilirubin

8.5.2. Laboratory urine test dashboard for safety

The clinical urine laboratory tests to evaluate the safety of the study subjects shall be made at Visit 1. The following determinations shall be made:

Color, appearance, density, pH, albumin, hemoglobin, glucose, ketonuria, bile pigments, bile salts, urobilin.

Microscope examination: cells, leukocytes, pyocytes, red cells, cylinders.

8.5.2.1. Detecting drugs of abuse

The detection of drugs of abuse [marijuana, cocaine, opiates and benzodiazepines] by means of a urine reactive dashboard at Visits 1 and 2.

8.5.3. Electrocardiogram

A 12-channel ECG shall be made at Visits 1, 2, 6, 9, 12 and 15.

8.5.4. Measuring blood pressure, heart rate, respiratory rate and axillary temperature

8.5.4.1. Blood pressure, heart rate and respiratory rate.

The measurements of blood pressure, heart rate and respiratory rate shall be made at Visits 1, 2, 5, 8, 10, 12 and 15

8.5.4.2. Axillary temperature

The measurement of axillary temperature shall be made at Visits 1, 2, 5, 8, 10, 12 and 15.

8.5.4.3. Schedule to measure blood pressure, heart rate, respiratory rate and axillary temperature during the study Visits

The measurements of blood pressure, heart rate, respiratory rate and axillary temperature at Visits 1, 5, 8, 10, 12 and 15 shall be performed after the study subject has remained in a sitting position, at rest, for approximately 5 minutes.

The measurements of blood pressure, heart rate, respiratory rate and axillary temperature at Visit 2 shall be prior to the administration of the product under investigation and after the PK sample draws of hours 2.00, 4.00, 8.00, 12.00 and 24.00 post dose.

8.5.5. Further evaluations

8.5.5.1. Body weight, size and body mass index (BMI)

The measurements for body weight, size and calculation of the body mass index shall be made at Visit 1.

The weight shall be checked at Visit 2 prior to the administration of the product under investigation.

8.5.5.2. Physical examination

A physical examination shall be conducted at Visits 1 and 15. It shall include the following: general appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdomen, lymph nodes, extremities, neurologic system, skin and muscular-skeletal system.

9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse event

An ***Adverse Event (AE)*** is defined as any adverse medical occurrence in a patient or subject of a clinical study of a product involving the health, or a therapeutic procedure and which does not have a necessary causal relationship with this treatment. An adverse event may be any unfavorable and unintended sign, including abnormal laboratory test results, symptoms or diseases temporarily associated with the use of the product under investigation, whether they are related or unrelated.

Some examples of adverse events include, but are not limited to:

Clinically significant symptoms and signs

Abnormal findings in clinically significant supplementary tests
Changes in the findings of the physical examination
Hypersensitivity
Progression/worsening of an underlying disease
Additionally, some signs and symptoms resulting from:
Lack of efficacy
Overdosing
Abandoning the medication
Misuse, abuse of the drug
Drug interactions
Drug dependence
Extravasation

9.1.2. Serious Adverse Event

A ***Serious Adverse Event (SAE)*** is defined as any unfavorable occurrence during the duration and in the context of an investigation of a product or a diagnostic or therapeutic procedure which results in the death, threat to the life, requires hospitalization or prolonging the existing hospitalization, results in persistent or significant incapacity or disability or is a congenital anomaly or birth defect or is medically significant according to the medical opinion: those events, that in the opinion of the investigator may harm the subject and/or require medical or surgical intervention to prevent any of the conditions mentioned above. The above also applies without the presumption of the existence of a causal link between the application of the product or treatment and the adverse event.

9.1.3. Unexpected Adverse Event

An ***Unexpected Adverse Event*** is defined as any adverse event which was not previously documented, from the perspective of previously observed and not on the basis of what could be anticipated from the pharmacological properties of a drug, that is, the nature or the severity is not consistent with the information in the corresponding source document(s) such as the investigator's brochure or product insert.

9.1.4. Adverse Drug Reaction

An ***Adverse Drug Reaction (ADR)*** is defined as a harmful and unintended response to a medicinal product related with any dose. In the clinical experience before the approval of a new medicinal product or new uses, especially when the therapeutic dose cannot be established, any adverse drug reaction is considered to be any reaction that implies a causal relationship between a medicinal product and an adverse event as a reasonable possibility, that is, that the relationship cannot be ruled out. In approved medicinal products that are sold on the market, an ADR is the harmful and

unintended response to a drug, harmful and unintended which occurs at doses normally used in humans for prophylaxis, diagnosis or therapeutics of the diseases or modification of physiological functions.

9.1.5. Serious and Unexpected Adverse Drug Reaction (SUADR)

A ***Serious and Unexpected Adverse Drug Reaction (SUADR)*** is defined as an adverse reaction resulting in death, threat to life, requires hospitalization or prolonging the existing hospitalization or causes persistent or significant incapacity or disability, and whose nature or severity is not consistent with the product information described in the investigator's brochure for a non approved product under investigation, or in the insert of an approved medicinal product.

9.2. Collection

All the adverse events observed or voluntarily reported by the study subject shall be collected during the course of the investigation study, irrespective of the treatment group or of the suspicion of a causal relationship with the product(s) under investigation.

The study subject is informed by the IP about their responsibility of reporting all the physical changes occurring during the investigation study.

For all adverse events, the IP or the staff appointed shall use their best efforts to obtain the adequate information regarding the beginning and end of the adverse event and its characteristics, which will enable a determination of its severity and causality, as well as evaluating if the event meets the classification criteria for a serious adverse event.

9.3. Evaluation

9.3.1. Evaluating the severity

The IP or the staff appointed shall determine the severity of the adverse event using the following categories: "mild, moderate, severe". These categories are required in the adverse event reporting form of the Clinical Data Form (FDC - CDF). For consistency purposes, the degrees of severity are defined as follows. Mild: It does not interfere with the subject's normal activity; moderate: It somehow interferes with the subject's normal activity; severe: It significantly interferes with the subject's normal activity. When applicable, the severity categories established by the Common Terminology Criteria for Adverse Events (CTCAE)

Grade 1 (mild): Asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated.

Grade 2 (Moderate): minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of the daily living, for example: preparing meals, shopping for groceries, using the telephone, managing money, etc.

Grade 3 (severe or medically significant but not immediately life-threatening); hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of the daily living, for example bathing, dressing and undressing, feeding self, using the toilet, taking medication and not bedridden.

Grade 4 (life threatening consequences): urgent intervention indicated.

Grade 5 (lethal): Death related to the adverse event. It must be noted that not all grades of this scale are appropriate for all adverse events, therefore, some adverse events may have fewer than 5 grades.

9.3.2. Evaluating the seriousness

The IP or staff appointed shall determine the seriousness of the adverse event. The adverse event shall be considered "serious" if it meets any of the characteristics described in the definition of serious adverse event.

Note the difference between severity and seriousness of an adverse event. A severe adverse event is not necessarily a serious adverse event. For example: a headache may be severe (it significantly interferes with the subject's normal daily activity), but it would not be classified as serious unless it meets one of the criteria of serious events listed above.

9.3.3. Evaluating the biological plausibility

The IP or staff appointed shall determine the biological plausibility by evaluating the consistency of the information of the adverse event with the safety information of the product described in the investigator's brochure or in the product insert. An adverse event is considered to be "unexpected" if the adverse event meets the characteristics described in the definition of unexpected adverse event. To that end, the following source document(s) or special circumstances are considered:

-Source document(s): For those medicinal products that are not approved to be sold in the country, the source document is the Investigator's Brochure of the medicinal product. For the medicinal products already approved for sale in the country, or comparator product, the latest version of the updated insert of the product sold in the country is used. For medicinal product having more than one presentation form (different formulations, doses, etc.) or having more than one use (different indications, populations, etc.) we check that the source document(s) consulted correspond to the same form of presentation of the medicinal product. If the adverse event is not listed in this/these source document(s), it is considered "unexpected".

-Special circumstances: The adverse events that add significant information about the specificity or the severity of an already documented adverse event are also considered as "unexpected" adverse events. In this way, a more specific or more severe adverse event than the one described in the Investigator's Brochure or insert of the medicinal product is considered "unexpected". Specific examples are (a) "acute renal insufficiency" as a documented adverse event with a new adverse event of "interstitial nephritis" and (b) "hepatitis" as a documented adverse event with a new adverse event of fulminant hepatitis.

9.3.4. Evaluating causality

The IP or staff appointed shall determine the causality of the adverse event by determining the existence of a reasonable possibility that the product under investigation has caused it or contributed to cause it. To evaluate the causality, the IP or staff appointed shall use Naranjo algorithm whereby the points obtained determine if the adverse event is related with the suspected product under investigation (point 1 or higher), in which case it is considered as an "ADR", or alternatively if it is not related with the medicinal product (point 0 or lower) in which case it is considered as an "unrelated adverse event".

If the causality cannot be determined by the Investigator, and the Investigator does not know whether the product under investigation caused the event or not, then the event is considered as "related with the product under investigation" for the purposes of the report. If the investigator considers that the causality "is not related with the product under investigation", then said evaluation shall be documented in the study records.

For the adverse events that have a causal relationship with the products under investigation, especially those serious or unexpected adverse events, follow up by the Investigator is required until the moment the event or its sequelae resolve or stabilize towards a condition that is considered acceptable by the investigator.

9.4. Records

All serious and non serious events shall be documented and their evolution described in the subject's clinical record by the IP or by duly delegated staff from the moment of the occurrence until its final resolution. The following shall be documented: beginning and end date and time, dose and actions taken with respect to the product under investigation, biological plausibility, causality, and seriousness and severity of the adverse event.

All serious and non-serious adverse events are recorded in the FDC by the IP or by staff duly delegated on the adverse event reporting page designed to that end. The events described in the FDC must be consistent with the ones described in the clinical record and further source documents.

The term "reasonable causal relationship" in general means that there are facts (for example, evidence such as the discontinuation or the reinstatement of the drug under study) or other arguments suggesting a positive causal relationship.

9.5. Adverse event reporting

9.5.1. Reporting non-serious adverse events

Non-serious adverse events are reported by the IP, or duly delegated staff, to the Sponsor of the study within the framework of the final report.

Non-serious adverse events are reported by the IP to the CEI and CODeI in the framework of the End of Study reports.

In the case of long term investigation studies, the adverse events are communicated to the CEI with a minimum frequency of once a year in the report sent to the CEI.

9.5.2. Reporting serious adverse events

In the case of a serious adverse event (SAE), the IP or delegated staff drafts a written report to be sent ***immediately*** to the Sponsor. When available, all the additional information shall be provided to determine the relationship of the SAE with the product under investigation. The initial reports are followed by follow up reports. Both the initial reports as well as follow up reports shall identify the subject using a single code. In the event of death, the IP shall provide the Sponsor, the CEI and the Regulatory Body any additional information required (for example: autopsies, medical reports, etc.). A CIOMS type form is used to report SAE; in the event that the Sponsor establishes its own SAE form, then that form shall be used.

The SAE report to the CEI shall be submitted ***in the due time and manner established in it.*** The CEI is requested to confirm reception, which will be filed in the Investigator's File.

The SAE report to the CODeI shall be submitted ***in the due time and manner established in it.*** The CODeI is requested to confirm reception, which will be filed in the Investigator's File.

Likewise, all SAE (with the exception of SUADR) occurred during the investigation study are recorded by the IP in the periodic report / final report of the study, using the appropriate form, in compliance with the national regulatory framework in force, with a minimum yearly frequency starting from the date of ANMAT authorization and at the end of the study, which shall be sent to the Sponsor.

The sponsor is responsible for reporting SAEs to the National Regulatory Authorities or to other applicable authorities.

For the case of SUADR reporting, the availability of the minimum required information is verified to have a swift reporting, namely: a) an identifiable volunteer, b) name of the suspicious medication, c) a source of information with personal identification, d) an event or a result that can be identified as a serious or unexpected, and for which there is a causal relationship of reasonable suspicion. In the case of a SUADR that does not comply with any of the criteria above, efforts shall be made to obtain the information as soon as possible.

All the SUADR related with the product under investigation, reported by the IP of the study, are reported by the sponsor expeditiously to the National Regulatory Authority (ANMAT) within **10 administrative working days** as from the moment they became aware of the event.

The SUADRs related with a comparator product already registered with ANMAT for sale in the country or those related with placebo are communicated by the sponsor only to ANMAT Pharmacovigilance System within **7 running days** after the initial reception of the information by the sponsor in case the outcome of the SUADR is death or a threat to life, or within **15 running days** after the reception of the information for all other severity categories.

Likewise, all SUADRs occurring during the investigation study shall be entered by the IP in the presentation of the Periodic Report / Final Report, in the appropriate form in compliance with the national regulatory framework in force, with a annual minimum frequency starting from the date ANMAT granted the authorization, which is sent to the sponsor.

The sponsor is responsible for reporting SUADRs to the National Regulatory Authorities or other applicable authorities.

In blinded treatment studies, when the sponsor receives a SAE report, it shall check the treatment the patient receives to establish whether it is indeed a SUADR as defined, however the blinding shall remain for the investigator or the persons in charge of the data analysis and interpretation.

The sponsor shall communicate the SUADRs related with a product under investigation to all the investigators and to all studies in progress with the product within a **14 day period after becoming aware of them**, in compliance with the national regulatory framework in force. The investigators shall inform these SUADR to the corresponding CEI in the timeframes established.

COMMUNICATION OF SAEs:

Dr. Myriam Rozenberg
Laboratorios Richmond S.A.C.I.F.
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9.6. Adverse event follow up

The IP or staff delegated shall adopt diagnostic and therapeutic measures required when the evolution of an eventual serious or non-serious adverse event so requires. The IP is responsible for ensuring the compliance with all the necessary procedures to address the medical emergencies arising during the course of the study.

The sponsor and the investigator shall ensure access to the necessary contraceptive methods to the participants during the course of the study.

9.7. Abnormal results in laboratory tests

All the results of the laboratory tests collected as part of the Clinical Investigation Protocol shall be recorded in the appropriate pages for the laboratory test results of the FDC. Additionally, the following abnormalities in laboratory tests shall also be recorded in the Adverse Events page of the FDC (hard copy or electronic):

- Any result of a laboratory test that is clinically significant or fits the definition of SAE.
- Any abnormal laboratory test result requiring the study subject to discontinue or interrupt the product under investigation.
- Any abnormal laboratory test result requiring the study subject to receive specific corrective therapy.

9.8. Overdosing

Overdosing is defined as the accidental or intentional intake or infusion of any dose of a product which is considered to be excessive and medically important. All the cases of overdosing shall be reported as SAE (See Section 9.5 "Adverse event reporting" to obtain details about reporting).

10. STATISTICAL CANSODERATIONS

10.1. Determining the sample size

The sample size was established as 90 subjects; with n being 30 for each treatment.

10.2. Population analysis

All the subjects in the study receiving at least one dose of the medication under study shall be included in the safety population analysis. All the data of the samples coming from study subjects receiving the study formulations shall be analyzed statistically.

10.3. Statistical analysis

- **Descriptive statistics**: The primary statistical analysis is defined by the descriptive statistics of the concentrations and the pharmacokinetic parameters introduced above in item 8.3.1. Main efficacy evaluation which will be calculated and presented for the study formulations.

- **Inferential statistics:** The statistical analysis includes the following pair-based comparisons between the products under investigation:

  a) Test Product 1 vs. Reference Product
  b) Test Product 2 vs. Reference Product
  c) As supplementary information, Test Product 1 vs. Test Product 2 shall also be compared.

For each pair-based comparison, variance analysis for a linear model of mixed effects shall be performed, considering the following null hypothesis:

$$H_0: \mu T = \mu R \text{ y } H_1: \mu T \neq \mu R$$

For each pair-based comparison, the variance analysis shall include the terms of the fixed effects of sequence, period, treatment and random subject, embedded inside the sequence. The degrees of freedom, the sum of the squares, the mean squares, the F statistic value and the corresponding p values shall all be specified.

For the pair-based comparison, the results of the percentages of inter and intra-individual variation coefficients for the following parameters: C_{max}, AUC_{0-t} and AUC_{0-inf} shall be presented. The point estimator and the 90% confidence intervals shall be calculated for the ratio of the geometric means for parameters C_{max}, AUC_{0-t} and AUC_{0-inf} to compare treatments, as follows:

For each pair-based comparison, the t test of Schuirmann and Hauck Anderson shall be performed.

10.4. Bioavailability acceptance criteria

The comparable bioavailability between Test Product 1 vs. Reference, and Test Product 2 vs. Reference is established if the ratios of the geometric means of the μT/μR ratios for C_{max} and AUC_{0-t} are within the acceptance bracket [0.80 y 1.25].

10.5. Outsiders and missing samples

Those study subjects with a differing behavior (remarkable difference of their results versus those of the rest) in the bioequivalence parameters, in comparison with the remaining subjects of the study shall be considered outsiders.

Their exclusion in the calculations shall be justified and the results of the pharmacokinetic parameters shall be submitted with and without the inclusion of their data.

10.6. Software used for efficacy analysis

The analysis shall be made using software Phoenix® WinNonlin® version 7.0 from Certara USA, Inc. The software is authorized by license granted to F.P. Clinical Pharma S.R.L.

11. ADMINISTRATIVE SECTION

11.1. Compliance

11.1.1. Compliance with the Clinical Investigation Protocol and its revisions

The study shall be conducted as described in the approved Clinical Investigation Protocol. All the revisions of the Clinical Investigation Protocol shall be discussed with Laboratorios Richmond S.A.C.I.F. The Investigator is not authorized to make any changes in the Clinical Investigation Protocol without the prior review and approval/favorable opinion documented by the CEI regarding an amendment, with the exception of when it is necessary to eliminate an immediate risk to the study subjects. Any significant deviation shall be documented in the FDC.

If a deviation or change is implemented in a Clinical Investigation Protocol to eliminate an immediate risk before obtaining the approval/favorable opinion of the CEI, said deviation or change shall be promptly notified to:

- Laboratorios Richmond S.A.C.I.F.;
- The CEI to be reviewed and grant their approval/favorable opinion;
- The regulatory authorities, when required by local regulations.

If a change substantially alters the design of the Clinical Investigation Protocol or increases the potential risk for the study subject: (1) the consent form shall be revised, which shall be submitted to the CEI for review and approval/favorable opinion, (2) the revised form shall be used to obtain the consent of the study subjects currently included in the Clinical Investigation Protocol if they are affected by the amendment, and (3) the new form shall be used to obtain the consent of new study subjects before they are included.

11.1.2. Monitoring

During the performance of the study, Laboratorios Richmond S.A.C.I.F may perform monitoring visits to ensure that the Clinical Investigation Protocol is executed in compliance with the Good Clinical Practices.

The Unidad de investigación clínica-farmacocinética where the study is conducted may be subject to reviews by the CODeI/CEI and/or quality assurance audits conducted by Laboratorios Richmond S.A.C.I.F and/or inspections by the local Regulatory Authority.

All the data referring to the participation of the study subject shall be documented in the subject's clinical record (independently of the FDC). The clinical record will be considered the source document. The case report forms, the progress reports, etc. shall always be available for inspection by Laboratorios Richmond S.A.C.I.F.

The Sponsor monitor may review all the FDS, clinical records, source documents and signed written informed consent forms. The monitor shall verify that the Clinical Investigation Protocol is conducted, in all its aspects, in full compliance with the Clinical Investigation Protocol.

11.2. Record keeping

The Investigator shall keep all the records regarding the disposal of the product under investigation (provided by the Sponsor or provided by the Investigator), the copies of the FDC (or electronic files) and the source documents for the maximum period established in the regulations and applicable guides, or in compliance with the procedures of the Unidad de investigación clínica-farmacocinética; or else during the period specified by the Sponsor, whichever is longer. The Investigator shall consult Laboratorios Richmond S.A.C.I.F before destroying any record related with the Clinical Investigation Protocol.

If the investigator withdraws from the Clinical Investigation Protocol (for example due to a position change or retirement), the records shall be delivered to a person appointed agreed with Laboratorios Richmond S.A.C.I.F. The notification of the information transfer shall be delivered in writing to Laboratorios Richmond S.A.C.I.F.

11.2.1. Clinical data forms

The Investigator shall prepare and keep adequate and accurate clinical records. The data recorded in the FDC, derived from the source documents, shall be consistent with said documents, or, in the case of discrepancies, these shall be explained.

One FDC shall be provided for each study subject included and randomized. The forms shall be filled out electronically. The Investigator shall ensure that all the data provided to the Sponsor in the FDC and in all the necessary reports are completed and accurate, legible and submitted in due time.

The confidentiality of the records which may identify the study subjects shall be protected, in order to respect the subject's intimacy and the confidentiality rules according to the applicable regulatory requirements.

The Investigator is responsible for ensuring the completeness, review and approval of all FDCs.

The FDCs shall be signed by the investigator or by an authorized member of his/her team. These signatures serve as an attestation that the information contained in FDC is true and that it can be checked against the source documents. During all the stages of the Clinical Investigation Protocol, the Investigator shall have the final responsibility for the accuracy and authenticity of all the clinical data and laboratory results entered in the FDC.

11.2.2. Records of the product under investigation

The Investigator is responsible for ensuring that an updated record is kept of the disposal of the product under investigation (provided by the Sponsor) in the Unidad de investigación clínica-farmacocinética where the product under investigation is inventoried and arranged. The records or notes shall comply with the appropriate regulations and guidelines.

11.3. Return and destruction of the product under investigation

11.3.1. Return of the product under investigation

Once the Clinical Investigation Protocol is deemed completed or finalized, the product under investigation which was not used and/or which was partially used shall be returned Laboratorios Richmond S.A.C.I.F.

11.3.2. Destruction of the product under investigation

Not applicable.

11.4. Confidentiality statement

The information regarding the data of the study subject obtained in this study is considered confidential information and its disclosure to third parties is expressly prohibited.

The confidentiality of the identity of the study subjects shall be kept using personal identification codes.

The medical information of each volunteer subject may be provided to the subject's individual clinician.

The data generated in this protocol shall be available for inspection upon request of FP. Clinical Pharma S.R.L., Laboratorios Richmond S.A.C.I.F monitors, the Ethics Committee and the Regulatory Health Authority.

11.5. Publications

The data collected during this Clinical Investigation Protocol are confidential and property of the Sponsor. The publication conditions of the results are defined in the contract between the parties.

12. LIST OF ABBREVIATIONS

AUC_{0-t}	Area under the concentration-time curve from time 0 to hour t
AUC_{0-inf}	Area under the concentration-time curve from time 0 to infinity
ANMAT	National Administration for Drugs, Food and Medical Technology
Anti HCV	Hepatitis C virus antibody
ALT	Alanine amino transferase
AST	Aspartate transaminase
C.A.B.A.	Autonomous city of Buenos Aires
CCRm	Metastatic carcinoma of the colon or rectum
CMm	Metastatic breast cancer
CPNM	Non-microcytic lung cancer
CRm	Advanced or metastatic renal cell cancer
CEI	Independent Ethics Committee

CEIC	Clinical Investigation Ethics Committee
CHCM	Mean corpuscular hemoglobin concentration (MCHC)
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum serum concentration
CODeI	Teaching and Institutional Investigation Committee
EA	Adverse event (AE)
EAS	Serious adverse event (SAE)
ECG	Electrocardiogram
FIGO	International Federation of Gynecology and Obstetrics
FDA	Food and Drug Administration
FDC	Clinical Data Form (CDF)
FSH	Follicle-stimulating hormone
g	Grams
h	Hour
HBsAg	Hepatitis B surface antigen
HCM	Mean corpuscular hemoglobin
HIV	Human Immunodeficiency Virus
IC	Confidence Interval (CI)
ICC	Congestive heart failure
ICH	International Conference on Harmonization
IFA	Active Pharmaceutical Ingredient (API)
IgG	Immunoglobulin G
IMC	Body mass index (BMI)
IV	Intravenous
IP	Principal Investigator
kg	Kilogram
KPTT	Kaolin activated partial thromboplastin time

l	Liter
m^2	Square meter
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
ml	Milliliter
mmHg	Milliliter of mercury
NYHA	New York Heart Association
OMS	World Health Organization (WHO)
pH	Ratio indicating the degree of acidity
PK	Pharmacokinetics
RAM	Adverse drug reaction (ADR)
RAMSI	Serious and unexpected adverse reaction (SUADR)
ReNIS	Registro Nacional de Investigaciones en Salud
RM	Magnetic Resonance Imaging (MRI)
SNC	Central Nervous System (CNS)
SEPR	Posterior reversible encephalopathy syndrome
TGO	Glutamic oxalacetic transaminase (GOT) |
TGP	Glutamic-pyrufic transaminase (SGPT)
T1/2	Elimination half life
T_{max}	Time to reach the maximum concentration
µg	Microgram
VCM	Mean corpuscular volume
VEGF	Vascular endothelial growth factor
VIH	Human immunodeficiency virus
vs.	Versus
λz	Elimination constant

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14. ANNEXES

14.1. Annex I- Indications and restrictions for the study subject

Clinical Investigation Protocol Code**: 0221**

Study title**:** **Double blind, randomized, parallel group, Phase 1 study comparing pharmacokinetics and safety of Bevacizumab**
Sponsor Laboratory**: Laboratorios Richmond S.A.C.I.F.**

-RESTRICTIONS FOR THE 72 hours PRIOR TO THE CONFINEMENT / HOSPITALIZATION VISIT

1. Do not drink beverages containing caffeine (coca-colas, coffee, tea, mate infusion)
2. Do not drink alcohol
3. Do not eat chocolate
4. Do not ingest any type of citrus (As fruit, juice or condiment)
5. Do not eat fried food or spicy sauces
6. Avoid extenuating exercises and contact sports
7. Do not sunbathe

- INDICATIONS FOR THE NIGHT PRIOR TO THE CONFINEMENT / HOSPITALIZATION VISIT

- **Dinner:** To be ingested until 9:00 pm of the day prior to hospitalization. The meal should be light and in a moderate quantity.

Option 1: 1 serving of roasted meat
1 serving of lettuce, tomato, carrot, pod salad dressed with oil and salt
1 piece of season fruit: apple, pear, etc.
Liquid: still or carbonated water, at ease

Option 2: 1 serving of roasted chicken
1 serving of mashed pumpkin with oil and salt
1 vanilla custard, no toppings
Liquid: still or carbonated water, at ease

Option 3: 1 serving of pasta with oil and salt
1 serving of lettuce, tomato, carrot pod salad dressed with oil and salt
1 piece of season fruit: apple, pear, etc.
Liquid: still or carbonated water, at ease

- **INDICATIONS FOR THE CONFINEMENT / HOSPITALIZATION VISIT AND OUTPATIENT VISITS:**
- For a more comfortable stay at Unidad de Investigación, reading material, radio or individual music players are allowed.
- On hospitalization day, present yourself wearing comfortable clothing.
- You are not allowed to ingest liquids starting 1 hour prior until 2 hours after the administration of the medication.
- You are not allowed to lie down until 2 hours after the administration of the medication.
- Breakfast will not be provided. This clinical investigation protocol requires fasting of at least 10 hours. A standardized diet will be provided for lunch (4 hours post dose approximately), snack (8 hours post dose approximately and dinner (12 hours post dose approximately). You are not allowed to ingest any other food that the standardized diet.
- For **lunch/dinner** you may receive:

a) A serving of chicken with baked potatoes and pumpkin and a tomato, carrot and lettuce salad, salt and oil as dressing, one portion of custard, 2 pieces of bread, and mineral water freely.

or

b) A serving of roasted meat with potatoes and pumpkin and tomato, carrot and lettuce salad, salt and oil as dressing, a piece of fruit (for example, peach preserve), 2 pieces of bread, and mineral water freely.

- As a **snack** you will receive 5 crackers, cheese spread, 1 vanilla yogurt, mineral water freely.

- **<u>GENERAL RESTRICTIONS</u>:**

- If your partner is of child bearing age, she must use an adequate contraceptive method before you enter the study and for at least 3 months after the study ends (any hormone-based or intra uterine device and the use of spermicide as barrier). The use of a barrier method alone or sexual abstinence are not considered adequate methods.
- You must not donate sperm during the study and for 4 months after the treatment.

YOU ARE NOT ALLOWED TO TAKE ANY MEDICATION 2 WEEKS PRIOR OR DURING THE DEVELOPMENT OF THE STUDY UNTIL ITS COMPLETION.