



**SPANISH REGISTRY ON ADVERSE EVENTS OF BIOLOGICAL  
THERAPIES IN RHEUMATIC DISEASES**

**(Phase III)**

**DECEMBER 2017 REPORT**

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## Current Status and Situation of BIOBADASER Phase III

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The second year of BIOBADASER Phase III started with the selection of 20 centers that have continued taking part in the study. The selection process, among the 35 centers that started the study, was based on the 2016 monitoring report, as well as on the proven recruitment capacity for new patients in the centers in this first year with Phase III.

This year, trying to emphasize the importance of the project, communication with centers and participant researchers has been strengthened. The main object has continued to be the collection of information regarding safety in the use of biological therapies, biosimilars, and small molecules with identifiable target.

As a matter of fact, the arrival of new molecules to the register, in addition to biological therapies and biosimilars, calls for a modification in the study protocol in order to adjust to these changes. Over the coming weeks, these minor changes will be reported to the Spanish Medicines and Health Products Agency (known in Spanish as *AEMPS*) and the referral Clinical Research Ethics Committee i.e. *Hospital Clinic*.

The Principal Investigator continues to be Dr. Juan Jesus Gomez-Reino, and the members of the Scientific Committee are as follows:

- M<sup>a</sup> Victoria Hernandez Miguel, *Hospital Clinic Barcelona*.
- Javier Manero, *Hospital Universitario Miguel Servet*.
- Rosa Rosello, *Hospital de San Jorge*.
- Cesar Hernandez Garcia, *AEMPS*.
- Dolores Montero Corominas, *AEMPS*.

The project Scientific Coordinator continues to be Carlos Alberto Sanchez Piedra; Jesus Tomas Sanchez Costa remains the CRA; and Fernando Sanchez Alonso remains Statistician of BIOBADASER.

For its part, AEMPS continues to be BIOBADASER's financial supporter and sponsor.

The pharmaceutical companies sponsoring BIOBADASER as of December 2017 are Biogen, BMS, Pfizer, Roche, Samsung Bioepis, Lilly, Regeneron and Novartis.

The study has the approval from the referral Clinical Research Ethics Committee (CREC) of *Hospital Clinic de Barcelona*.

## **New Developments in BIOBADASER Phase III**

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This year it has been decided to maintain the structure of the project and of the electronic Data Collection Logbook (DCL). “Non medical changes” has been added as a reason for discontinuation. This option refers to those cases where an initial biological treatment can be replaced by a biosimilar for non medical reasons.

This year, serious adverse reactions have continued to be reported to FEDRA. The switch to NotificaRAM, which is adapted to the new European legislation on adverse events reporting, was carried out in November.

## **New Treatments Included in BIOBADASER in 2017**

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The following treatments have been included in the DCL of the study between January 1<sup>st</sup> and November 15<sup>th</sup> 2017:

- Truxima.
- Xeljanz.
- Olumiant.
- Erelzi.

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## Participant Centers

A data download was performed on September 1<sup>st</sup> 2016 to carry out an estimation of the number of patients included in each center. Based on these data along with the reports generated in the online monitoring, the best 20 recruitment centers were selected.

In December 2016, each center was informed whether they continued or not in the study by means of a letter addressed to the researchers.

During the year 2017, BIOBADASER has counted on the participation of the following 20 active centers:

### Participant Centers

CENTERS
<i>Hospital Universitario Virgen Macarena</i>
<i>Hospital Clínico Universitario de Santiago</i>
<i>Hospital Universitario Miguel Servet</i>
<i>Hospital Clínic I Provincial</i>
<i>Hospital de Gran Canaria Dr. Negrín</i>
<i>Hospital General Carlos Haya</i>
<i>Hospital General San Jorge</i>
<i>Hospital General Universitario de Valencia</i>
<i>Hospital Universitario de La Princesa</i>
<i>Complejo Hospitalario Universitario de Granada</i>
<i>Hospital de la Santa Creu i Sant Pau</i>
<i>Hospital General Universitario de Alicante</i>
<i>Hospital General Universitario de Elda</i>
<i>Hospital Universitario de Canarias</i>
<i>Hospital Universitario Príncipe de Asturias</i>
<i>Hospital Universitario Reina Sofía</i>
<i>Hospital Universitario Germans Trias i Pujol</i>
<i>Hospital Universitario Virgen del Rocío</i>
<i>Complejo Hospitalario Universitario A Coruña</i>
<i>Complejo Hospitalario de Salamanca</i>

## List of Participant Researchers in BIOBADASER Phase III

Below is a list of the participant researchers in active centers in BIOBADASER in 2017:

- Dolores Ruiz Montesinos (*Hospital Universitario Virgen Macarena*).
- Eva Perez-Pampin (*Hospital Clínico Universitario de Santiago*).
- Francisco Javier Manero, Chesus Beltran, Jesus Marzo, Marta Medrano, Angela Pecondon, Alvaro Lesta Arnan, Carlos Vazquez (*Hospital Universitario Miguel Servet*).
- Maria Victoria Hernandez, Sebastian C. Rodriguez-Garcia (*Hospital Clinic I Provincial*).
- Carlos Rodriguez Lozano, Antonio Naranjo, Soledad Ojeda, Felix Francisco Hernandez, 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, Isabel Balaguer Trull, Javier Calvo (*Hospital General Universitario de Valencia*).
- Ana Ortiz (*Hospital Universitario de La Princesa*).
- Maria Jose Soto, Enrique Raya, Irene Notario, Rafael Caliz Caliz (*Complejo Hospitalario Universitario de Granada*).
- Cesar Diaz Torne, Helena Borrell, 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, M<sup>a</sup> Paz Martinez, Carlos Perez Barba (*Hospital General Universitario de Elda*).
- Sagrario Bustabad, Lorena Exposito, Beatriz Tejera (*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 Rocío*).

- 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 (*Complejo Hospitalario de Salamanca*).

## Monitoring

In this new phase of the study, 11 centers out of the 20 participant centers are new, while the rest of centers took part in Phase II.

During this year, patients have been monitored by two procedures: the online monitoring of patients included from September 2016 until September 2017, and the on-site monitoring of the 20 active centers.

### Online Monitoring

#### Objectives

The online monitoring objectives are the following:

- To review data from all patients included from each center on the platform.
- To reduce the amount of missing data from patients, by requesting this information from researchers.
- To trace wrong, contradictory, or problematic data by reflecting the incidences in an Excel document for researchers to solve afterwards.

#### Online Monitoring Process

The following measures and deadlines were established regarding this monitoring process:

- All patients who were newly included from September 2016 up to the data download date in September 2017 were reviewed.
- In August, some of the incidences reported in the SPSS syntax were reviewed and other ones were added. Some interesting aspects regarding the online monitoring this year are detailed below:
  - Patients included in the established recruitment period (starting treatment on December 17<sup>th</sup>, 2013).

- Patients must receive, at least, one biological treatment.
  - Collection of adverse events and completion of the Naranjo algorithm included in the non-serious events.
  - Performing annual follow-up visits and the completion of documentation in reference to them.
  - Data collection regarding activity index in patients with RA, PsA, AS, and lupus.
  - Completion of the Charlson Comorbidity index.
  - Collecting data on weight and height at the moment of the patient inclusion.
  - Including patient's weight data in annual check-up visits.
  - This year, special emphasis has been placed on the adequate collection of data regarding doses and treatment frequency.
  - An attempt to minimize errors has been made regarding the observation in the collection of data regarding concomitant treatments with biological drugs, especially with anti-TNF.
- A total of 964 newly included patients have been monitored online.
  - Baseline data, biological treatments, check-ups and collected data on adverse events have been reviewed for all these patients.
  - Incidences in each center were reflected in an Excel document which was sent to each center before November 1<sup>st</sup> in order to resolve them and send the answers back before November 13<sup>th</sup>.

This second year of BIOBADASER Phase III, the collection of data and their quality have improved with regard to the first year, a decrease in the number of incidences having been observed. However, there are still some aspects that must be improved:

- The **missing** data: Researchers are urged to fill in all variables of the DCL. For example, rheumatoid factor levels, Anti-CCP levels, ANA, HLA-B27 that have not been determined in any check-ups should be collected as 'Undetermined.' Researchers are instructed to always answer the comorbidities section “Patient Comorbidities” and “Charlson Index” and not to leave the variables as 'Not specified'. It has also been stressed to collect the dates of the comorbidities of the patient. The collection of concomitant treatments that patients received at the time of the adverse events is another emphasized incidence.
- **DAS28**: Again, researchers have been reminded about the importance of having the data from annual check-ups for patients with rheumatoid and psoriatic arthritis. Researchers have also been urged to show whether DAS28 is calculated with VSG or PCR.
- **Height and weight**: Among the most prevalent incidences found are the lack of height and weight data. Researchers have been requested to make an effort, both at the moment of the patient’s inclusion and at the moment of subsequent visits when collecting these data.

### On-site Monitoring

As was pointed out in the 2016 report, this year has started with the on-site monitoring of the participant centers.

### Objectives

On-site monitoring objectives are as follows:

- To review the collection of informed consent forms (ICs) from patients included in Phase III.
- To review all source documents used for the BIOBADASER platform and check if this information has been properly collected.
- To review and update the researcher's records of each center.

### On-site Monitoring Duration

Between the months of June, July, September, and October, visits to the 20 active centers of the study were scheduled and performed.

### Patient Selection for Monitoring

Once the visit was scheduled, and 15 days prior it, a list containing the codes of the 20 patients who were going to be checked-up was sent. The access to the platform was blocked to impede the collection of new information or any corrections on the already collected information.

For patient selection purposes, a data download was performed in each center, and 20 patients were randomly selected.

Some considerations related to the on-site monitoring:

- Incidences occurring in the three months prior the beginning of the on-site monitoring in the center would not be taken into account. They would be collected but not be considered as incidences.
- Only patients and visits included after December 17<sup>th</sup>, 2013, would be reviewed.
- A filter was applied during the process of selection of the 20 patients to be monitored: 40% (8 patients) suffered from RA, and the other 60% (12 patients) suffered from any other condition. This filter intended to adjust the percentage of the total of patients suffering from rheumatoid arthritis in BIOBADASER, (approximately 40% of patients included in the platform have rheumatoid arthritis).

### On-site Monitoring Procedure

- **Informed consent:** The 20 ICs from the selected patients were requested from each researcher.
- **Study files:** Researchers' records were reviewed and updated in each center, confirming that all the study documentation was contained and identified the research team, checking any missing signatures on commitments and delegation of responsibilities.
- Review of the '**Patient**' section in the DCL:
  - With patients newly included special attention was given to monitoring clinical data such as: activity index and variables used to calculate them, date of diagnosis, Charlson index, and previous biological treatments.
  - Special focus was placed on patients without previous biological treatment (naive) to ensure that they had not received any previous therapies.
  - Missed follow-up appointments, death, or other causes to end the patient's follow-up were confirmed. In the event of death, it was verified that the adverse event had been recorded on the platform.
- Review of "**Treatments**" section in DCL:

- The data obtained regarding activity indexes that was required for some pathologies was reviewed in detail for patients of new inclusion. Special attention was also given to the review of collected data on concomitant treatments.
- Regarding changes of treatment, confirmation had to be made that the reasons for finishing the treatment were reflected, both in the DCL and the medical record. If the reason was the occurrence of an adverse event, there was need to make sure that the information was recorded.
- Special attention was given to the proper collection of data regarding doses and timeline.
- The collection of data and the fulfillment of documents regarding annual check-ups were reviewed.
- Review of the '**Adverse events**' section in the DCL:
  - Special care was placed to ensure that, at the end of a treatment due to adverse event, the information was included in the platform.
  - Particular attention was paid to collection of data regarding concomitant treatments for adverse events.
  - Serious and not serious adverse events needed the Naranjo algorithm to be completed.
- During the on-site monitoring visits, it was found that there was not enough time to review the medical histories from the 20 selected patients. The average of patients reviewed was 12. In the following monitoring visits, the request of patients will adjust to this number.

### **Description of Major/ Minor Incidences and Mild/ Serious Protocol Deviations**

In order to assess data quality in each center after the on-site monitoring, it was decided what would be defined as mild and serious protocol deviation, and what would be defined as minor or major incidence.

During the monitoring quality assessment, these two parameters were taken into consideration: the incidences percentage and the deviations percentage. The incidences percentage is the number of patients with, at least, one mild incidence, divided by the number of patients reviewed in the visit. The deviations percentage is the number of patients with, at least, one deviation divided by the number of patients reviewed in the visit.

Through these percentages, we can assess data quality in each center and compare each center with the average of all centers.

Incidences and deviations are outlined below.

**Minor deviations:**

- One or two missing medical histories (not taking into consideration those of deceased patients). More than 3 medical histories were considered as a serious deviation.
- Doctor or patient's signature missing on an IC.
- Doctor or patient's date missing on an IC.
- The 'Delegation of Responsibilities' document is signed during the first visit. It will be reviewed during subsequent visits in order to verify that functions are delegated only to all who signed the researcher's commitment and delegation of responsibilities documents.

**Mild incidences:**

- Comorbidities not entered.
- Absence of diagnostic tests for TB.
- Absence of any data that may be required to calculate activity index.
- Typographical errors: date of birth, date of diagnosis, date of beginning or ending of treatment, and/ or wrong medication.
- Absence of concomitant medication in adverse events already recorded.
- Not reported non-serious adverse event.

**Major deviations:**

- Patient without signed IC.
- Center without dated and signed researcher undertaking. (*\*Not considered serious in the first visit, but during this visit the absence of any undertakings must be solved*). In the following visits, it will be considered major protocol deviation if there is a new researcher and there is no researcher undertaking.
- Absence of the responsibilities delegation document. (*\*it must be completed in the first visit and it will be considered serious when the document is not updated during the following visits*).
- Not having a list or method to identify patients.
- Absence of any of the main documents of the study (see 4.2).

**Serious incidences:**

- Start of biological treatment not reported.
- Discontinuation of not reported biological treatment.

- Change in biological medication not reported.
- Patient not identified. (There is an identification code that cannot be linked with any names or surnames).
- Serious adverse event not reported.
- Serious adverse event without fulfilling the Naranjo algorithm.
- Death not recorded.

**Table 1** shows the on-site monitoring outcomes in 2017.

The mild incidence percentage is high (the number of variables increased, and therefore, the number of errors and missing data increased). However, as it is mentioned above, these incidences and deviations are considered to have little effect on data and study quality. Mild incidences can be reduced if researchers pay more attention when entering the information in the platform.

With regard to minor deviations, the majority refer to problems with the IC fulfillment, and the absence of doctor's signature or date.

Regarding serious incidences and major deviations, problems have actually occurred in some centers and they must be kept under 20% in order to ensure the quality and compliance of the BIOBADASER protocol because these incidences could definitely become a major issue with respect to BIOBADASER quality and study protocol compliance. The most common incidences and deviations were change of treatment not being reported and serious deficiencies in the IC collection.

After the on-site monitoring visits, conference calls and meetings were held with centers where the clinical research associate detected major problems at *Hospital Virgen Macarena*, *Hospital Univ. de Salamanca*, *Hospital Carlos Haya* and *Hospital Virgen del Rocio*. At these meetings, problems detected were discussed with researchers with the objective of achieving a solution and observing improvement during following on-site visits.

**Table 1** also shows the number of patients monitored in each visit. This first year 20 patients were requested, but due to a higher number of variables and annual reviews, the total of 20 patients could not be monitored. The average number of patients reviewed was 12.1.

**Table 1. % of incidences and deviations**

center	Reviewed patients	Minor incidences	Major incidences	Patients minor incidences	Patients major incidences	Mild deviation	Serious deviation	Patient mild deviation	Patient serious deviation	% minor incidences	% major incidences	% mild deviation	% serious deviation
<i>Hosp. Virgen Macarena</i>	14	55	4	14	1	0	0	0	0	100%	7%	0%	0%
<i>Hosp. Virgen del Rocío</i>	10	19	2	8	1	0	2	0	2	80%	10%	0%	20%
<i>Hosp. Univ. Salamanca</i>	13	48	9	12	5	10	3	10	3	92%	38%	77%	23%
<i>Hosp. Univ. De Granada</i>	11	53	0	11	0	1	0	1	0	100%	0%	9%	0%
<i>Hosp. Univ. Santiago</i>	14	41	2	12	2	1	2	1	2	86%	14%	7%	14%
<i>Hosp. Univ. Canarias</i>	11	45	3	10	3	2	0	2	0	91%	27%	18%	0%
<i>Hosp. San Jorge</i>	10	35	2	10	2	1	0	1	0	100%	20%	10%	0%
<i>Hosp. Reina Sofía</i>	15	34	2	13	2	7	0	6	0	87%	13%	40%	0%
<i>Hosp. Príncipe de Asturias</i>	15	27	0	15	0	0	0	0	0	100%	0%	0%	0%
<i>Hosp. Miguel Servet</i>	14	78	0	14	0	0	0	0	0	100%	0%	0%	0%
<i>Hosp. La Princesa</i>	14	23	0	10	0	0	1	0	1	71%	0%	0%	7%
<i>Hosp. Gral. De Valencia</i>	13	38	1	11	1	2	1	2	1	85%	8%	15%	8%
<i>Hosp. Gral. De Alicante</i>	11	42	1	11	1	0	0	0	0	100%	9%	0%	0%
<i>Hosp. Univ. De A Coruña</i>	10	34	0	9	0	0	0	0	0	90%	0%	0%	0%
<i>Hosp. Germans Trias i Pujol</i>	14	59	3	12	2	8	2	8	2	86%	14%	57%	14%
<i>Hosp. Dr. Negrín</i>	10	48	0	10	0	3	2	3	2	100%	0%	30%	20%
<i>Hosp. De Elda</i>	11	38	1	11	1	0	0	0	0	100%	9%	0%	0%
<i>Hosp. Carlos Haya</i>	11	57	2	10	2	4	2	4	2	91%	18%	36%	18%
<i>Hosp. Clinic</i>	10	54	0	10	0	3	3	3	3	100%	0%	30%	30%
<i>Hosp. Sant Creu i San Pau</i>	11	38	1	11	1	0	0	0	0	100%	9%	0%	0%

## Aspects Related to Monitoring

### Researcher's Records

At the beginning of the study, all centers were sent a file containing the essential study documentation (researcher's records). The file should contain the following documentation:

- Approval from CREC of the referral *Hospital Clinic*.
- Approval from CREC in each center.
- Document of AEMPS classifying the study.
- Document of AEMPS authorizing the study.
- Protocol, latest version
- Patient information sheet (PIS) and IC, latest versions.
- Investigator's manual, latest version.
- Patient selection and inclusion algorithm.
- Contract and/or compliance document of the center.
- Researcher's undertaking by the principal investigator and researcher team.
- Delegation of responsibilities.
- Monitoring visits log.
- Site monitoring visits log.
- Signed patient consent forms.
- On-site monitoring manual, latest version.

In the first monitoring visit, all the files of the centers have been updated and completed and any pending documentation such as researcher team's undertakings, delegation of responsibilities of all participants in each center, inclusion of the onsite monitoring manual and the signature of the monitoring visits log, must be provided.

All researchers have been informed about their responsibility to maintain the study records and report any changes in the research team to the sponsor. If these recommendations are not observed, they will be considered as deviations during the following on-site visits.

### Informed Consent

Regarding ICs, these have been collected correctly, although there are some aspects which must be improved:

- The informed consent forms must be fulfilled by patients, the researcher must only sign. In some centers this is not being followed.
- The informed consent forms remaining in the center must be also signed by researchers (it is not enough that they are only signed by patients).
- In some centers, researchers have been required to sort the ICs by patient code. This way it is easier for the research associate to perform the review.

### Assessment of Centers

In this second year, 20 centers were eventually selected to continue their participation in BIOBADASER.

During the on-site monitoring visit to a center from Phase 2.0, a problem was detected while reviewing the recovered patients' source documents, so patients could not be completely reviewed. After a conversation with the Principal Investigator of the center, it was decided not to retrieve more patients from Phase 2.0 and to make an effort to include new patients.

In some other centers, several major problems have been detected in data collection (change of treatments, adverse events collection, and clinical data such as weight or height). After the visit, some meetings were held with the researchers in order to look for solutions to these deficiencies.

It is expected to find a significant improvement during the following monitoring visit.

Online monitoring has definitely shown improvement, because the number of incidences sent to each center has decreased.

### ***Pharmacovigilance: Serious Adverse Events Report***

**Table 2** shows the number of serious adverse events reported at each center after January 2017 until December 2017.

In the table, the total amount of serious adverse events are divided into two types: serious adverse reactions (Naranjo algorithm over zero) which have been reported to the Spanish System of Pharmacovigilance through FEDRA, and serious adverse events, which are effects that appear during the biological treatment, but where the Naranjo algorithm is under or equal to zero.

The mean of the total of serious adverse events reported through BIOBADASER in 2017 was 6.5 events. The mean of serious adverse reactions was 3.5, and the mean of non-communicable serious adverse events was 3.

**Table 2. Report of Serious Adverse Events in 2017**

Centros	Acontecimiento Adverso Grave	Reacción Adversa Grave	Total Acontecimientos graves comunicados 2017
<i>Hospital Carlos Haya</i>	5	2	7
<i>Hosp. Clinic i Provincial</i>	3	8	11
<i>Hosp. Dr. Negrin</i>	7	5	12
<i>Hosp. General Valencia</i>	7	5	12
<i>Hosp. German Trias i Pujol</i>	40	27	67
<i>Hosp. Gral. de Elda</i>	3	8	11
<i>Hosp. Gral. de Alicante</i>	0	3	3
<i>Hosp. Granada</i>	1	1	2
<i>Hosp. La Princesa</i>	4	4	8
<i>Hosp. Miguel Servet</i>	5	8	13
<i>Hosp. Principe de Asturias</i>	14	7	21
<i>Hosp. Reina Sofia</i>	1	1	2
<i>Hosp. San Creu i San Pau</i>	0	2	2
<i>Hosp. San Jorge</i>	42	22	64
<i>Hosp. Santiago</i>	5	1	6
<i>Hosp. Univ. A Coruña</i>	0	4	4
<i>Hosp. Univ. de Canarias</i>	1	2	3
<i>Hosp. Univ. de Salamanca</i>	1	0	1
<i>Hosp. Virgen Macarena</i>	2	0	2
<i>Hosp. Virgen del Rocio</i>	0	0	0

## Others

### News/Developments

During the year, different actions have been performed in order to promote the recruitment of patients and the register of participants. Among these actions the following should be noted:

- Meeting of researchers at the 2017 National Congress of the Spanish Society of Rheumatology (SER, by its Spanish acronym), Bilbao (Spain).
- Continued updating of the biobadaser.ser.es website with information and documents of interest.
- Quarterly newsletters to promote communication among participant researchers.
- Automatic alert system to remind of the annual follow-up visits.

## Description of the Register Including All Biological Therapies

The results of the current report refer to data downloaded on November 15<sup>th</sup>, 2017. At the moment, the project counts on the participation of 20 hospitals, and all centers have entered data this year 2017. Moreover, all participant centers have included, at least, ten new patients on the platform.

Since the last annual report, more than a thousand new participants have been registered in the project. **Table 3** shows the patients description.

**Table 3.- Characteristics of Patients Included in BIOBADASER 3.0.**

All Biological Agents			
Number of patients (%)		3479	
Women (%)		2116 (60.8)	
Current mean age (SD)		54.2 (14.9)	
Mean age at the beginning of treatment (SD)		50.2 (14.4)	
Median time (P <sub>50</sub> ) of disease at the beginning of treatment [P <sub>25</sub> -P <sub>75</sub> ]		8.1 [3.2-14.8]	
Diagnosis	n (%)		n (%)
Rheumatoid arthritis	1331 (38.3)	Primary Sjögren's syndrome	11 (0.3)
Arthritis or PsA Psoriatic	702 (20.2)	Still's Disease	10 (0.3)
Ankylosing spondylitis	692 (19.9)	Polymyositis / Dermatomyositis	9 (0.3)
Undifferentiated spondyloarthropathy	176 (5.1)	Reactive arthritis	9 (0.3)
Juvenile idiopathic arthritis	103 (3.0)	Juvenile undifferentiated spondyloarthropathy	8 (0.2)
Osteoporosis	68 (2.0)	Juvenile AS	6 (0.2)
Enteropathic arthritis	62 (1.8)	Anti-inflammatory syndromes	6 (0.2)
Systemic lupus erythematosus	59 (1.7)	Scleroderma	5 (0.1)
Seronegative chronic polyarthritis	44 (1.3)	Undifferentiated connective tissue disease	5 (0.1)
Non-radiographic axial ankylosing spondylitis	34 (1.0)	Sarcoidosis	3 (0.1)
Seronegative chronic oligoarthritis	31 (0.9)	Polymyalgia rheumatica	3 (0.1)
Uveitis without rheumatic disease	30 (0.9)	Relapsing polychondritis	1 (0.0)
Vasculitis	26 (0.8)	Psoriasis	1 (0.0)
SAPHO syndrome	16 (0.5)	Arthropathy due to pyrophosphate	1 (0.0)
Overlap syndrome	14 (0.4)	Primary antiphospholipid syndrome	1 (0.0)
Behcet's disease	12 (0.3)		
<b>Total</b>		<b>3479 (100.0)</b>	

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

The average profile of patient included in BIOBADASER is a woman around 54 who started biological treatment four years ago. The most frequent diagnosis is rheumatoid arthritis (38.3%), followed by psoriatic arthritis (20.2%) and ankylosing spondylitis (19.9%). There was a slight percentage decrease for patients diagnosed with rheumatoid arthritis in comparison with other options and psoriatic arthritis itself (which has overstepped ankylosing spondylitis).

**Table 4** shows the description of cycles of used treatments. Data appear divided according to whether therapy was used as a first treatment option, second option, or later options. That is to say that, at least, the patient has received one prior biological treatment which has been discontinued, except for Mabthera, for which, given its administration protocol, second cycles are taken into consideration even though the treatment has not been discontinued (with Mabthera, each cycle of treatment is considered a new treatment).

**Table 4.- Description of Biological Therapies.**

Drug	First Option Treatment n (%)	Second or Later Option Treatment n (%)	All n (%)
Humira	615 (23.0)	558 (14.0)	1173 (17.6)
Mabthera	118 (4.4)	1024 (25.6)	1142 (17.1)
Enbrel	534 (20.0)	523 (13.1)	1057 (15.9)
Remicade	437 (16.4)	230 (5.8)	667 (10.0)
Simponi	231 (8.6)	359 (9.0)	590 (8.9)
Roactemra	140 (5.2)	440 (11.0)	580 (8.7)
Orencia	81 (3.0)	299 (7.5)	380 (5.7)
Cimzia	140 (5.2)	177 (4.4)	317 (4.8)
Cosentyx	44 (1.7)	139 (3.5)	183 (2.7)
Inflectra	64 (2.4)	100 (2.5)	164 (2.5)
Benepali	71 (2.7)	21 (0.5)	92 (1.4)
Stellara	23 (0.9)	62 (1.6)	85 (1.3)
Prolia	67 (2.5)	1 (0.0)	68 (1.0)
Bemlysta	40 (1.5)	7 (0.2)	47 (0.7)
Remsina	30 (1.1)	17 (0.4)	47 (0.7)
Otezla	18 (0.7)	16 (0.4)	34 (0.5)
Kineret	16 (0.6)	10 (0.3)	26 (0.4)
Olumiant	2 (0.1)	5 (0.1)	7 (0.1)
Illaris	0 (0.0)	4 (0.1)	4 (0.1)
Truxima	2 (0.1)	2 (0.1)	4 (0.1)
Xeljanz	0 (0.0)	1 (0.0)	1 (0.0)
Treatment cycles	2673 (100.0)	3995 (100.0)	6668 (100.0)
Reasons for discontinuation	n (%)	n (%)	n (%)

Inefficacy or loss of efficacy	558 (43.7)	832 (33.1)	1390 (36.7)
Adverse events	343 (26.9)	348 (13.8)	691 (18.2)
Pregnancy or desire to be pregnant	36 (2.8)	35 (1.4)	71 (1.9)
Patient lost	11 (0.9)	18 (0.7)	29 (0.8)
Remission	49 (3.8)	39 (1.6)	88 (2.3)
Change for non-medical reasons	0 (0.0)	4 (0.2)	4 (0.1)
Others	167 (13.1)	963 (38.3)	1,130 (29.8)
Unknown	113 (8.9)	276 (11.0)	389 (10.3)
<b>Total discontinuations</b>	<b>1277 (100.0)</b>	<b>2515 (100.0)</b>	<b>3792 (100.0)</b>

The reason for the discontinuation identified as “Others” refers essentially to Mabthera cycles. Due to this drug dosage regimen, cycles of treatment are registered, and the reason for discontinuation in these cases is reflected under “Others”. The category “Change for non-medical reasons” was added last summer. It refers to treatment changes not responding to medical criteria. These changes habitually occur forced by hospital management.

Biological agents most frequently used as first option are Humira (17.6%) and Enbrel (15.9%). Mabthera (25.6%), followed by Humira (14.0%), and Enbrel (13.1%) are the most used as second or later treatment options. In percentage terms, the figures have been stable in comparison to last year. A minor decrease in using Humira and Enbrel as second option has been noticed in BIOBADASER.

The substantial increase in the use of Mabthera as second or later biological treatment option is due to its different administration protocol: two cycles 6 months apart (the usual intervals between cycles for this biologic) are considered as separate treatments; unlike Remicade, to take another example of intravenously administered biological agent.

When it comes to the reasons for discontinuation of a first-option treatment, loss of efficacy is the most reported one accounting for 36.7% of cases, followed by the occurrence of adverse events accounting for 18.2%.

The frequency and percentage of the different adverse events presented in MedDRA on “System Organ Classes” appears on **Table 5**. The most common ones are infections and infestations, accounting for 23.9% of all registered adverse events, followed by skin and subcutaneous tissue disorders accounting for 12.3% (compared to last year, there has been a decrease of more than one point in the percentage of this group). Infections and infestations continue to be the first group.

**Table 5.- Frequency of Adverse Events by Groups.**

Adverse Events (AE)	n	% of total AE
Infections and infestations	1348	23,9

Adverse Events (AE)	n	% of total AE
Skin and subcutaneous tissue disorders	696	12.3
Respiratory, thoracic and mediastinal disorders	339	6.0
Gastrointestinal disorders	313	5.5
Injury, poisoning and complications during surgical procedures	275	4.9
Vascular disorders	255	4.5
Nervous system disorders	253	4.5
Surgical and medical procedures	247	4.4
Complementary examinations	241	4.3
Musculoskeletal and connective tissue disorders	237	4.2
Metabolism and nutrition disorders	199	3.5
Renal and urinary disorders	180	3.2
Blood and lymphatic system disorders	155	2.7
General disorders and administration-site conditions	139	2.5
Immune system disorders	136	2.4
Eye disorders	99	1.8
Cardiac disorders	89	1.6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	81	1.4
Reproductive system and breast disorders	80	1.4
Hepatobiliary disorders	79	1.4
Ear and labyrinth disorders	63	1.1
Psychiatric disorders	61	1.1
Pregnancy, puerperium, and perinatal conditions	36	0.6
Endocrine disorders	35	0.6
Congenital, familial and genetic disorders	13	0.2
Social circumstances	3	0.1
Problems regarding products	1	0.0
Total	5653	100.0

Of the adverse events registered, 80.7% (4,808) were considered as 'non-serious' (the number increased by 2,800 adverse events in contrast with the last report), 14.8% (834, more than 300 new serious adverse events this year) were reported as 'serious,' and 0.2% (11) were 'fatal.' This year, seven new deaths have been reported.

**Table 6** shows the frequency of registered serious adverse events. The most common are still infections and infestations; followed by surgical and medical procedures; and respiratory, thoracic and mediastinal disorders (vascular disorders ranked third in the last report).

### ***Table 6.- Frequency of Serious Adverse Events.***

Adverse Events (AE)	n	% of Total of AE
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Infections and infestations	196	23.2
Surgical and medical procedures	109	12.9
Respiratory, thoracic and mediastinal disorders	64	7.6
Vascular disorders	63	7.5
Injury, poisoning and complications of therapeutic procedures	57	6.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	45	5.3
Musculoskeletal and connective tissue disorders	45	5.3
Gastrointestinal disorders	43	5.1
Nervous system disorders	34	4.0
Cardiac disorders	30	3.6
Skin and subcutaneous tissue disorders	28	3.3
Blood and lymphatic system disorders	19	2.3
Renal and urinary disorders	19	2.3
Hepatobiliary disorders	17	2.0
Reproductive system and breast disorders	14	1.7
Pregnancy, puerperium, and perinatal conditions	12	1.4
Immune system disorders	12	1.4
General disorders and administration-site conditions	10	1.2
Metabolism and nutrition disorders	8	1.0
Psychiatric disorders	8	1.0
Complementary examinations	5	0.6
Eye disorders	5	0.6
Social circumstances	1	0.1
Ear and labyrinth disorders	1	0.1
<b>Total</b>	<b>845</b>	<b>100.0</b>

There have been a total of 11 fatal adverse events which correspond to the following groups of organs and systems: respiratory, thoracic, and mediastinal disorders (four cases); infections and infestations (two cases); benign, malignant and unspecified neoplasms (three); gastrointestinal disorders; and vascular disorders.

The appendix contains a table showing reported deaths in BIOBADASER Phase III. Throughout the year reminders have been issued in order to reinforce the notification of adverse events of any severity, but especially those which are serious and fatal.

**Table 7** presents the incidence rate of all adverse events organized by System Organ Classes. The total incidence rate is 438.3 (422.7-454.5) adverse events per 1,000 patient/year. Regarding adverse events, it is 73.4 (67.2-80.2) per 1,000 patient/year. And for fatal adverse events, it is 0.8 (0.3-1.8) per 1,000 patient/year. This incidence rate continues to be stable since last year.

**Table 7.- Incidence Rate of Adverse Events.**

Incidence Rate (95% CI) /x 1,000 Patient/year	First Option Treatment n (%)	Second and Later Option Treatments n (%)	Total n (%)
Total adverse events	374.3 (364.7-384.2)	323.9 (312-336.3)	438.3 (422.7-454.5)
Serious	55.9 (52.3-59.9)	42.2 (38.1-46.8)	73.4 (67.2-80.2)
Fatal	0.7 (0.4-1.3)	0.7 (0.3-1.6)	0.8 (0.3-1.8)
<b>By system organ class</b>			
Infections and infestations	89.3 (84.6-94.1)	73.1 (67.5-79.1)	109.8 (102.1-118.1)
Skin and subcutaneous tissue disorders	46.1 (42.8-49.6)	40.9 (36.8-45.5)	52.6 (47.4-58.5)
Respiratory, thoracic and mediastinal disorders	22.4 (20.2-25.0)	20.2 (17.4-23.5)	25.3 (21.7-29.4)
Gastrointestinal disorders	20.7 (18.6-23.2)	16.2 (13.7-19.2)	26.5 (22.8-30.7)
Injury, poisoning and complications of therapeutic procedures	17.8 (15.8-20.1)	16.3 (13.8-19.3)	19.7 (16.6-23.4)
Vascular disorders	17.1 (15.2-19.4)	15.1 (12.7-18.0)	19.7 (16.6-23.4)
Nervous system disorders	16.9 (14.9-19.1)	15.0 (12.6-17.9)	19.3 (16.2-22.9)
Surgical and medical procedures	16.4 (14.4-18.5)	12.3 (10.1-14.9)	21.5 (18.3-25.3)
Complementary examinations	16.0 (14.1-18.1)	17.3 (14.7-20.3)	14.3 (11.7-17.5)
Musculoskeletal and connective tissue disorders	15.7 (13.8-17.8)	11.8 (9.7-14.4)	20.6 (17.4-24.4)
Metabolism and nutrition disorders	13.2 (11.5-15.1)	12.7 (10.5-15.3)	13.8 (11.3-17.0)
Renal and urinary disorders	11.9 (10.3-13.8)	10.5 (8.6-13.0)	13.7 (11.1-16.8)
Blood and lymphatic system disorders	10.3 (8.8-12.0)	9.2 (7.4-11.5)	11.6 (9.3-14.5)
General disorders and administration-site conditions	9.2 (7.8-10.9)	8.6 (6.9-10.9)	9.9 (7.8-12.6)
Immune system disorder	9.0 (7.6-10.7)	7.9 (6.2-10.1)	10.4 (8.2-13.1)
Eye disorders	6.6 (5.4-8.0)	5.4 (4.1-7.3)	8.0 (6.1-10.4)
Cardiac disorders	5.9 (4.8-7.3)	5.7 (4.3-7.5)	6.2 (4.5-8.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5.4 (4.3-6.7)	5.4 (4.1-7.3)	5.3 (3.8-7.3)
Hepatobiliary disorders	5.3 (4.3-6.6)	4.0 (2.9-5.6)	6.9 (5.2-9.2)
Reproductive system and breast disorders	5.2 (4.2-6.5)	4.6 (3.4-6.3)	6.0 (4.4-8.2)
Psychiatric disorders	4.2 (3.3-5.3)	3.2 (2.2-4.7)	5.4 (3.9-7.5)
Ear and labyrinth disorders	4.0 (3.1-5.2)	4.0 (2.9-5.6)	4.1 (2.8-5.9)
Pregnancy, puerperium, and perinatal conditions	2.4 (1.7-3.3)	1.8 (1.1-2.9)	3.2 (2.1-4.8)
Endocrine disorders	2.3 (1.7-3.2)	1.5 (0.9-2.6)	3.3 (2.2-5.0)
Congenital, familial and genetic disorders	0.9 (0.5-1.5)	0.9 (0.5-1.9)	0.8 (0.3-1.8)
Social circumstances	0.2 (0.1-0.6)	0.0 (-)	0.5 (0.1-1.4)

The incidence of those adverse events that researchers considered as serious, is shown in **Table 8**. Serious infections and infestations present a rate of incidence of 16.5 (13.7-19.9) serious adverse events per 1,000 patients/ year. Medical and surgical procedures are performed in 9.9

(7.8-12.6) per 1,000 patients/year, and the neoplasms incidence rate is 2.6 (1.6-4.1) per 1,000 patients/year.

**Table 8.- Incidence Rate of Serious Adverse Events.**

Incidence Rate (95% CI) /x 1,000 Patient/Year	First Option Treatment n (%)	Second and Later Option Treatments n (%)	Total n (%)
Infections and infestations	13.0 (11.3-14.9)	10.2 (8.2-12.6)	16.5 (13.7-19.9)
Surgical and medical procedures	7.2 (6.0-8.7)	5.1 (3.8-6.9)	9.9 (7.8-12.6)
Respiratory, thoracic and mediastinal disorders	4.2 (3.3-5.4)	3.0 (2.0-4.4)	5.9 (4.3-8.0)
Vascular disorders	4.2 (3.3-5.3)	3.4 (2.4-4.9)	5.1 (3.7-7.2)
Injury, poisoning and complications of therapeutic procedures	3.8 (2.9-4.9)	2.7 (1.8-4.1)	5.1 (3.7-7.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3.0 (2.2-4.0)	3.3 (2.3-4.8)	2.6 (1.6-4.1)
Musculoskeletal and connective tissue disorders	3.0 (2.2-4.0)	1.3 (0.7-2.3)	5.1 (3.7-7.2)
Gastrointestinal disorders	2.8 (2.1-3.8)	2.1 (1.3-3.4)	3.8 (2.5-5.6)
Nervous system disorders	2.3 (1.6-3.2)	2.1 (1.3-3.4)	2.4 (1.5-3.9)
Cardiac disorders	2.0 (1.4-2.8)	1.5 (0.9-2.6)	2.6 (1.6-4.1)
Skin and subcutaneous tissue disorders	1.9 (1.3-2.7)	1.2 (0.6-2.2)	2.7 (1.7-4.3)
Blood and lymphatic system disorders	1.3 (0.8-2.0)	0.7 (0.3-1.6)	2.0 (1.1-3.4)
Renal and urinary disorders	1.3 (0.8-2.0)	0.7 (0.3-1.6)	2.0 (1.1-3.4)
Hepatobiliary disorders	1.1 (0.7-1.8)	0.5 (0.2-1.3)	2.0 (1.1-3.4)
Reproductive system and breast disorders	0.9 (0.5-1.6)	0.9 (0.5-1.9)	0.9 (0.4-2.0)
Immune system disorder	0.8 (0.5-1.4)	0.7 (0.3-1.6)	0.9 (0.4-2.0)
Pregnancy, puerperium, and perinatal conditions	0.8 (0.5-1.4)	0.4 (0.1-1.1)	1.4 (0.7-2.6)
General disorders and administration site conditions	0.7 (0.4-1.2)	0.4 (0.1-1.1)	1.1 (0.5-2.2)
Psychiatric disorders	0.5 (0.3-1.1)	0.7 (0.3-1.6)	0.3 (0.1-1.2)
Metabolism and nutrition disorders	0.5 (0.3-1.1)	0.7 (0.3-1.6)	0.3 (0.1-1.2)
Complementary examinations	0.3 (0.1-0.8)	0.0 (-)	0.8 (0.3-1.8)
Eye disorders	0.3 (0.1-0.8)	0.5 (0.2-1.3)	0.2 (0.0-1.1)
Social circumstances	0.1 (0.0-0.5)	0.0 (-)	0.2 (0.0-1.1)
Ear and labyrinth disorders	0.1 (0.0-0.5)	0.1 (0.0-0.8)	0.0 (-)

The following table shows information on activity data at the moment of starting treatment, as well as in subsequent follow-up. A steady decrease in the activity indexes is observed. The information is offered by line for treatment and in total.

**Table 9.- Description of Disease Activity Index.**

Index	First Option Treatment n	Second and Later Option	Total
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	(%)			Treatment n(%)			n (%)		
	Start	1 year	2 or more years	Start	1 year	2 or more years	Inicio	1 año	2 o más
<b>DAS28-VSG (RA)</b>	4.9 (1.3)	3.1 (1.3)	2.8 (1.0)	4.2 (1.5)	3.2 (1.3)	2.9 (1.1)	4.6 (1.4)	3.1 (1.4)	2.8 (1.0)
<b>DAS28-PCR (RA)</b>	4.8 (1.7)	3.6 (1.6)	2.4 (0.9)	4.5 (1.5)	3.0 (1.7)	2.4 (1.1)	4.6 (1.5)	3.2 (1.7)	4.6 (1.5)
<b>DAS28-VSG (PsA)</b>	4.3 (1.3)	2.6 (1.2)	2.5 (0.9)	4.2 (1.5)	2.9 (1.2)	2.7 (1.2)	4.2 (1.4)	2.7 (1.2)	2.7 (1.0)
<b>DAS28-PCR (PsA)</b>	4.3 (1.6)	2.6 (1.1)	3.0 (0.4)	4.5 (1.3)	2.9 (1.8)	2.1 (1.0)	4.4 (1.4)	2.8 (1.4)	2.4 (0.9)
<b>Number of tender joints</b>	6.3 (6v0)	1.7 (3.3)	0.8 (1.9)	5.6 (6.0)	2.2 (3.9)	1.5 (3.1)	5.8 (6.0)	2.0 (3.6)	1.1 (2.6)
<b>Number of swollen joints</b>	4.3 (4.6)	0.8 (2.0)	0.5 (1.5)	4.1 (4.9)	1.3 (2.5)	0.8 (2.2)	4.2 (4.8)	1.1 (2.3)	0.6 (1.9)
<b>Patient visual analog scale</b>	5.7 (2.2)	3.7 (2.3)	3.3 (1.9)	5.4 (2.4)	4.0 (2.3)	3.8 (1.9)	5.5 (2.3)	3.8 (2.3)	3.5 (1.9)
<b>Erythrocyte sedimentation rate (ESR)</b>	29.3 (23.6)	18.9 (16.5)	20.8 (17.6)	28.7 (24.0)	21.0 (19.6)	20.1 (19.4)	28.9 (23.8)	20.1 (18.4)	20.5 (18.4)
<b>BASDAI</b>	5.5 (2.0)	3.2 (2.0)	2.9 (1.8)	5.6 (2.3)	3.9 (2.3)	3.4 (2.2)	5.5 (2.2)	3.5 (2.1)	3.0 (1.9)
<b>ASDAS-CRP</b>	3.2 (1.4)	1.7 (1.0)	2.0 (1.0)	3.4 (1.5)	2.0 (0.9)	2.3 (1.1)	3.3 (1.4)	1.8 (1.0)	2.1 (1.1)
<b>SLEDAI</b>	7.7 (3.3)	3.7 (2.1)	3.6 (2.4)	5.5 (2.9)	4.1 (1.7)	3.2 (1.3)	7.0 (3.3)	3.8 (2.0)	3.4 (2.0)

## APPENDIX

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**Table I.- Itemized Frequency of Fatal Adverse Events**

Adverse event	N (%)
Respiratory, thoracic disorders	4 (36.4)
Neoplasms benign, malignant and unspecified	3 (27.3)
Infections and infestations	2 (18.2)
Gastrointestinal disorders	1 (9.1)
Vascular disorders	1 (9.1)
Total	11 (100.0)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>( )</b>
Interstitial lung disease	1 (25.0)
Acute respiratory failure	1 (25.0)
Chronic respiratory insufficiency	1 (25.0)
Pneumonitis	1 (25.0)
Total	4 (100.0)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>( )</b>
Myeloid leukemia	1 (33.3)
Lymphoma	1 (33.3)
Malignant pulmonary neoplasm	1 (33.3)
Total	3 (100.0)
<b>Infections and infestations</b>	<b>( )</b>
Infectious exacerbation of chronic obstructive airways disease	1 (50.0)
Pneumonia	1 (50.0)
Total	2 (100.0)
<b>Gastrointestinal disorders</b>	<b>( )</b>
Intestinal ischemia	1 (100.0)
Total	1 (100.0)
<b>Vascular disorders</b>	<b>( )</b>
Intracranial hematoma	1 (100.0)
Total	1 (100.0)

## BIOBADASER Publications 2017

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International collaborative projects where BIOBADASER takes part:

- PanEuropean database analysis of Abatacept Effectiveness (Panaba project).
- Tocilizumab Collaboration of European Registries in RA (TOCERRA).
- European registries for rituximab in rheumatoid arthritis (CERERRA).

Retention and effectiveness of TNF inhibitor treatment in psoriatic arthritis and axial spondyloarthritis: results from the EuroSpA collaboration.

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