SPANISH REGISTER OF ADVERSE EVENTS WITH BIOLOGIC THERAPIES IN RHEUMATIC DISEASES

(Phase III)

DECEMBER 2020 REPORT

Contents

Current Status and Situation of BIOBADASER Phase III

Fifth year of BIOBADASER Phase III. The Project continues to be a register open for new patient recruitment. The number of patients under active follow-up has continued increasing throughout the whole year in consistency with data obtained from previous years.

Impact of the COVID-19 Pandemic

The emergence of the COVID-19 pandemic has mildly affected this Study's recruitment (the drop in the number of new patients when compared to 2019 is lower than 20%). By contrast, follow-up visits have been greatly affected. Researchers from many centers have reported problems carrying out this type of visit due to recommendations made on public health and alterations in Rheumatology Departments' functioning throughout this year. Due to this situation, participant centers have been instructed to prioritize on-site visits and avoid entering data that was obtained from phone calls. This decision was based on potential bias that could be caused by the collection of some data from on-site visits and other data from phone visits, particularly in relation to the Project's primary objective (safety) and some of the secondary objectives (effectiveness). On-site follow-up visits are expected to be recovered during 2021.

The impact of the COVID-19 pandemic has affected some of the core activities of this Study, such as on-site monitoring and the annual researcher meeting (deferred due to the current health situation).

New Developments Regarding the BIOBADASER Participant Centers

At the time of drafting this report, there are 28 centers actively taking part in this Study. The last centers recruited in BIOBADASER were *Hospital de Ourense* and *Hospital Doce de Octubre*. Throughout this last year, different measures have been taken to ensure all centers' participation in this Study. Specific situations have been identified in some of the hospitals, such as *Hospital Virgen del Rocio* (visited by the Research Unit staff in 2019 to relaunch the Project) and *Hospital de Salamanca* (the data manager in charge of data entry is teleworking, so has no access to medical histories; therefore, no patient from this center was included in the Study this year).

This year, new biosimilars and other molecules considered of interest for the Project have been included.

Principal Investigator and Scientific Committee

In June 2020, Dr. Juan Jesus Gomez-Reino resigned as Principal Investigator of this Project. In September 2020, the position was plublicly offered to rheumatologists who are partners of the Spanish Society of Rheumatology (SER, by its Spanish acronym)

and have interest in the position. At the time of drafting this report, the selection process is still in progress.

The Scientific Committee renovation will not take place until 2021. In the meantime, the members of the current Scientific Committee are as follows:

- Javier Manero, *Hospital Universitario Miguel Servet*.
- Rosa Rosello, *Hospital de San Jorge*.
- Cesar Hernandez Garcia, Spanish Agency of Medicines and Medical Devices (AEMPS, by its Spanish acronym).
- Dolores Montero Corominas (AEMPS).

Dr. Manuel Pombo, rheumatologist at *Hospital de Santiago,* continues his collaboration as External Consultant.

The Project's Scientific Coordinator continues to be Carlos Alberto Sanchez Piedra. Nuria Montero and Jesus Tomas Sanchez Costa continue as CRAs. Fernando Sanchez Alonso continues to be the BIOBADASER Statistician.

The AEMPS continues to be BIOBADASER's financial supporter and sponsor.

The pharmaceutical companies sponsoring BIOBADASER as of December 2020 are Abbvie, BMS, Celltrion, Gilead-Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Regeneron, Samsung Bioepis and UCB.

Change of Reference Clinical Research Ethics Committee (CREC)

The study has the approval from the reference CREC of *Hospital Clinic de Barcelona*. In July 2020, a change of the reference CREC took place. First, *Hospital Clinic de Barcelona* was informed of this request, that was due to that center having stopped taking part in this Study, then the CREC of *Hospital Universitario de Canarias* was requested to be the new reference CREC (this request was approved as documented in this Study's files).

New Developments in BIOBADASER 2020 Phase III

This year, it was decided that the Project and the electronic Data Collection Logbook's structures would remain the same. Two years ago, the condition that prevented patients diagnosed with rheumatoid arthritis and under treatment with Enbrel, Humira or Remicade from being included in the Study was removed.

This year, serious adverse reactions have continued to be reported on the new platform NotificaRAM. In order to establish a causal relationship between an adverse event and the BIOBADASER's drug of interest, the following question continues to be used: "Based on your own medical judgement, do you consider the reported adverse event potentially related to the biologic therapy, biosimilar or the small molecule under study?". This question with dichotomous reply options (yes/no), along with the Naranjo algorithm, serves to double check a causality.

New Treatments Included in BIOBADASER in 2020

The following treatments were included in the Study's DCL between December 1st, 2019 and November 15th, 2020:

- Idacio.

The complete list of drugs available in BIOBADASER as of the date of this report is as follows:

1 Enbrel
2 Remicade
3 Humira
4 Kineret
5 Mabthera
6 Orencia
7 Roactemra
8 Ocrevus
9 Simponi
10 Cimzia
11 Ilaris
12 Benlysta
13 Stelara
14 Remsima

15 Inflectra
16 Prolia
17 Otezla
18 Cosentyx
19 Benepali
20 Flixabi
21 Truxima
22 Xeljanz
23 Olumiant
24 Erelzi
25 Kevzara
26 Rixathon
27 Riximyo
28 Taltz
29 Amgevita
30 Upadacitinib
31 Hyrimoz
32 Imraldi
33 Hulio
34 Zessly
35 Idacio

Participant Centers

On September 1st, 2016, a data download was performed to obtain an estimation of the number of patients included at each center. Based on these data, along with reports generated during online monitoring, the 20 centers ranked as the highest recruiters were selected.

In December 2016, each center was informed whether they would continue or not in the Study by means of a letter addressed to its researchers. The number of active participant centers remained steady throughout 2017.

During 2018, BIOBADASER counted on the participation of 20 active centers until September, when the number of participant centers increased up to 28.

In September 2019, the *Complejo Hospitalario de Jaen* stopped participating in BIOBADASER. In December 2019 and January 2020, the *Hospital Clinic i Provincial* and *Hospital La Princesa*'s respective terminations, due to prolonged inactivity reflected in the register, were communicated. The withdrawal of these three centers has been compensated with the incorporation of *Hospital Doce de Octubre* (December 2019), *Hospital de Ourense* (May 2020), and *Hospital Gregorio Marañon* (July 2020).

The updated list of active participant centers on 15th November 2020 was as follows:

Participant Centers

CENTERS
Hospital Universitario Virgen Macarena
Hospital Clinico Universitario de Santiago
Hospital Universitario Miguel Servet
Hospital Gregorio Marañon
Hospital de Gran Canaria Dr. Negrin
Hospital General Carlos Haya
Hospital General San Jorge
Hospital General Universitario de Valencia
Hospital Ourense
Complejo Hospitalario Universitario de Granada
Hospital de la Santa Creu i Sant Pau
Hospital General Universitario de Alicante
Hospital General Universitario de Elda
Hospital Universitario de Canarias
Hospital Universitario Principe de Asturias
Hospital Universitario Reina Sofia
Hospital Universitario Germans Trias i Pujol

Hospital Universitario Virgen del Rocio
Complejo Hospitalario Universitario A Coruña
Complejo Hospitalario de Salamanca
Hospital Universitario Doce de octubre
Hospital General de Granollers
Hospital del Mar
Hospital de Burgos
Hospital Son Llatzer
Hospital de Basurto
Hospital Puerta de Hierro
Hospital Virgen de la Arrixaca

List of Participant Researchers in BIOBADASER Phase III

Below is a list of researchers in active centers who have taken part in BIOBADASER in 2020.

- Dolores Ruiz Montesinos, Silvia Ricca (*Hospital Universitario Virgen Macarena*).
- Manuel Pombo, Eva Perez-Pampin (*Hospital Clinico Universitario de Santiago*).
- Francisco Javier Manero, Chesus Beltran, Jesus Marzo, Marta Medrano, Angela Pecondon, Alvaro Lesta Arnan, Carlos Vazquez, Erardo Meriño Ibarra (*Hospital Universitario Miguel Servet*).
- Javier Garcia Gonzalez, Patricia Lavilla, Manuela Castilla, Miriam Retuerto (*Hospital Doce de Octubre*).
- Carlos Rodriguez Lozano, Yanira Perez Vera, Antonio Naranjo, Soledad Ojeda, Felix Francisco Hernández, Juan Carlos Quevedo, Celia Erausquin, Cristina Hernandez Santana, Iñigo Rua (*Hospital de Gran Canaria Dr. Negrin*).
- Sara Manrique, Marta Rojas Gimenez, Antonio Fernandez Nebro, Maria Victoria Irigoyen, Inmaculada Ureña (*Hospital General Carlos Haya*).
- Rosa Rosello Pardo, Blanca Garcia Magallon (*Hospital General San Jorge*).
- Cristina Campos, Javier Calvo, Isabel Balaguer Trull (*Hospital General Universitario de Valencia*).
- Isabel Castrejon (*Hospital Universitario Gregorio Marañon*).
- Rafael Caliz Caliz (*Complejo Hospitalario Universitario de Granada*).
- Cesar Diaz Torne, Ana Milena Millan Arciniegas, Jose Maria de Llobet (*Hospital de la Santa Creu i Sant Pau*).
- Paloma Vela, Rocio Caño, Silvia Gomez (*Hospital General Universitario de Alicante*).
- Raquel Martin Domenech, Francisca Sivera, Cristina Fernandez Carballido, Carlos Perez Barba (*Hospital General Universitario de Elda*).
- Sagrario Bustabad, Lorena Exposito (*Hospital Universitario de Canarias*).
- Eduardo Cuende Quintana, Melchor Alvarez de Mon, Ana Turrion, Laura Barrio, Cristina Bohorquez, Ana Sanchez Atrio, Ana Perez Gomez, Atusa Morasat (*Hospital Universitario Principe de Asturias*).
- Maria del Carmen Castro Villegas, Eduardo Collantes, Montserrat Romero Gomez, Rafaela Ortega, Jerusalem Calvo, Pilar Font, Desire Ruiz (*Hospital Universitario Reina Sofia*).

- Lourdes Mateo, Susana Holgado, Melania Martinez Morillo, Agueda Prior (*Hospital Universitario Germans Trias i Pujol*).
- Raul Menor, Juan Povedano, Esteban Rubio (*Hospital Universitario Virgen del Rocio*).
- Jesus Carlos Fernandez Lopez, Mercedes Freire, Francisco Javier de Toro (*Complejo Hospitalario Universitario A Coruña*).
- Javier del Pino, Olga Martinez, Cristina Hidalgo, Alba Quesada Moreno, Carlos Montilla, Jose Hernandez Madrid (*Complejo Hospitalario de Salamanca*).
- Diana Sueiro (*Hospital de Ourense*).
- Xavier Suris Armangue, Noemi Busquets, Maria Pascular Pastor (*Hospital General de Granollers*).
- Carolina Perez Garcia (*Hospital del Mar*).
- Maria Colazo Burlato, Jose Luis Alonso Valdivielso (*Hospital de Burgos*).
- Inmaculada Ros, Catalina Melia Mesquida (*Hospital de Son Llatzer*).
- Juan Maria Blanco Madrigal, Maria Luz Garcia Vivar (*Hospital Universitario de Basurto*).
- Jose Campos Esteban (*Hospital Puerta de Hierro*).
- Manuel Jose Moreno Ramos, Lola Beteta Fernandez (*Hospital Virgen de la Arrixaca*).

Other Aspects

Periodic Reports

Throughout the year, follow-up newsletters have been sent monthly to report to researchers on study developments.

International Collaborations

International collaborations where BIOBADASER is involved:

- Group BIOBADAMERICA. This year, a training meeting with Latin American researchers while EULAR was taking place in Madrid.
- Foreum-OMOP. Work group led by Dr. Daniel Prieto Alhambra, professor at Oxford.
- Eurospa. Collaborative Project coordinated in Denmark with the participation of different European registers containing data referring to the spondyloarthropathies area.
- JAK-POT (formerly TOCERRA).

Description of the Register With All Biologic Therapies

Results in this annual report refer to data downloaded on 14th October 2020 (the previous data download for an annual report was done on 11th October 2019). At the time of download, the number of participant centers was 28. Since the last annual report, more than 1300 new patients have been recruited for the Study (+22.8% of interannual growth). **Table 1** shows a description of patients included in BIOBADASER. The profile corresponds to a woman (62.4%) at a current mean age slightly over 55 years with a disease duration longer than seven years at the beginning of treatment. These values have remained stable in comparison with the last annual report of this Project.

Table 1.- Characteristics of Patients Included in BIOBADASER 3.0.

All Biologic Agents			
Number of Patients (%)	7485		
Woman (%)	4670 (62.4)		
Current mean age (SD)	55.4 (15.0)		
Mean age at the beginning of treatment (SD)	51.4 (14.7)		
Median duration of disease (P_{50}) at the beginning of treatment [P_{25}-P_{75}]	7.4 [2.8-14.3]		
Diagnosis	**n (%)**		**n (%)**
Rheumatoid arthritis	2924 (39.06)	Reactive arthritis	21 (0.28)
Arthritis or Psoriatic SpA	1518 (20.28)	Still's disease	19 (0.25)
Ankylosing spondylitis	1303 (17.41)	Anti-inflammatory syndromes	16 (0.21)
Undifferentiated spondyloarthropathy	366 (4.89)	Escleroderma	15 (0.2)
Juvenile idiopathic arthritis	211 (2.82)	Arthropathy due to pyrophosphate	11 (0.15)
Osteoporosis	193 (2.58)	Juvenile AS	9 (0.12)
Non-radiographic axial ankylosing spondylitis	132 (1.76)	Juvenile undifferentiated spondyloarthropathy	8 (0.11)
Systemic lupus erythematosus	121 (1.62)	Undifferentiated connective tissue disease	8 (0.11)
Enteropathic arthritis	110 (1.47)	Sarcoidosis	6 (0.8)
Seronegative chronic polyarthritis	99 (1.32)	Polymyalgia rheumatica	6 (0.08)
Vasculitis	82 (1.1)	Psoriasis	5 (0.07)
Uveitis without rheumatic disease	80 (1.07)	Relapsing polychondritis	2 (0.03)

Seronegative chronic oligoarthritis	51 (0.68)	Pyoderma gangrenosum	1 (0.01)
Primary Sjögren's syndrome	39 (0.52)	Felty's syndrome	1 (0.01)
Behcet's disease	38 (0.51)	Eosinophilic fasciitis	1 (0.01)
Overlap sydndrome	38 (0.51)	Primary antiphospholipid syndrome	1 (0.01)
SAPHO syndrome	25 (0.33)	IgG4 syndrome	1 (0.01)
Polymyositis / dermatomyositis	23 (0.31)	Amyloidosis	1 (0.01)
Total			7485 patients

Abbreviations: SD, Standard Deviation; SpA, spondyloarthritis; AS, ankylosing spondylitis

The most frequent diagnosis is rheumatoid arthritis (39.1%), followed by psoriatic arthritis (20.3%) and ankylosing spondylitis (17.4%). Over the last year, the percentage of patients with ankylosing spondylitis diagnosis in the Study has decreased.

Table 2 presents a description of treatment cycles used from the beginning of the BIOBADASER Study. Data are shown according to lines of treatment: whether therapy was used as a first option or as a second or later treatment option (that is, the patient received at least one prior biological treatment which was suspended).

Table 2.- Description of Biologic Therapies.

Drug	First Option Treatment n (%)	Second or Later Option Treatment n (%)	All n (%)
Humira	911 (16.6)	887 (11.7)	1798 (13.7)
Enbrel	695 (12.7)	709 (9.3)	1404 (10.7)
Simponi	356 (6.5)	674 (8.9)	1030 (7.9)
Roactemra	232 (4.2)	782 (10.3)	1014 (7.7)
Orencia	150 (2.7)	606 (8.0)	756 (5.8)
Cosentyx	206 (3.8)	546 (7.2)	752 (5.7)
Remicade	483 (8.8)	266 (3.5)	749 (5.7)
Cimzia	249 (4.5)	413 (5.4)	662 (5.1)
Benepali	347 (6.3)	241 (3.2)	588 (4.5)
Hyrimoz	293 (5.3)	173 (2.3)	466 (3.6)
Xeljanz	91 (1.7)	361 (4.7)	452 (3.5)
Mabthera	143 (2.6)	292 (3.8)	435 (3.3)
Olumiant	105 (1.9)	294 (3.9)	399 (3.1)
Inflectra	126 (2.3)	215 (2.8)	341 (2.6)
Erelzi	206 (3.8)	114 (1.5)	320 (2.4)
Stellara	44 (0.8)	233 (3.1)	277 (2.1)
Amgevita	154 (2.8)	113 (1.5)	267 (2.0)

Prolia	187 (3.4)	16 (0.2)	203 (1.6)
Otezla	113 (2.1)	71 (0.9)	184 (1.4)
Kevzara	36 (0.7)	146 (1.9)	182 (1.4)
Truxima	71 (1.3)	108 (1.4)	179 (1.4)
Remsima	50 (0.9)	97 (1.3)	147 (1.1)
Imraldi	103 (1.9)	41 (0.5)	144 (1.1)
Bemlysta	69 (1.3)	42 (0.6)	111 (0.9)
Taltz	6 (0.1)	91 (1.2)	97 (0.7)
Rixathon	17 (0.3)	53 (0.7)	70 (0.5)
Kineret	32 (0.6)	16 (0.2)	48 (0.4)
Illaris	2 (0.0)	8 (0.1)	10 (0.1)
Idacio	7 (0.1)	2 (0.0)	9 (0.1)
Riximyo	0 (0.0)	1 (0.0)	1 (0.0)
Treatment Cycles	3 (0.1)	1 (0.0)	4 (0.1)
Reasons for discontinuation	**n (%)**	**n (%)**	**n (%)**
Inefficacy or loss of efficacy	1164 (45.2)	2195 (52.9)	3359 (50.0)
Adverse events	661 (25.7)	894 (21.6)	1555 (23.1)
Pregnancy or desire to be pregnant	70 (2.7)	83 (2.0)	153 (2.3)
Loss of patient	48 (1.9)	51 (1.2)	99 (1.5)
Remission	85 (3.3)	70 (1.7)	155 (2.3)
Change for non-medical reasons	54 (2.1)	103 (2.5)	157 (2.3)
Others	392 (15.2)	603 (14.5)	995 (14.8)
Unknown	101 (3.9)	148 (3.6)	249 (3.7)
Total discontinuations	2575 (100.0)	4147 (100.0)	6722 (100.0)

* This table contains information on treatment cycles. Data does not refer to individual patients, but to treatments used and registered in the study (a patient might have been administered different treatments).

Drugs most frequently used as first option are Humira (16.6% vs. 19.9% in year 2019) and Enbrel (12.7% vs. 15.3% in last report). The use of habitual anti-TNF as a first-line treatment has experienced a significant decline in BIOBADASER. As for second and later treatment options, Humira continues to be the most used (11.7% vs. 13.8% in last year's report), followed by Roactemra (10.3%). During this last year, there has been a significant increase in the registration of biosimilars and JAK kinase inhibitors in this Study.

The category "Others" as a reason for discontinuation mainly relates to Mabthera cycles. Due to this biologic's dosage regimen, treatment cycles are collected and the reason for discontinuation is registered under the category "Others". In 2017, the

category “Change for Non-Medical Reasons”, was added to refer to changes in treatment not based on medical judgement but normally forced by the centers’ management. “Inefficacy and loss of efficacy” is still the main reason for discontinuation (50.0%), followed by adverse events (23.1% of all changes). A total of 157 changes in treatment due to non-medical reasons have been recorded since year 2017. These numbers remain stable when compared to previous reports.

Table 3 shows frequency and percentages of different adverse events recorded by System Organ Class (medDRA). “Infections and infestations” are the most frequent, accounting for 28% of all adverse events registered, same as in prior reports, followed by “Gastrointestinal disorders” and “General disorders and administration-site conditions”. The frequency of these adverse events has not been altered in comparison to prior reports.

Table 3.- Frequency of All Adverse Events by Group.

Adverse Events (AE)	n	% of total AE
Infections and infestations	4455	27.6
Gastrointestinal disorders	2002	12.4
General disorders and administration-site conditions	882	5.5
Injury, poisoning and procedural complications	709	4.4
Eye disorders	673	4.2
Skin and subcutaneous tissue disorders	672	4.2
Nervous system disorders	640	4.0
Respiratory, thoracic, and mediastinal disorders	601	3.7
Surgical and medical procedures	569	3.5
Musculoskeletal and connective tissue disorders	540	3.3
Immune system disorders	528	3.3
Cardiac disorders	510	3.2
Blood and lymphatic system disorders	487	3.0
Complementary examinations	409	2.5
Metabolism and nutrition disorders	376	2.3
Ear and labyrinth disorders	313	1.9
Renal and urinary disorders	292	1.8
Vascular disorders	292	1.8
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	286	1.8
Hepatobiliary disorders	234	1.5
Psychiatric disorders	202	1.3
Endocrine disorders	183	1.1
Pregnancy, puerperium, and perinatal conditions	137	0.9

Reproductive system and breast disorders	110	0.7
Congenital, familial, and genetic disorders	41	0.3
Social circumstances	17	0.1
Product issues	1	0.0
Total	16161	100.00

As for the severity of reported adverse events, 86.69% (14010) were classified as “non serious” (+0.2% in comparison to previous report) and 13.31% (2151) as “serious”. This year there have been 31 new deaths reported (in 2019 there were 22 deaths reported). Among serious and fatal adverse events reported, 2089 events were found to have a score over 0 in the Naranjo Scale, which suggests some association between the event and drug of interest in BIOBADASER.

Table 4 presents the frequency of registered serious and fatal adverse events. A total of 2151 serious events have been reported since the beginning of Phase III in this Study. Over the last year, 574 new serious adverse events (but not fatal) have been reported.

“Infections and infestations” continue to be the most frequent adverse event reported, followed by “Surgical and medical procedures” and “Gastrointestinal disorders”. This ranking remains stable with respect to the last report, and the frequency of the main adverse event groups occurrence remains stable with just slight changes in distribution.

Table 4.- Frequency of Serious Adverse Events.

Adverse Events (AE)	n	% of total AE
Infections and infestations	605	28.1
Surgical and medical procedures	220	10.2
Gastrointestinal disorders	209	9.7
Cardiac disorders	154	7.2
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	132	6.1
Injury, poisoning and procedural complications	126	5.9
Nervous system disorders	101	4.7
Musculoskeletal and connective tissue disorders	73	3.4
Blood and lymphatic system disorders	64	3.0
Respiratory, thoracic, and mediastinal disorders	58	2.7
General disorders and administration-site conditions	56	2.6
Pregnancy, puerperium, and perinatal conditions	48	2.2
Hepatobiliary disorders	46	2.1
Renal and urinary disorders	39	1.8
Immune system disorders	38	1.8
Vascular disorders	35	1.6
Eye disorders	31	1.4
Psychiatric disorders	27	1.3
Endocrine disorders	22	1.0
Metabolism and nutrition disorders	19	0.9
Skin and subcutaneous tissue disorders	16	0.7
Reproductive system and breast disorders	13	0.6
Complementary examinations	10	0.5
Congenital, familial, and genetic disorders	4	0.2
Ear and labyrinth disorders	3	0.1
Social circumstances	2	0.1
Total	2151	100.00

Over the last year, 31 fatal adverse events occurred. The total number of adverse events ending in death is 88. This corresponds to the following System Organ Class: “Infections and infestations” (24 cases), “Neoplasms” (12 cases), “Cardiac disorders” (12), “Nervous system disorders” (10), “Gastrointestinal disorders” (9), “General disorders and administration-site conditions” (6), “Metabolism and nutrition disorders” (4), “Injury, poisoning and procedural complications” (3), “Blood and lymphatic system disorders” (2), “Immune system disorders” (1), “Respiratory disorders” (2),

"Complementary examinations" (1), "Renal and urinary disorders" (1) and "Vascular disorders" (1 case).

A table containing the deaths reported to BIOBADASER Phase III can be found in the Appendix.

Table 5 shows the incidence rate of all adverse events organized by System Organ Class. The total incidence rate is 516.8 (508.9-524.9) adverse events per 1000 patient-years (550.9 (537.0-563.4) adverse events per 1000 patient-years in year 2019). Incidence rate of serious adverse events is 68.8 (65.9-71.8), and incidence rate of fatal adverse events is 2.8 (2.3-3.5) per 1000 patient-years. There has been a decrease (-20%) in the incidence rate of serious adverse events compared to last annual report. On the other hand, the incidence rate of fatal adverse events has experienced a slight increase.

The recent trend of growing incidence rates, in general terms, was broken this year. Reasons for this change can be a decrease in adverse event reports because of the lack of on-site follow-up visits in many Rheumatology Departments due to the COVID-19 pandemic, or due to rates' tendency to stabilize after several years experiencing an increase.

"Infections and infestations" are an adverse event group presenting a higher incidence rate in both biologic therapies used as first option and in other treatment lines with a total rate of 142.5 events per 1000 patient-years.

Table 5.- Incidence Rate of Adverse Events.

Incidence Rate (95% CI) per 1000 Patient-Years	First Option Treatment	Second and Later Option Treatments	Total
Total adverse events	445.4 (435.0-456.0)	587.7 (575.8-599.8)	516.8 (508.9-524.9)
Serious	53.7 (50.1-57.4)	83.8 (79.4-88.4)	68.8 (65.9-71.8)
Fatal	2.7 (2.0-3.7)	2.9 (2.2-3.9)	2.8 (2.3-3.5)
By System Organ Class			
Infections and infestations	120.4 (115.1-126.0)	164.3 (158.1-170.8)	142.5 (138.4-146.7)
Gastrointestinal disorders	54.6 (51.1-58.4)	73.3 (69.2-77.7)	64.0 (61.3-66.9)
General disorders and administration-site conditions	24.1 (21.8-26.7)	32.3 (29.6-35.2)	28.2 (26.4-30.1)
Injury, poisoning and procedural complications	17.6 (15.6-19.8)	27.7 (25.2-30.4)	22.7 (21.1-24.4)
Eye disorders	17.7 (15.8-20.0)	25.3 (22.9-27.9)	21.5 (20.0-23.2)
Skin and subcutaneous tissue disorders	19.0 (17.0-21.3)	23.9 (21.6-26.5)	21.5 (19.9-23.2)
Nervous system disorders	18.7 (16.7-21.0)	22.2 (20.0-24.7)	20.5 (18.9-22.1)
Respiratory, thoracic, and mediastinal disorders	15.8 (14.0-17.9)	22.6 (20.4-25.1)	19.2 (17.7-20.8)
Surgical and medical procedures	13.4 (11.7-15.4)	22.9 (20.7-25.4)	18.2 (16.8-19.8)
Musculoskeletal and connective tissue disorders	13.2 (11.5-15.1)	21.3 (19.2-23.7)	17.3 (15.9-18.8)
Immune system disorder	14.9 (13.1-17.0)	18.8 (16.8-21.1)	16.9 (15.5-18.4)
Cardiac disorders	12.6 (11.0-14.5)	20.0 (17.9-22.3)	16.3 (15.0-17.8)
Blood and lymphatic system disorders	13.6 (11.8-15.5)	17.6 (15.6-19.8)	15.6 (14.3-17.0)
Complementary examinations	14.6 (12.8-16.6)	11.6 (10.0-13.4)	13.1 (11.9-14.4)
Metabolism and nutrition disorders	11.8 (10.2-13.6)	12.3 (10.7-14.1)	12.0 (10.9-13.3)
Ear and labyrinth disorders	8.4 (7.0-9.9)	11.7 (10.1-13.5)	10.0 (9.0-11.2)
Vascular disorders	8.8 (7.4-10.4)	9.9 (8.4-11.5)	9.3 (8.3-10.5)
Renal and urinary disorders	9.8 (8.4-11.5)	8.8 (7.5-10.4)	9.3 (8.3-10.5)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	10.7 (9.2-12.4)	7.6 (6.4-9.1)	9.1 (8.1-10.3)
Hepatobiliary disorders	6.5 (5.3-7.9)	8.5 (7.1-10.0)	7.5 (6.6-8.5)
Psychiatric disorders	5.8 (4.8-7.2)	7.1 (5.9-8.5)	6.5 (5.6-7.4)
Endocrine disorders	4.7 (3.7-5.9)	7.0 (5.8-8.4)	5.9 (5.1-6.8)
Pregnancy, puerperium, and perinatal conditions	3.8 (2.9-4.9)	5.0 (4.0-6.2)	4.4 (3.7-5.2)
Reproductive system and breast disorders	3.0 (2.3-4.0)	4.0 (3.1-5.1)	3.5 (2.9-4.2)
Congenital, familial, and genetic disorders	1.4 (0.9-2.1)	1.2 (0.8-1.9)	1.3 (1.0-1.8)
Social circumstances	0.4 (0.2-0.9)	0.7 (0.4-1.3)	0.5 (0.3-0.9)

Table 6 shows the incidence of those adverse events considered as serious by researchers**. "**Infections and infestations" present an incidence rate of 19.3 (17.9-

21.00), which is slightly lower than the incidence rate registered last year. “Medical and surgical procedures” occur in 7.0 (6.2-8.0) cases per 1000 patient-years. Rate of incidence of “Neoplasms” is 4.2 (3.6-5.0) per 1000 patient-years.

Table 6.- Incidence Rate of Serious Adverse Events.

Incidence Rate (95% CI) per 1000 Patient-Years	First Option Treatment	Second and Later Option Treatment	Total
Infections and infestations	15.4 (13.6-17.5)	23.2 (21.0-25.7)	19.3 (17.9-21.0)
Surgical and medical procedures	4.3 (3.4-5.5)	9.7 (8.3-11.4)	7.0 (6.2-8.0)
Gastrointestinal disorders	4.6 (3.7-5.8)	8.7 (7.4-10.3)	6.7 (5.8-7.7)
Cardiac disorders	3.7 (2.8-4.7)	6.2 (5.1-7.5)	4.9 (4.2-5.8)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	4.9 (3.9-6.1)	3.6 (2.7-4.6)	4.2 (3.6-5.0)
Injury, poisoning and procedural complications	3.0 (2.2-3.9)	5.1 (4.1-6.3)	4.0 (3.4-4.8)
Nervous system disorders	2.8 (2.1-3.8)	3.6 (2.8-4.7)	3.2 (2.7-3.9)
Musculoskeletal and connective tissue disorders	1.4 (0.9-2.1)	3.2 (2.5-4.3)	2.3 (1.9-2.9)
Blood and lymphatic system disorders	2.1 (1.5-2.9)	2.0 (1.4-2.9)	2.0 (1.6-2.6)
Respiratory, thoracic, and mediastinal disorders	1.5 (1.0-2.2)	2.2 (1.6-3.1)	1.9 (1.4-2.4)
General disorders and administration site conditions	1.2 (0.8-1.9)	2.4 (1.7-3.3)	1.8 (1.4-2.3)
Pregnancy, puerperium, and perinatal conditions	1.1 (0.7-1.8)	2.0 (1.4-2.8)	1.5 (1.2-2.0)
Hepatobiliary disorders	1.0 (0.6-1.6)	2.0 (1.4-2.8)	1.5 (1.1-2.0)
Renal and urinary disorders	1.2 (0.7-1.8)	1.3 (0.9-2.1)	1.2 (0.9-1.7)
Immune system disorders	0.4 (0.2-0.9)	2.0 (1.4-2.8)	1.2 (0.9-1.7)
Vascular disorders	0.8 (0.5-1.4)	1.4 (0.9-2.1)	1.1 (0.8-1.6)
Eye disorders	0.9 (0.5-1.5)	1.1 (0.7-1.7)	1.0 (0.7-1.4)
Psychiatric disorders	1.1 (0.7-1.8)	0.6 (0.3-1.2)	0.9 (0.6-1.3)
Endocrine disorders	0.6 (0.3-1.1)	0.8 (0.5-1.4)	0.7 (0.5-1.1)
Metabolism and nutrition disorders	0.5 (0.3-1.0)	0.7 (0.4-1.3)	0.6 (0.4-1.0)
Skin and subcutaneous tissue disorders	0.3 (0.1-0.8)	0.7 (0.4-1.3)	0.5 (0.3-0.8)
Reproductive system and breast disorders	0.4 (0.2-0.9)	0.4 (0.2-0.9)	0.4 (0.2-0.7)
Complementary examinations	0.2 (0.1-0.6)	0.4 (0.2-0.9)	0.3 (0.2-0.6)
Congenital, familial, and genetic disorders	0.1 (0.0-0.5)	0.1 (0.0-0.5)	0.1 (0.0-0.3)
Ear and labyrinth disorders	0.1 (0.0-0.5)	0.1 (0.0-0.5)	0.1 (0.0-0.3)
Social circumstances	0.1 (0.0-0.5)	0.1 (0.0-0.5)	0.1 (0.0-0.3)

The table bellow contains data regarding activity indexes obtained at the time the treatment starts, as well as in later follow-up. A steady decrease is observed. This information is provided by treatment line and in total. DAS28 components are also collected in BIOBADASER Phase III. The table presents data on the number of tender

joints, number of swollen joints, visual analog scale, and erythrocyte sedimentation rate.

Table 7.- Description of Disease Activity Index.

Index	First Option Treatment			Second and Later Option Treatment			Total		
	Start	1 year	2 or more	Start	1 year	2 or more	Start	1 year	2 or more
DAS28-ESR (RA)	4.7 (1.3)	2.8 (1.3)	2.7 (1.1)	4.6 (1.6)	3.1 (1.4)	2.9 (1.3)	4.6 (1.5)	3.0 (1.3)	2.8 (1,2)
DAS28-CRP (RA)	3.4 (1.1)	2.0 (0.9)	1.7 (0.7)	3.3 (1.2)	2.1 (0.9)	2.0 (0.8)	3.4 (1.1)	2.1 (0.9)	1.9 (0,8)
DAS28-ESR (PsA)	4.0 (1.4)	2.4 (1.3)	2.3 (1.0)	4.1 (1.5)	2.8 (1.3)	2.6 (1.2)	4.1 (1.4)	2.6 (1.3)	2.4 (1,1)
DAS28-CRP (PsA)	3.0 (1.0)	1.8 (0.8)	1.6 (0.6)	2.9 (1.1)	2.0 (0.9)	1.8 (1.8)	3.0 (1.1)	1.9 (0.8)	1.7 (0,7)
Number of tender joints	6.1 (5.8)	1.6 (3.1)	0.9 (2.2)	6.2 (6.2)	2.1 (3.9)	1.7 (3.4)	6.2 (6.1)	1.9 (3.6)	1.3 (3,0)
Number of swollen joints	4.2 (4.5)	0.7 (1.7)	0.5 (1.4)	4.1 (4.8)	1.1 (2.4)	0.8 (2.1)	4.1 (4.7)	1.0 (2.2)	0.7 (1.8)
Patient visual analog scale	5.9 (.2)	3.3 (2.4)	3.1 (2.2)	5.9 (2.4)	3.8 (2.5)	3.8 (2.3)	5.9 (2.3)	3.7 (2.4)	3.5 (2,3)
Erythrocyte sedimentation rate (ESR)	27.2 (22.8)	17.9 (16.8)	19.9 (18.1)	28.2 (25.1)	20.9 (19.6)	19.5 (18.9)	27.8 (24.3)	19.8 (18.7)	19,7 (18,6)
BASDAI	5.5 (2.2)	3.2 (2.2)	2.9 (2.1)	5.3 (2.5)	3.8 (2.5)	3.4 (2.4)	5.4 (2.4)	3.5 (2.4)	3.1 (2,2)
ASDAS-CRP	3.3 (1.2)	1.9 (1.0)	1.8 (0.9)	3.2 (1.4)	2.2 (1.2)	2.1 (1.1)	3.2 (1.3)	2.1 (1.1)	2.0 (1,0)
SLEDAI	7.5 (3.7)	3.9 (3.4)	3.1 (2.6)	6.1 (6.1)	2.4 (2.8)	2.6 (2.0)	7.0 (4.7)	3.9 (3.3)	3.0 (2,5)

APPENDIX

Table I.- Itemized Frequency of Adverse Events by SOC Reported to BIOBADASER Phase III.

SOC	N (%)
Infections and infestations	4455 (27.6)
Gastrointestinal disorders	2002 (12.4)
General disorders and administration-site conditions	882 (5.5)
Injury, poisoning and procedural complications	709 (4.4)
Eye disorders	673 (4.2)
Skin and subcutaneous tissue disorders	672 (4.2)
Nervous system disorders	640 (4.0)
Respiratory, thoracic, and mediastinal disorders	601 (3.7)
Surgical and medical procedures	569 (3.5)
Musculoskeletal and connective tissue disorders	540 (3.3)
Immune system disorders	528 (3.3)
Cardiac disorders	510 (3.2)
Blood and lymphatic system disorders	487 (3.0)
Complementary examinations	409 (2.5)
Metabolism and nutrition disorders	376 (2.3)
Ear and labyrinth disorders	313 (1.9)
Renal and urinary disorders	292 (1.8)
Vascular disorders	292 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	286 (1.8)
Hepatobiliary disorders	234 (1.5)
Psychiatric disorders	202 (1.3)
Endocrine disorders	183 (1.1)
Pregnancy, puerperium, and perinatal conditions	137 (0.9)
Reproductive system and breast disorders	110 (0.7)
Congenital, familial and genetic disorders	41 (0.3)
Social circumstances	17 (0.1)
TOTAL	16160

BIOBADASER International Collaborations in 2019

International collaborative projects where BIOBADASER is involved are as follows:

- PanEuropean database analysis of Abatacept Effectiveness (Panaba Project).
- Tocilizumab Collaboration of European Registries in RA (TOCERRA).
- Retention and effectiveness of TNF inhibitor treatment in psoriatic arthritis and axial spondyloarthritis: results from the EuroSpA collaboration.
- Burden and impact of co-morbidity and frailty in patients with RMDs in Europe: a multi-national analysis of big healthcare data. FOREUM.

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