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RETROSPECTIVE STUDY ON DRUG UTILIZATION, AVAILABILITY AND AFFORDABILITY OF BIOSIMILAR MEDICINAL PRODUCTS CONTAINING MONOCLONAL ANTIBODIES IN BULGARIA

ABSTRACT

INAUGURAL-DISSERTATION

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The public defense of the dissertation will take place on ……..2023. from ……. hours in room 501 of the Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", Sofia

Content:

Abbreviations used

BIA	Budget impact analysis
CD	Crohn's disease
BMP	Biological medicinal product
PMARDs	Pain-modifying antirheumatic drugs
BSMP	Biosimilar medicinal product
GIT	Gastrointestinal tract
DBE	Double-balloon enteroscopy
LMPHM	Law on Medicinal Products in Human Medicine
CDM	Complex dispensary (ambulatory) monitoring
CS	Corticosteroids
CT	CT
BDP	Brief description of the product
Med	Medicinal Product
MOH	Ministry of Health
MCC	Metastatic carcinoma of the colon or rectum
MRE	Magnetic resonance enterography
MBC	Metastatic breast cancer
MRT	Magnetic resonance tomography
NSCLC	Non-small cell lung cancer
NHIF	National Health Insurance Fund
ADR	Adverse drug reactions
NSAIDs	Nonsteroidal anti-inflammatory drugs
NCPRM	National Council on Pricing and Reimbursement of Medicinal Products
NHL	Non-Hodgkin lymphoma
HTA	Health Technology Assessment
PDL	Positive drug list
RA	Rheumatoid arthritis
MA	Marketing Authorization
WHO	World Health Organization
ESR	Erythrocyte sedimentation rate
UC	Ulcerative colitis
PES	Pharmacoeconomic studies
CIBD	Chronic inflammatory bowel diseases

CLL	Chronic lymphocytic leukemia
ACPAs	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
axSpA	Axial spondyloarthritis
bDMARD	Biologic disease-modifying antirheumatic drugs
CADREAC	Collaboration Agreement between Drug Regulatory Authorities in Central and Eastern European Countries
C-AxSpAnd	Multicenter Study Evaluating Certolizumab Pegol Compared to Placebo in Subjects With axSpA Without X-ray Evidence of Axial Spondyloarthritis
CHMP	Committee for Medicinal Products for Human Use
CRIB	Clinical Risk Index for Babies
CRP	C-Reactive Protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drugs
DMARDs	Disease-modifying antirheumatic drugs
EC	European Commission
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
IBD	Inflammatory Bowel Disease
IgG	Immunoglobulin G
IM	Intramuscular
INN	International Nonproprietary Name
M05.0	Felty syndrome
M05.1	Rheumatoid lung disease
M05.3	Rheumatoid arthritis with involvement of other organs and systems
M05.8	Other seropositive rheumatoid arthritis
M08.1	Juvenile ankylosing spondylitis
M08.2	Juvenile arthritis with systemic onset
M08.3	Juvenile polyarthritis (seronegative)
M08.4	Pauciarticular juvenile arthritis
M.A	Moving average
mAbs	Monoclonal antibodies
nCADREAC	New Collaboration Agreement between Drug Regulatory Authorities in Central and Eastern European Countries
NYHA III-IV	New York Heart Association

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
RF	Rheumatoid Factor
sDMARD	Synthetic disease-modifying antirheumatic drugs
TNF-a	Tumor necrosis factor-alpha
tsDMARD	Targeted synthetic disease-modifying antirheumatic drugs
ESSO	European Crohn's and Colitis Organization
CMV	Cytomegalovirus

I. INTRODUCTION

Biological medicinal products (BMPs) containing monoclonal antibodies are massively entering various therapeutic areas of real clinical medicine such as rheumatology, oncology, gastroenterology and others. Entering the BMP market presents a series of complex scientific-regulatory, clinical-therapeutic and scientific-practical questions to the interested parties – patients, doctors, funding public institutions. BMPs, on the one hand, represent new therapeutic alternatives, which is based on their pharmacodynamic properties and qualitative composition, on the other hand, from a pharmacoeconomic point of view, these MPs represent a serious challenge for health systems, since the costs of biological therapies are many times higher in comparison with conventional medicinal products. Directive 2001/83/ EC defines that BMP is a medicinal product whose active substance is a biological substance. Biological is any substance that is produced from or extracted from a biological source, such as microorganisms, organs or tissues of plant or animal origin, cells or biological fluids (including blood or plasma) of human or animal origin, biotechnological cell constructs (cell substrates , whether they are recombinant or not, including primary cells), and a combination of physical, chemical and biological tests is required to characterize and determine their quality. BMPs produced by recombinant DNA technology are divided into 3 main groups: Substances that are identical (similar) to their own key signaling proteins, such as: erythropoietin; growth hormone; biosynthetic human insulin and its analogs; Monoclonal antibodies (mAbs); Receptor constructs (fusion proteins), based on a naturally occurring receptor linked to the immunoglobulin structure .

Biological medicinal products are authorized for use (MA) under a centralized procedure by the European Medicines Agency (EMA) in accordance with Regulation (EC) No. 726/2004 of the European Parliament and of the Council.

Biosimilar medicinal products (BSMPs) are, by their very nature, biological medicines that have a great similarity with other biological medicinal products already approved in the EU - the so-called "reference biological medicinal products". The “similar biological” medicinal product and the “reference” medicinal product are expected to have the same safety and efficacy profile and are used to treat the same conditions. The main objective of the European regulatory framework is to determine the similarity of a given biological product to a reference biological medicinal product. Biosimilar medicinal products are also subject to a Centralized Procedure under Regulation (EC) No 726/2004. EMA-approved biosimilar medicinal products should be as safe and effective as their reference products. If a biosimilar has proven similarity to a reference medicinal product and has comparable safety and efficacy in one therapeutic indication, the safety and efficacy data can be extrapolated to all other indications already approved for the reference medicinal product. Extrapolation must be supported by all scientific evidence obtained during preclinical and/or clinical trials . According to Article 10 of the Directive, a biosimilar medicinal product is not allowed on the EU market until 10 years have passed after the initial marketing authorization of the reference product. The ten-year period is referred to as the "data exclusivity " period . The "data exclusivity" periods of the reference BMPs are in the process of expiring and there are already available BMPs on the market. It is expected that the share of BPLB will gradually increase and lead to a decrease in the cost of providing medicinal products and an increase in patient access to biological treatment.

The aim of the national drug policies of the EU member states is to market quality, safe and effective biosimilar drugs, to ensure the availability and accessibility of these drugs and to stimulate rational drug use.

In accordance with the Law on Medicinal Products in Human Medicine (LMPHM), medicinal products can be placed on the market only after they have received authorization for use in the relevant order and have a price registration. I.e. a medicinal product can only be defined as available if it is authorized for use and has a registered price. The same medicinal product is defined as affordable if it is available and included in the reimbursement system from the public fund.

Rational drug use requires that patients receive medicinal products appropriate to their clinical needs in doses that meet their individual needs for a sufficient period of time and at the lowest possible cost to them and their community.

Despite the large number of bodies and institutions involved in the preparation and establishment of the National Drug Policy, the introduction of the norms of the health economics into pricing and reimbursement policies, in particular the pharmacoeconomic studies (Ph) and the assessment of health technologies (HTA), have not yet been found published in the scientific literature significant representative studies for the country to assess the availability and accessibility of biosimilar medicinal products (BSMP) containing monoclonal antibodies in clinical practice in Bulgaria.

Decisions on "substitutability/interchangeability/switching" of biological and biosimilar medicinal products are not part of authorization procedures. Such decisions are the responsibility of the national competent authorities (Ministry of Health, Health Insurance Fund, scientific societies, etc.) and are outside the competence of the EMA. EU Member States have access to the scientific assessment carried out by the Committee for Medicinal Products for Human Use (CHMP) and any data submitted to justify their decisions. Drug interchangeability is possible and permissible - there are the same therapeutic indications, the same dosage form, the same amount of active substance, the same dosage regimen and the same route of administration of the drug. Drug interchangeability is acceptable, both in terms of the quality of similar biological drugs, and also due to the presence of no less safety and efficacy. However, decisions of this nature are not always based on scientific criteria, but rather depend on financial, economic and psycho-social factors.

In this dissertation, we will investigate the availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria, through a retrospective study of medicinal use .

We will assess the availability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria by calculating and analyzing the costs of medicinal therapies with this type of products by measuring absolute and relative market shares and macro-level budgetary parameters for medicinal usability.

We will assess the availability of criteria for rational medicinal use by measuring the medicinal usability of biosimilar medicinal products containing monoclonal antibodies used for the treatment of socially significant diseases - Rheumatoid arthritis (RA) and Inflammatory bowel diseases (ulcerative colitis (UC), Crohn's disease (CD) and undifferentiated colitis).

We will prepare a comparative quantitative and qualitative analysis of medicinal use and usability between biological and biosimilar medicinal products containing monoclonal antibodies in the treatment of socially significant diseases - Rheumatoid arthritis and Inflammatory bowel diseases (ulcerative colitis, Crohn's disease and undifferentiated colitis).

We chose and formulated the topic of the dissertation because:

1. **The introduction of biologic therapies into clinical practice raises a series of complex regulatory issues as well as significant pharmacoeconomic concerns, as the costs of biologic therapies are dramatically higher than conventional drugs.**

2. **There is a definite similarity in quality, safety and efficacy between the biosimilar and the reference medicinal product, and the introduction of biosimilars should reduce the profitability of biologics and reduce costs for patients and healthcare systems.**

3. **Decisions on "substitutability/interchangeability/switching" of biologics and biosimilars are not part of authorization procedures. Such decisions are the responsibility of the national competent authorities (in our case - Ministry of Health, National Health Insurance Fund, Executive Agency for Medicines, Expert Councils of the Ministry of Health, Scientific Societies, etc.) and are outside the competence of EMA.**

4. **Drug interchangeability is possible and permissible - there are the same therapeutic indications, the same dosage form, the same amount of active substance, the same dosage regimen and the same route of introduction of the drug, both in terms of the quality of the biosimilar medicinal products, and also due to the presence of no less safety and efficacy. However, decisions of this nature are not always based on scientific criteria, but rather depend on financial, economic and psycho-social factors.**

5. **There is no evidence that such studies have been conducted in Bulgaria.**

II. AIMS AND OBJECTIVES

2.1. AIMS:

1. To determine the medicinal use, availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria at a macro level.

2. To determine the medicinal use of biosimilar medicinal products containing monoclonal antibodies in Bulgaria in specific therapeutic areas - rheumatology and gastroenterology by analyzing the medicinal usability of two main socially significant diseases - Rheumatoid arthritis and Inflammatory bowel diseases (ulcerative colitis, Crohn's disease and undifferentiated colitis).

2.2.OBJECTIVES:

Tasks related to the implementation of objective No. 1:

1. To determine the availability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria by assessing their registration status.

2. To determine the availability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria, by assessing the availability of registered prices of authorized biosimilar medicinal products in Bulgaria.

3. To determine the availability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria by assessing their inclusion in reimbursement systems.

4. To assess the availability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria by calculating and analyzing the costs of drug therapies with this type of medicinal products by measuring absolute and relative market shares and macro-level budgetary parameters for medicinal usability.

Tasks related to the implementation of objective No. 2:

1. To conduct a comparative quantitative and qualitative analysis of drug use and usability between biological and biosimilar medicinal products containing monoclonal antibodies in the treatment of Rheumatoid Arthritis and Inflammatory Bowel Disease.

2. To assess the level of knowledge and willingness of specialists to prescribe biological and biosimilar medicinal products containing monoclonal antibodies in Bulgaria.

III. MATERIALS AND METHODS

3.1. MATERIALS

3.1.1. Materials for Task No. 1

To identify all biosimilar medicinal products we used the EMA Search engine medicines with the following keywords: "Similar biological medicinal products containing monoclonal antibodies".

To conduct a retrospective observational study of data from the public registers of EMA, National Council for Prices and Reimbursement of Medicinal Products and the National Health Insurance Fund (NHIF) in Bulgaria for the period 2015 - 2019 we used as a source of information the Brief characteristics of the permitted for use of biological and biosimilar medicinal products as published on the Internet EMA and European Commission page, section " Public health - Register of medicinal products" - as of 21.02.2021. For for the purposes of the comparative analysis, we used the sections of the SPC: 4.1 Therapeutic indications and 5.1 Pharmacodynamic properties.

3.1.2. Materials for Task No. 2

In order to evaluate the process of inclusion in the reimbursement systems of biosimilar medicinal products we used as a source of information The Ordinance on the conditions, rules and procedure for regulating and registering the prices of medicinal products.

3.1.3. Materials for Task No. 3

From the public registers of the National Council for Prices and Reimbursement of Medicinal Products (NCRCLP), we have determined which BSMPs containing monoclonal antibodies have a registered price in Bulgaria and/or are included in the Positive Drug List .

3.1.4. Materials for Task No. 4

From the NHIF registers, we determined the costs of BSMP drug therapies containing monoclonal antibodies and included in the NHIF reimbursement system.

3.1.5. Materials for Task No. 5

To calculate and analyze the costs of drug therapies with biological and biosimilar medicinal products containing monoclonal antibodies for the treatment of Rheumatoid Arthritis and Inflammatory Bowel Diseases (Ulcerative Colitis, Crohn's Disease and Undifferentiated Colitis), we used officially submitted data from the NHIF, requested through an official Application for access to public information.

3.1.6 . Materials for Task No. 6

In order to assess the degree of knowledge and willingness of specialists to prescribe biological and biosimilar medicinal products containing monoclonal antibodies in Bulgaria, we conducted a survey among medical specialists in Rheumatology and Gastroenterology.

3.2.METHODS

3.2.1. Methods for task No. 1

To evaluate the information in the brief characteristics of the biosimilar medicinal products, we used the Desk research method. The main goal of the study was to build a basis for a subsequent stage of our empirical research by giving us the most general information about the medicinal products, the subject of our research.

3.2.2. Methods for task No. 2

In order to thoroughly understand the complicated process of pricing and inclusion in the reimbursement systems of biosimilar medicinal products described in the texts of the Ordinance on the conditions, rules and procedure for regulating and registering the prices of medicinal products, we again used the Desk research method. .

3.2.3. Methods for task No. 3

Using a quantitative method for secondary data analysis, we collected primary quantitative data and specified which BSMPs containing monoclonal antibodies have a registered price in Bulgaria and/or are included in the Positive Drug List.

3.2.4. Methods for task No. 4

To calculate the costs of BSMP drug therapies containing monoclonal antibodies and included in the NHIF reimbursement system through the method of secondary data analysis, we collected partially processed data from the NHIF registries and determined the costs of BSMP drug therapies containing monoclonal antibodies.

3.2.5. Methods for task No. 5.

Through a formal Request for Access to Public Information, we requested access to a full set of data from the NHIF. We used a common method to perform a financial analysis of the costs of drug therapies with biological and biosimilar medicinal products containing monoclonal antibodies used for the treatment of Rheumatoid Arthritis and Inflammatory Bowel Diseases (Ulcerative Colitis, Crohn's Disease and Undifferentiated Colitis) .

3.2.6. Methods for task No. 6.

In order to assess the degree of knowledge and continuity of specialists prescribing biological and biosimilar medicinal products containing monoclonal antibodies in

Bulgaria, we used a survey method in the form of a written questioning (survey card). We used two main approaches in conducting the questionnaire survey - in-person interviewing through a direct group survey and in-person absentee interviewing through a direct e-mail survey.

The direct group survey was conducted among leading specialists in Rheumatology at the Second Interdiscipline Rheumatology Forum, organized by the Bulgarian Medical Society for Osteoporosis and Osteoarthritis. The interviewed specialists filled in the questionnaire distributed to them by the interviewer personally and at the same time in a group. Direct contact was made with the interviewer. The completed questionnaires are collected in an appropriate way (in envelopes), guaranteeing the anonymity of the respondents.

The direct survey by e-mail is a form of in-person absentee interviewing, where the subject fills out the questionnaire by hand, but it reaches him and is returned to the researcher by e-mail (online). We distributed the survey among specialists in Rheumatology and Gastroenterology.

IV. RESULTS OF OWN RESEARCH AND ANALYSIS

4.1. Results for Task No. 1

In accordance with the Law on Medicinal Products in Human Medicine (LMPHM), medicinal products can be placed on the market only after they have received authorization for use in the relevant order and have a price registration. I.e. a medicinal product can only be defined as available if it is authorized for use and has a registered price. The same medicinal product is defined as affordable if it is available and included in the reimbursement system from the public fund.

As of December 31, 2019, EMA has issued authorizations for the use of 67 biosimilar medicinal products, of which 14 products contain monoclonal antibodies. The share of BSMP containing monoclonal antibodies is 1/5 of the total number or 20.89%. Approved BSMPs are divided into 6 INNs - Adalimumab, Infliximab, Rituximab, Bevacizumab, Trastuzumab and Trastuzumab emtansine. In tabular form, we present a comparative analysis and distribution of the reference and biosimilar products by INN and periods of authorization for use (Table 1).

Table 1. Biosimilar medicinal products authorized for use in the EU and available in Bulgaria

INN	Reference medicinal product	Date of Marketing Authorization	Biosimilar medicinal product	Date of Marketing Authorization
Adalimumab	**Humira**		**Amgevita**	24/03/2017
		10.09.2003	**Hyrimoz**	30.07.2018
			Julio	19.10.2018
Infliximab	**Remicade**	10.09.2003	**Inflectra**	12.09.201 3
			Remsima	12.09.2013
			Zessly	05/23/2018 8
Rituximab	**MabThera**	06/03/1998	**Rixathon**	19.06.2017
			Truxima	22.02.2017
Bevacizumab	**Avastin**	12.01.2005	**Zirabev**	14.02.2019
			Mvasi	15.01.2018
Trastuzumab	**Herceptin**	09/04/2000	**Herzuma**	13/02/2018
			Kanjinti	18.05.2018
			Ogivri	14.12.2018
			Trazimera	30.07.2018
Trastuzumab emtansine	**Kadcyla**	19.11.2013	**x**	x

The marketing periods of the first BSMPs in the mass case are in the range of 15 years and more from the date of authorization for use of the reference BMP. The first monoclonal antibody Rituximab was approved in 1998, while the first BSMP with INN Rituximab only appeared in 2017.

INN is similar Adalimumab - BSMP with the same INN was marketed in the EU 14 years after the reference. The only biosimilars granted marketing authorization immediately after the end of the exclusive data protection period are the products with INN Infliximab - exactly 10 years.

4.2.Results for Task No. 2

In a theoretical aspect, all medicinal products - reference and biosimilar, once authorized for use could be considered available on the market in Bulgaria from the date of their authorization.

In practice, this is not the case, because the LMPHM, respectively the Ordinance on the conditions, rules and procedure for regulating and registering the prices of medicinal products, introduces a mandatory condition that a "medicinal product can be sold on the territory of the country only after the entry into force of a decision on approval of a price/limit price or price registration issued by the NCPRM". In case of non-compliance with this condition, the law provides for administrative penalties.

Pricing is at the discretion of Licensees. Depending on the type of prescription of the medicinal products - with or without a doctor's prescription, different procedures are followed in terms of type and duration. The type of product – reference or biosimilar – is also essential.

All biosimilar drugs are prescription-only and can choose two paths for price formation: registration of a marginal price for the free market (direct payment by the patient without reimbursement by the NHIF) or the price of a medicinal product included in the Positive Medicines List (PDL) and paid for with public funds (Ministry of Health (MOH) or NHIF). In Figure 1, we present the BSMP pricing process.

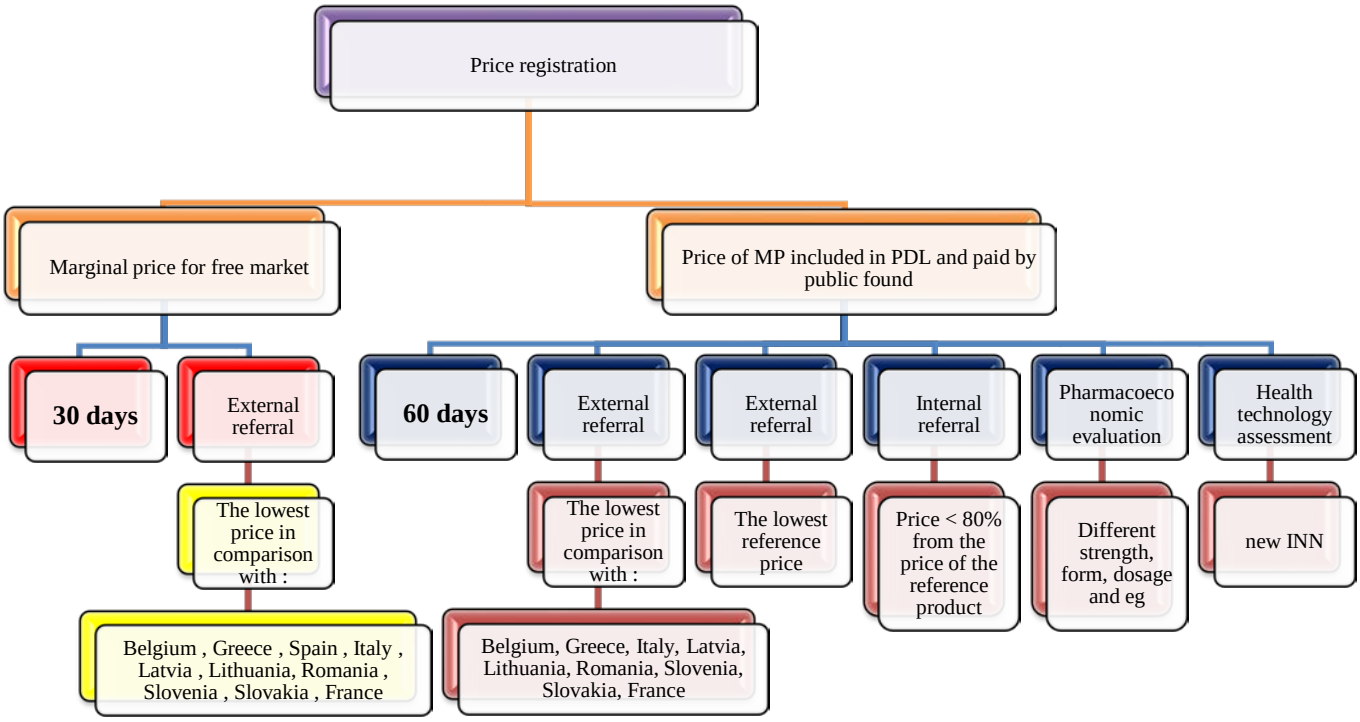

Figure 1. Diagram of procedures and conditions for price registration of biosimilar medicinal products

From the diagram presented, it is clear that the procedures for registering the price of BMP are one of the shortest in the EU member states – 30 or 60 days, respectively. For comparison, Directive 89/105 sets deadlines of 90 or 180 days, respectively, for price registration or price registration and inclusion in reimbursement systems. To the terms of 30 or 60 days, we must add 14 days for the entry into force of the administrative decisions and another 30 days for entry into the system for effective reimbursement, in the cases of registration of the price of a medicinal product included in the PDL and paid for with public funds. The maximum duration of the periods for registration of the price for the free market is 44 days, and for the registration of the price of a medicinal product included in the PDL and paid for with public funds is 104 days.

We determined in which periods after authorization for use the reference biological medicinal products and their biosimilar medicinal products become available for Bulgarian patients, i.e. the two cumulative conditions are met - availability of MA and registered price. The prices of BMP and BSMP, as well as the price of one therapeutic course, significantly exceed the average income of Bulgarian citizens, which is why this type of products are considered affordable only after their inclusion in the reimbursement system.

4.3.Results for Task No. 3

A review of the NCPRM registers reveals that all BMPs and BSMPs are included in the reimbursement system. No BMP or BSMP has registered a price only for the free market in Bulgaria. The data are presented in Table 2.

Table 2. Periods of inclusion of BMP and BSMP in the system of the Positive Drug List in Bulgaria and access to effective reimbursement

MA of reference biological product	PDL inclusion	Biosimilar	MA of biosimilars	PDL inclusion
Humira (INN Adalimumab) 10.09.2003	12.02.2009	**Amgevita**	24/03/2017	22.10.2018
		Hyrimoz	30.07.2018	18.03.2019
		Julio	19.10.2018	22.03.2019
Remicade (INN Infliximab) 10.09.2003	20.04.2019	**Inflectra**	12.09.201 3	28.11.2013
		Remsima	12.09.2013	12/12/2013
		Zessly	05/23/2018 8	12.04.2019
MabThera (INN Rituximab) 06/03/1998	13.02.2009	**Rixathon**	19.06.2017	01.11.2018
		Truxima	22.02.2017	04.01.2019
Avastin (INN Bevacizumab) 12.01.2005	02.03.2009	**Zirabev**	14.02.2019	**x**
		Mvasi	15.01.2018	**x**
Herceptin (INN Trastuzumab) 09/04/2000	02.03.2009	**Herzuma**	13/02/2018	27.10.2018
		Kanjinti	18.05.2018	08/02/2018
		Ogivri	14.12.2018	04/02/2019
		Trazimera	30.07.2018	04/02/2019
Kadcyla (Trastuzumab emtansine) 19.11.2013	10.11.2015	**x**	**x**	**x**

The results show that the reference BMPs were included in the reimbursement system relatively late compared to other EU member states. It is important to note that Bulgaria became a member of the EU on January 1, 2007, and only from that date the centralized RUs become directly valid for Bulgaria.

Before this period BMP with INN Rituximab , Infliximab , Adalimumab , Trastuzumab and Bevacizumab , authorized in EU member states under a centralized procedure, in Bulgaria, as a third EU country, these products are authorized under a pure national procedure, although accelerated under the so-called initiative CADREAC (Collaboration Agreement between Drug

Regulatory Authorities in Central and Eastern European Countries) and nCADREAC , which circumstance by definition has long been the main reason for delayed access to innovative therapies.

Although we have taken this circumstance into account, it is obvious that the first BMPs containing monoclonal antibodies appear on the Bulgarian market with an average of 5.5 years of delay, compared to the EU member states.

This fact is not established for BSMPs containing monoclonal antibodies, which received authorization for use after 2007, under the conditions of effective membership of Bulgaria in the EU. 12 BSMPs are included in the PDL. The average term established by us for inclusion in the reimbursement in Bulgaria of BSMP after issuance of the MA is 6.3 months.

In a series of graphs, we present BMPs and their BSMPs included in the PDL with the corresponding registered prices - figures 2-5.

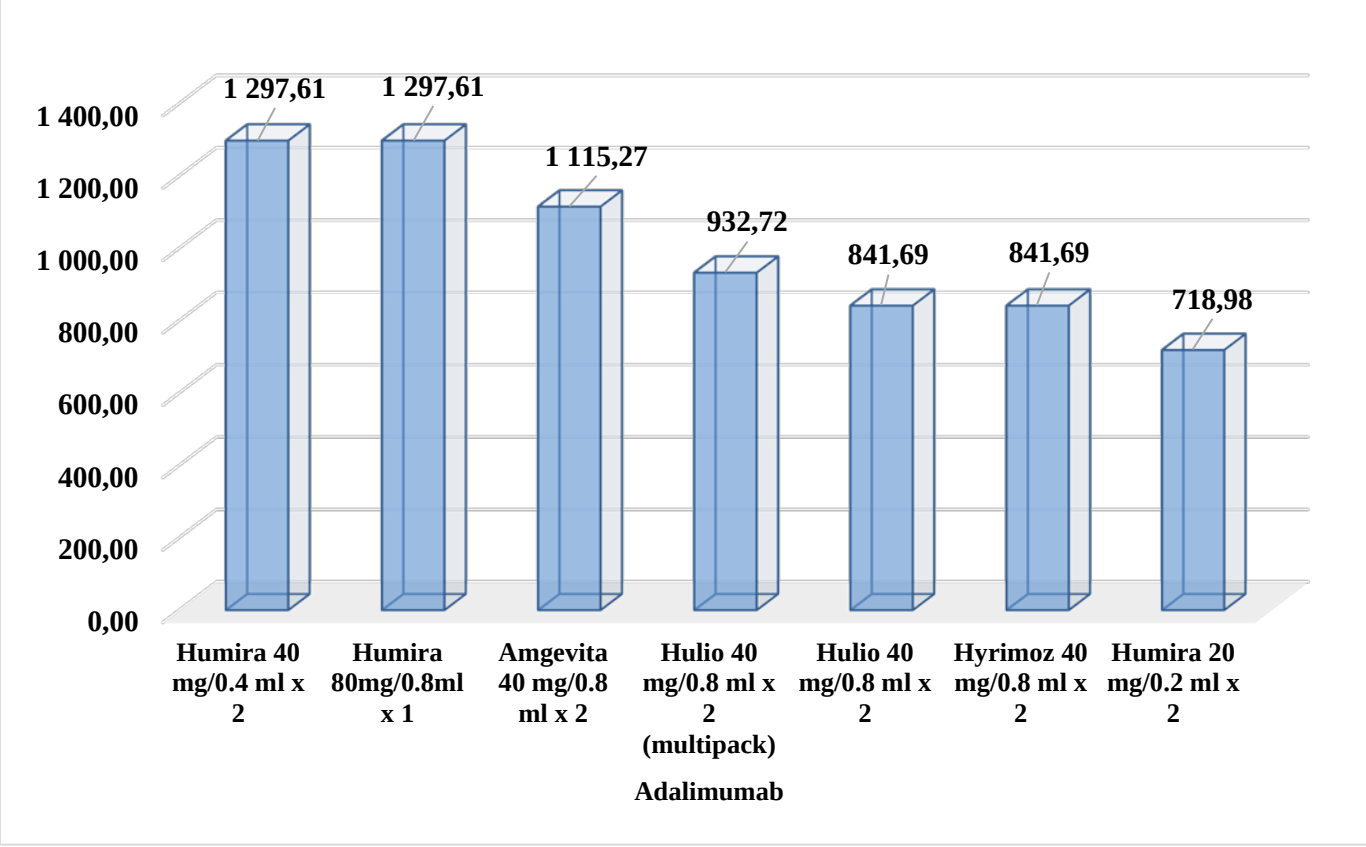

Figure 2. Medicinal products with INN Adalimumab

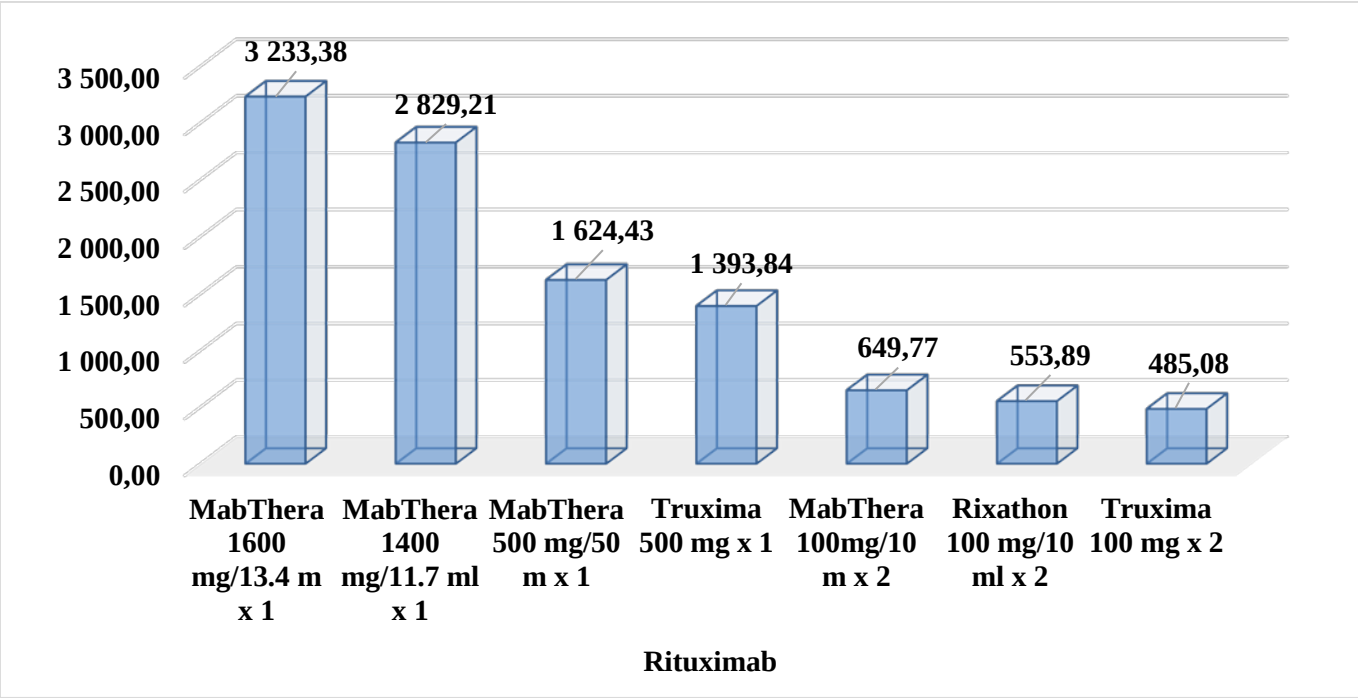

Figure 3. Medicinal products with INN Rituximab

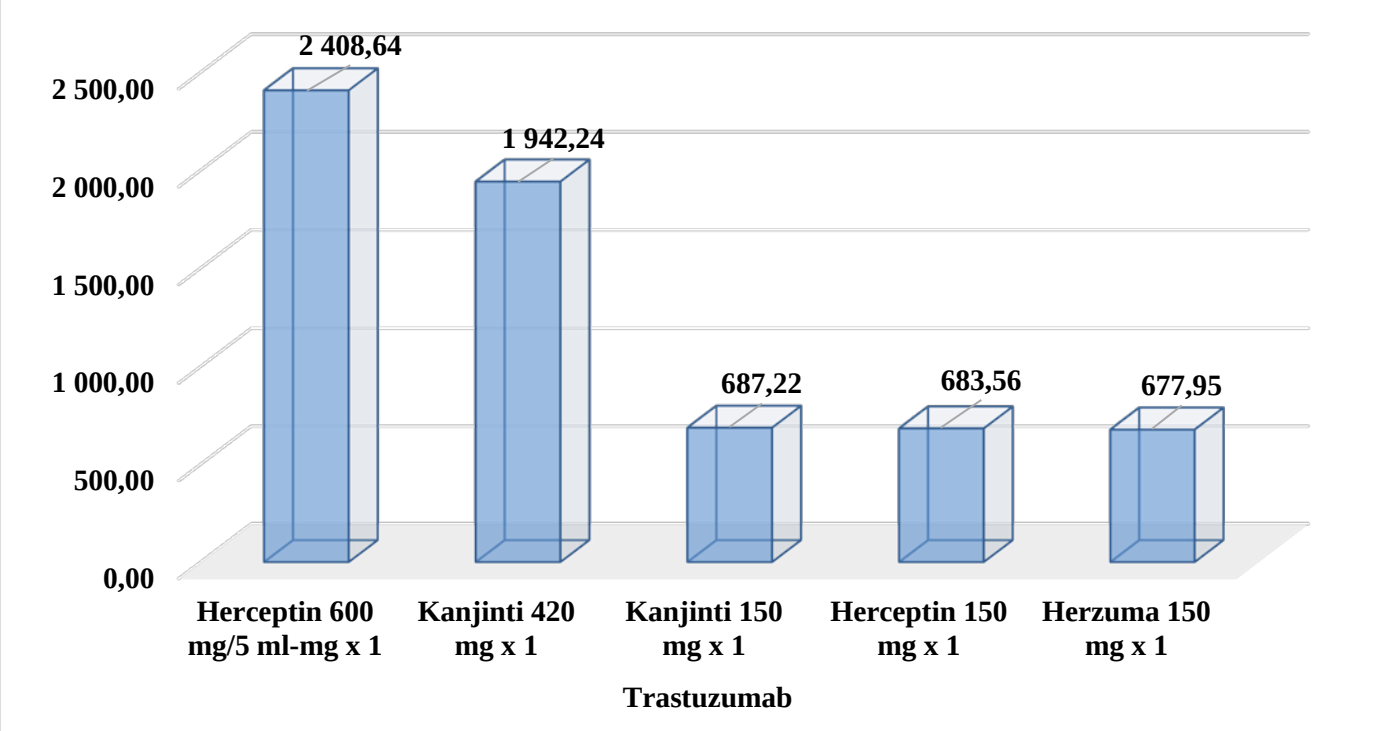

Figure 4. Medicinal products with INN Trastuzumab

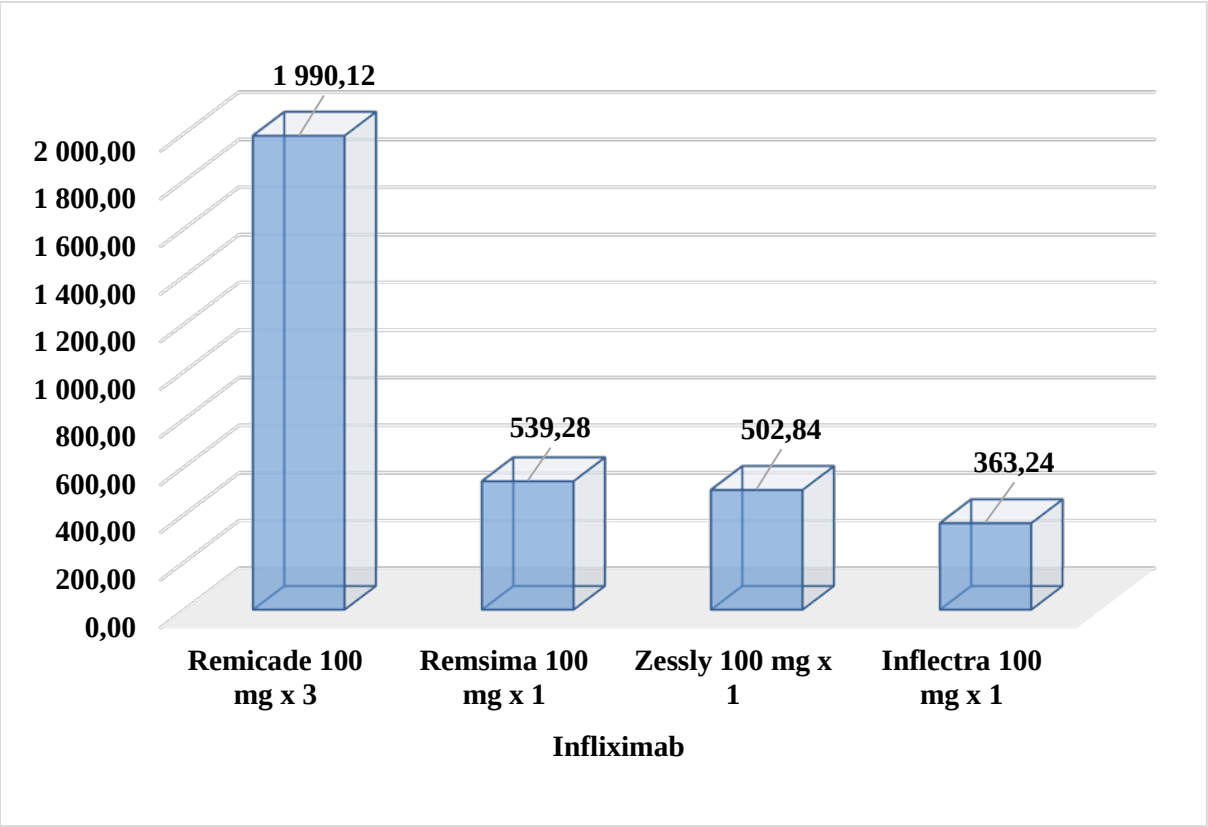

Figure 5. Medicinal products with INN Infliximab

4.4.Results for Task No. 4

As we have already shown in Fig. 3, in accordance with the Bulgarian regulations, the price of BSMP cannot exceed 80% of the registered price of BSMP with the same INN . From the data reflected in Figures 2-5, it is found that this condition is strictly observed and BSMPs should lead to a reduction in the costs of public institutions for biological therapies.

The inclusion of BSMP in the same reimbursement group with BMP leads to the determination of a lower reimbursement amount for payment by the NHIF on the basis of the so-called internal referencing in the relevant INN. The lower registered price of BSMP becomes the reference price for the corresponding INN.

To find out if this is the case, we analyzed public data on drug utilization at a macro level for the period 2015-2019 inclusive.

We analyzed the total costs of treatment with BMP and BSMP, also distributed by INN . The total costs for biological products for the five-year period are BGN 716,360,871. Of them, 95.25% is the share of reference biological products, while the share of biosimilar medicinal products is only 4.75% - table 3 and figure 6.

Table 3. Expenses of the NHIF for biological and biosimilar medicinal products for the period 2015-2019 as a total amount and distribution by INN in BGN

Medicinal product INN	Cost of INN	Cost of biological medicinal product	Cost of biosimilars
Adalimumab	214 770 069	214 347 286	422,783
Infliximab	31,480,469	75 138	31,405,331
Rituximab	57 656 146	56,327,865	1,328,281
Bevacizumab	224 715 377	224 715 377	x
Trastuzumab	161 642 549	160 768 458	874 091
Trastuzumab emtansine	26,096,261	26,096,261	x
Total cost	**716 360 871**	**691 673 158**	**34 030 486**
Relative share	**100%**	**95.25%**	**4.75 %**

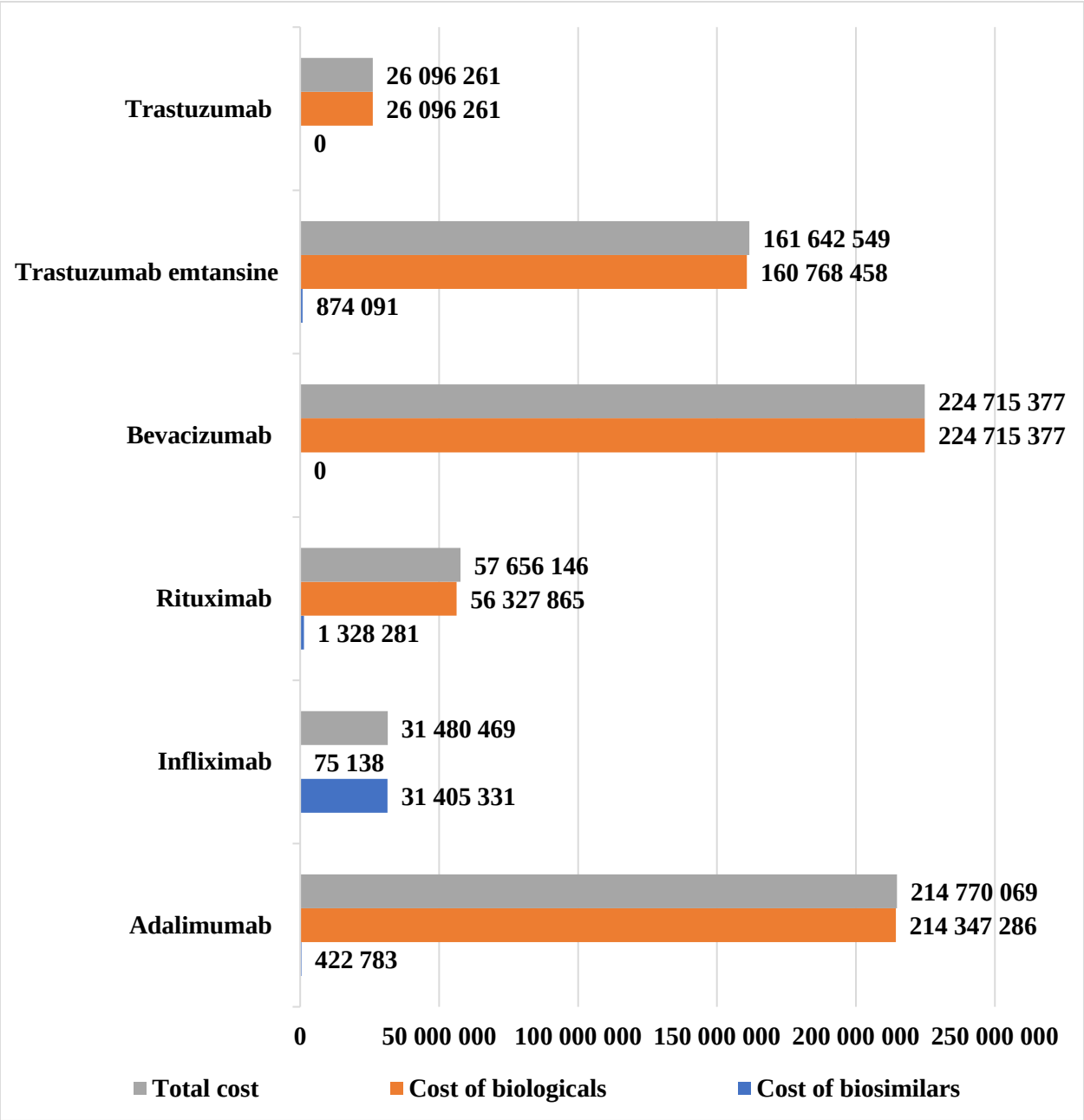

Figure 6. Graphic presentation of the expenses of the NHIF for biological and biosimilar medicinal products for the period 2015-2019 as a total amount and distribution by INN in BGN

An exception to the "rule" of prescribing predominantly reference products is established in the INN Infliximab . We see that a reimbursement amount of BGN 31,480,469 for MP with this INN is aimed at paying for the biosimilar medicinal products Inflectra , Remsima and Zessly – 99.76%.

Only 75 BGN 138 or 0.24% of the costs are aimed at paying for the reference biological product. During the analyzed period, the reference product Remicade was not presented on the Bulgarian market - table 4.

Table 4. Costs for medicinal products with INN Infliximab for the period 2015-2019 in BGN

Year	Reimbursement cost	Reference medicinal product Remicade	Biosimilar Inflectra , Remsima , Zessly
2015	**5,741,432**	**x**	**5,741,432**
2016	**6,297,574**	**x**	**6,297,574**
2017	**6,653,423**	**x**	**6,653,423**
2018	**7,244,173**	**x**	**7,244,173**
2019	**5 5 43 867**	**75 138**	**5 4 68 729**
Total cost	**31,480,469**	**75 138**	**31,405,331**
Relative share	**100%**	**0.24%**	**99.76%**

The situation with the usability of biosimilar medicinal products with INN Infliximab has no counterpart in other INNs with biosimilars. We decided to calculate the share of costs for biosimilar medicinal products without the INN products Infliximab . We subtracted the absolute share of BSMP with INN Infliximab in the amount of BGN 31,405,331 from the total amount of the budget expenditures of the NHIF for biological products for the analyzed period 2015-2019 and we obtained that the real share in the absolute amount of used BSMP in Bulgaria is equal to BGN 2,625,155.

As a relative share, BSMP represent 0.37% of the total budget expenditures for biological products in general.

We have determined the budget costs of the NHIF for medicinal products for home treatment and for the treatment of malignant diseases for the five-year period 2015-2019. The total amount of the costs for medicinal products for 5 years is equal to BGN 4,350,461,600 - the results are presented in a table 5.

Table 5. Budgetary expenses of the NHIF for medicinal products for the period 2015-2019.

Year	Cost of medicinal product for treatment of outpatients	Cost of medicinal product for treatment of oncology diseases	Total cost
2015	544,164,000	175,000,000	719,164,000
2016	540,926,000	210,000,000	750,926,000
2017	537,006,000	225,565,600	798 571 6 00
2018	718,000,000	282,000,000	1,000,000,000
2019	732,800,000	385,000,000	1,117,800,000
Total cost	**3,072,896,000**	**1,277,565,600**	**4,350,461,600**

We determined a cost ratio for the studied international generic names - Adalimumab , Infliximab , Rituximab , Bevacizumab , Trastuzumab and Trastuzumab emtansine (reference and biosimilar) to the total cost of medicinal products for the study period 2015-2019.

The share of the studied products is close to 1/5 of the total costs for drug therapy in Bulgaria in general, as, as we have already established, the usability of biosimilar medicinal products is negligibly small.

4.5.Results for Task No. 5

We conducted a comparative study of the therapeutic indications according to SPC and ICD-10 for INN Adalimumab, Infliximab, Rituximab, Trastuzumab and Bevacizumab. We present the costs of BMP and BSMP according to ICD-10 in graphic form. The data replicate the results obtained under Task No.4, when the referent is not available on the market, biosimilar medicinal products are the definitive choice of prescribers.

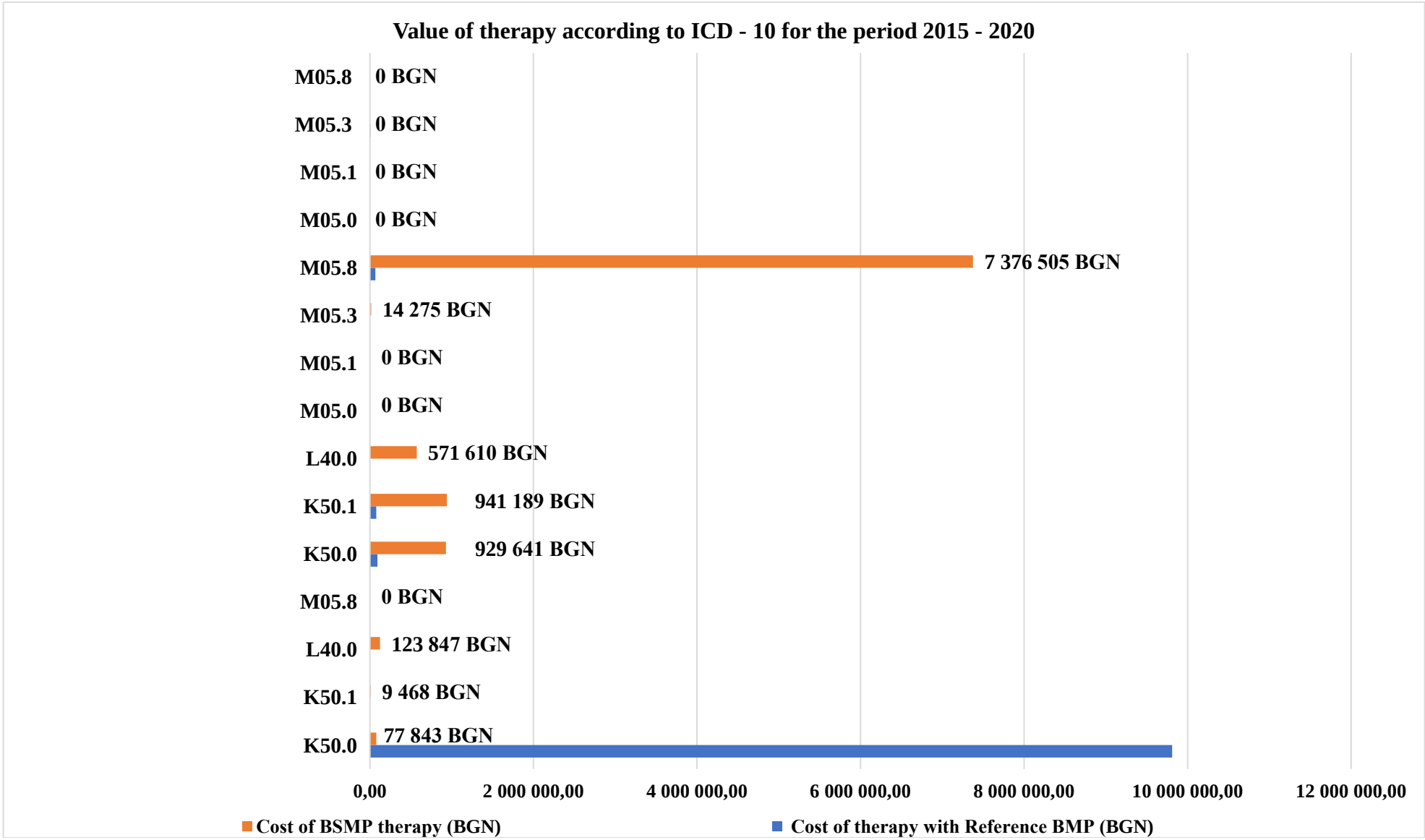

Figure 7. Cost of therapy according to ICD-10 for the period 2015-2020

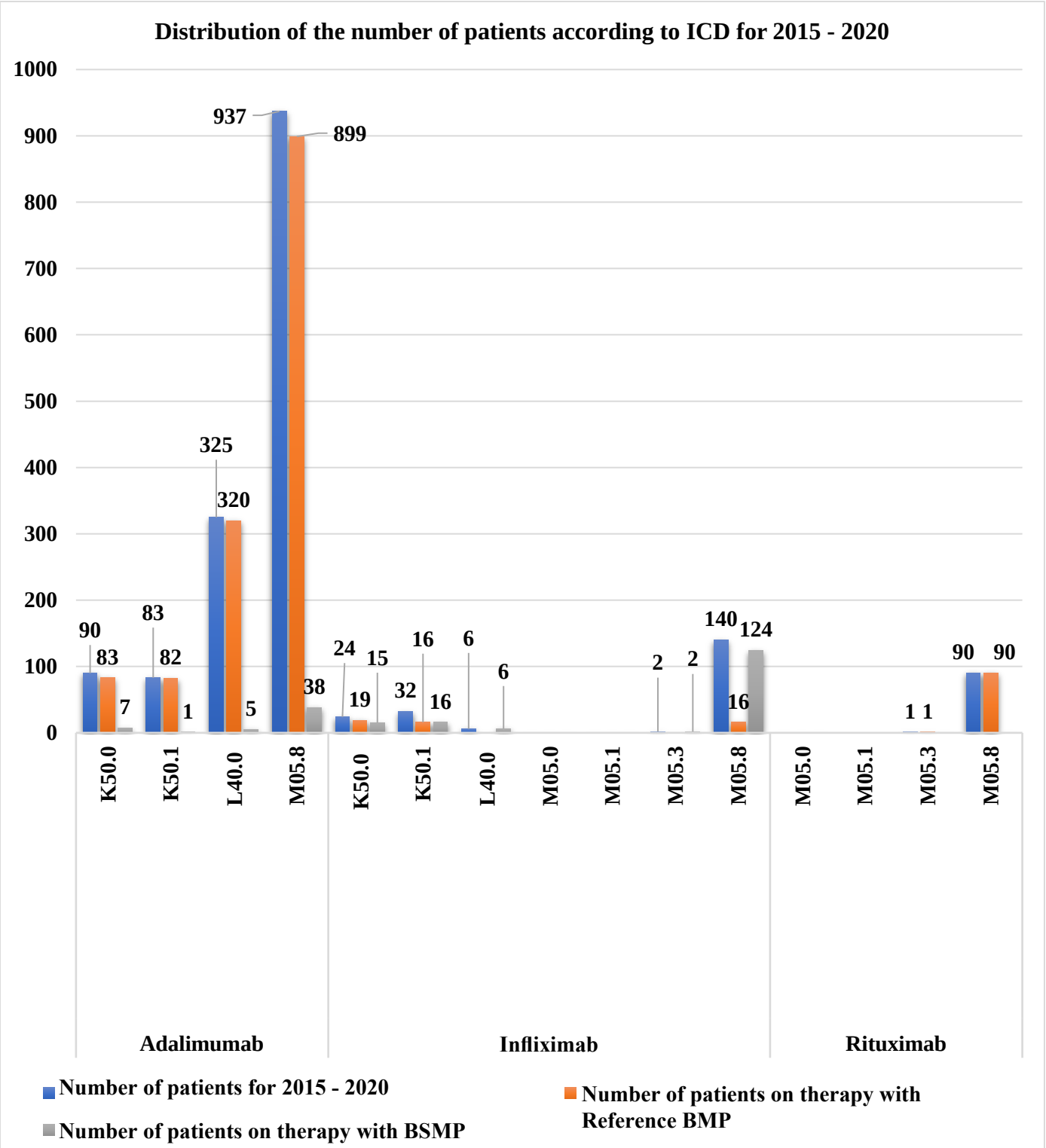

Figure 8. Distribution of the number of patients by ICD for 2015 – 2020

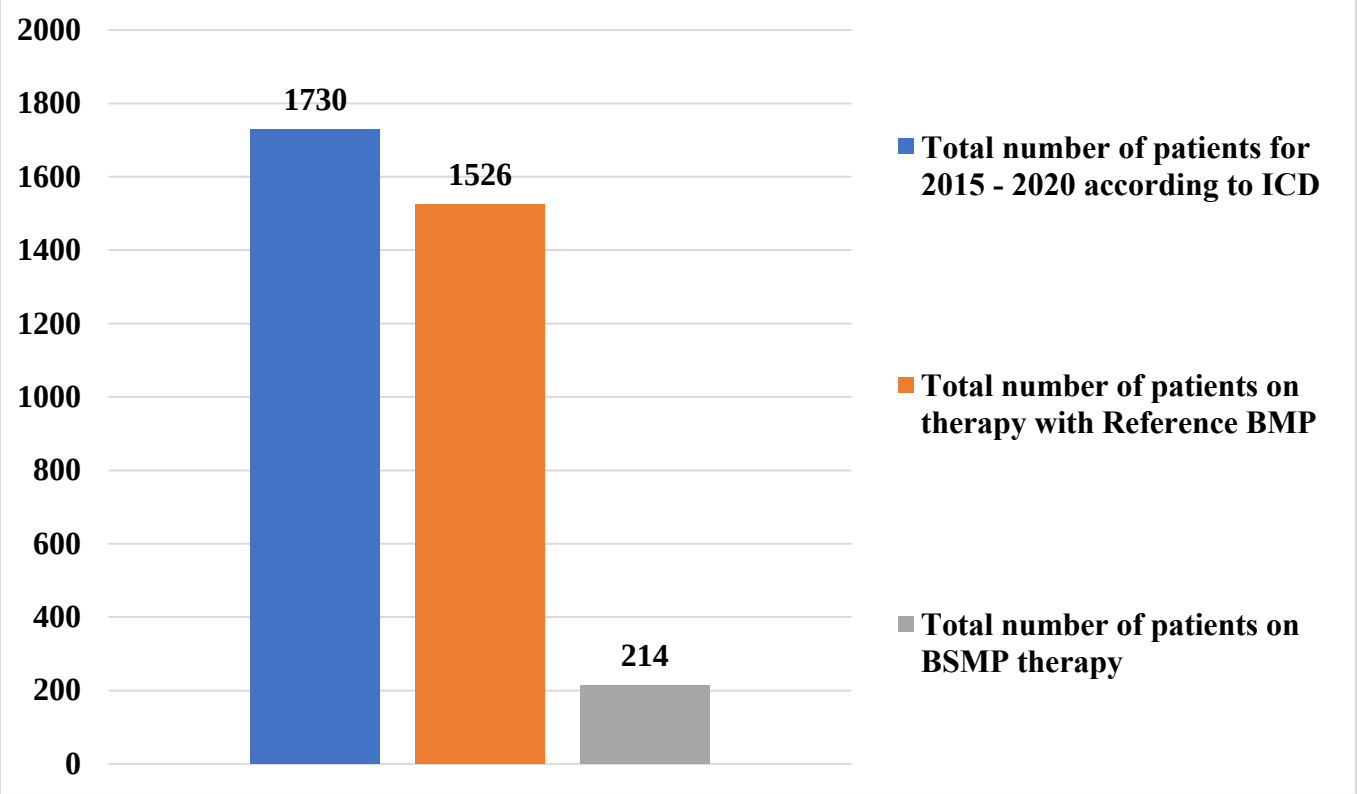

Figure 9. Distribution of the number of patients by ICD for 2015 – 2020

Only 12.36% of the total number of patients are on BSMP therapy.

In Figure 10, we present graphically in the form of a moving (moving) average value (Moving Average - MA) of BSMP and BMP therapy costs from 2015 to 2020. Each node represents 1 year.

At first glance, figure 11 shows a sharp drop in the costs of the reference biological medicinal product by BGN 4,871,877 (19.39%) immediately after the appearance of biosimilar medicinal products in 2019.

From the yellow MA in the table, it is clear that the costs for BSMP for 2019 do not exceed BGN 224,222 in total. There is a difference of BGN 4,647,655.

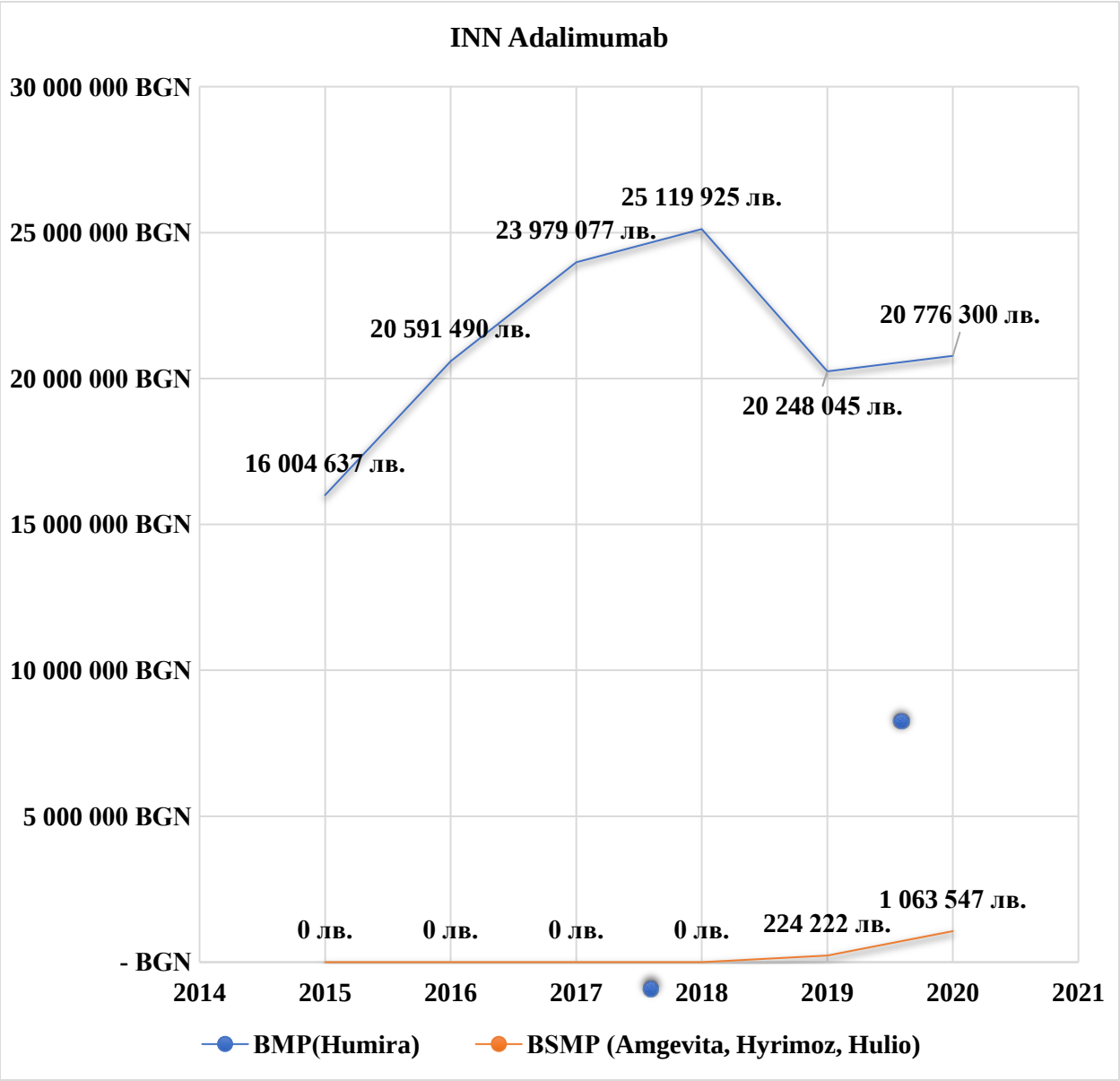

Figure 10. Distribution of BMP and BSMP costs for INN Adalimumab

For INN Infliximab in figure 11, a decrease in the costs of BSMP is observed by BGN 586,932 (28.31%) after the appearance on the market of the reference Remicade in 2019. This trend continues dynamically in 2020, while at the same time Remicade increases its market share 13.76 times while BSMP loses another 37.84% market share. The continuation of this trend portends a definite "reversal" of market positions and total dominance of the reference Remicade over BSMP. Proof of this is the market exit of Remsima in 2022.

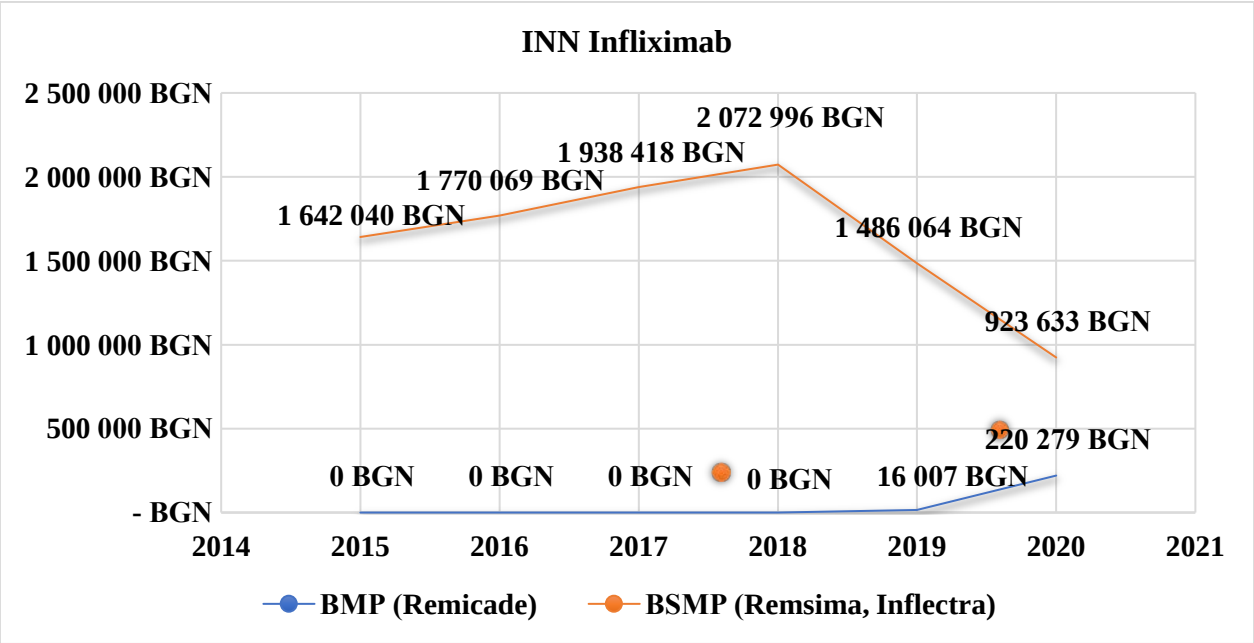

Figure 11. Distribution of BMP and BSMP costs for INN Infliximab

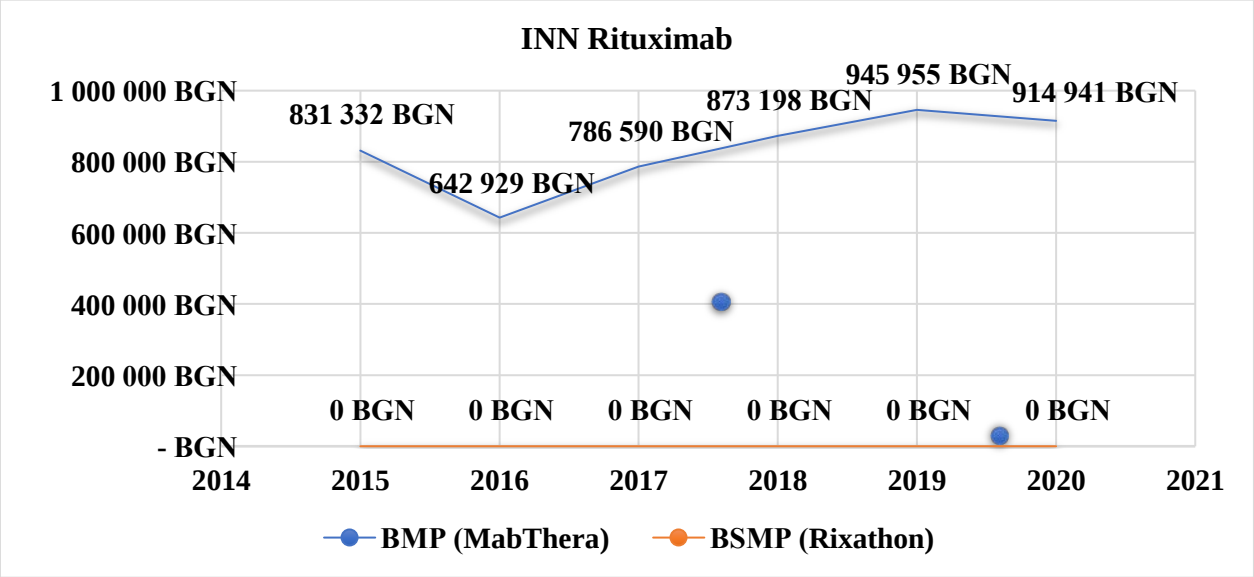

Figure 12. Distribution of BMP and BSMP costs for INN Rituximab

Although it is included in the PDL, BSMP Rixathon does not hold any market share in the INN Rituximab .

BMP Adalimumab occupies 89% of the entire market of biological and biosimilar medicinal products.

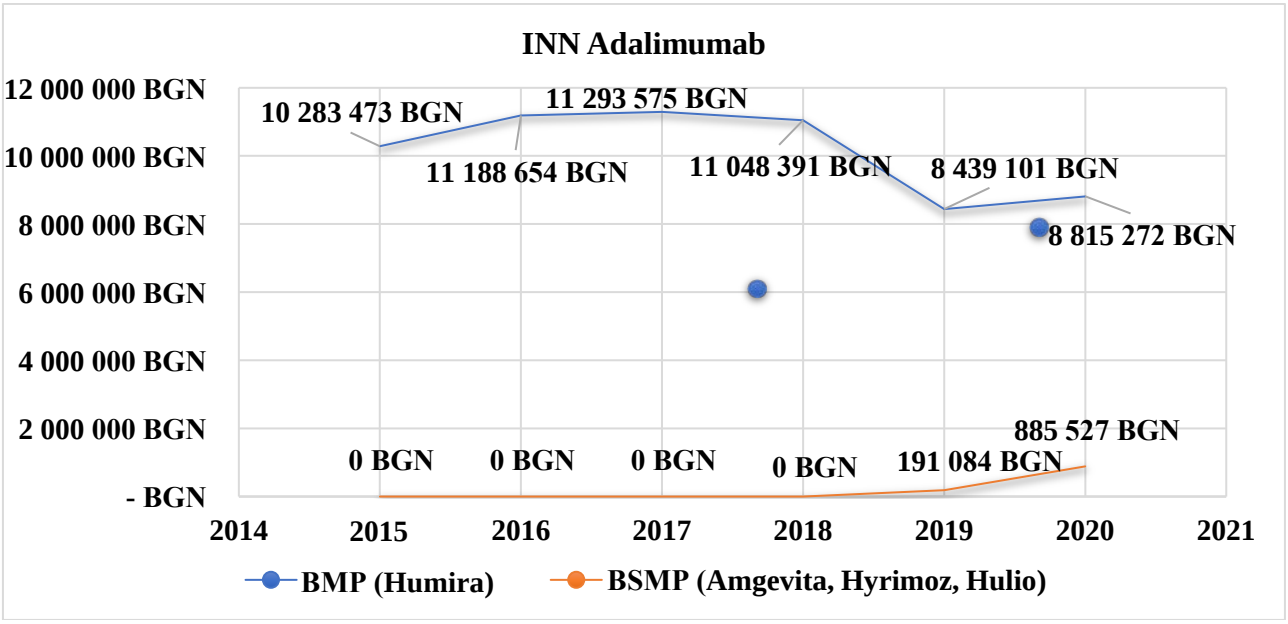

Figure 13. Distribution of BMP and BSMP costs for INN Adalimumab for M 05.8 Other seropositive rheumatoid arthritis

As is clear from the data presented in Figure 13 the reference biological medicinal product for INN Adalimumab in the period from 2015 to 2020 underwent a number of price metamorphoses:

- In the period from 2015 to 2016, its relative share increased from BGN 10,283,473 to BGN 11,188,654 and marked an increase of 8.5%
- In the period from 2016 to 2017, its relative share increased from BGN 11,188,654 to BGN 11,293,575 and marked an increase of 0.95%
- In the period from 2017 to 2018, its relative share decreased from BGN 11,293,575 to BGN 11,048,390, a decrease of 1.21%
- In the period from 2018 to 2019, its relative share decreased from BGN 11,048,390 to BGN 8,439,100, a decrease of 23.37%
- In the period from 2019 to 2020, its relative share increased from BGN 8,439,100 to BGN 8,815,271 and marked an increase of 4.54%

After entering PDL in 2018. biosimilar medicinal products with INN Adalimumab :

- In the period from 2018 to 2019, together they realize a relative market share of BGN 191,083.
- In the period from 2019 to 2020, their relative share increased from BGN 191,083 to BGN 885,527 and marked a growth of 362.88%

The data presented in Figure 14 reveal what effect the appearance of the reference biological medicinal product has on the INN Infliximab .

Until 2018, biosimilar medicinal products with INN Infliximab are on the market in the absence of the reference and in the period 2015-2018 they have a relatively stable and predictable market share:

- In the period from 2015 to 2016, their relative market share decreased from BGN 1,582,166 to BGN 1,522,813 and marked a drop of 3.7%
- In the period from 2016 to 2017, their relative market share decreased from BGN 1,522,813 to BGN 1,487,901 and marked a drop of 2.32%
- In the period from 2017 to 2018, their relative market share decreased from BGN 1,487,901 to BGN 1,390,567 and marked a drop of 6.66%
- In the period from 2018 to 2019, their relative market share decreased from BGN 1,390,567 to BGN 889,023 and marked a drop of 36.07%, immediately after the appearance of the referent in PDL.
- In the period from 2019 to 2020, their relative market share decreased from BGN 889,023 to BGN 504,032 and marked a drop of 43.15%. immediately after the appearance of the referent in the PDL.

For two years, the market share of biosimilar medicinal products in INN Infliximab merged with 63.6% after the appearance of the reference biologic medicinal product in the PDL.

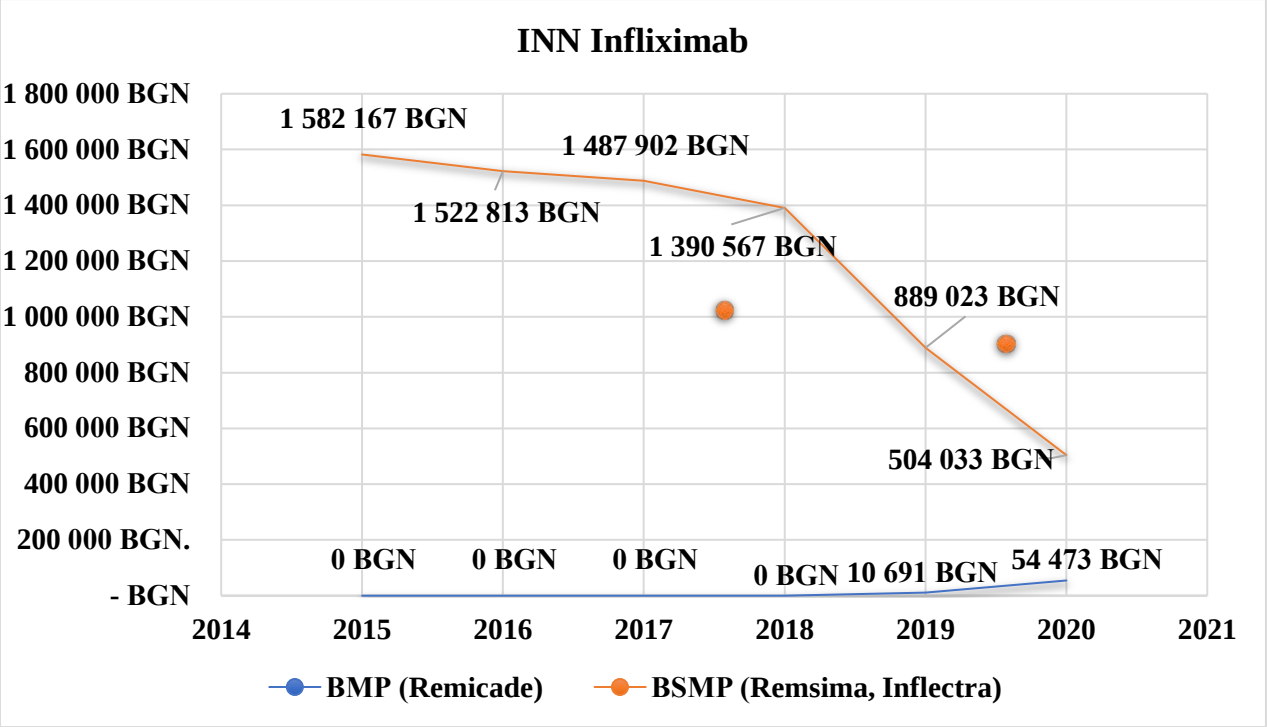

Figure 14. Distribution of BMP and BSMP costs for INN Infliximab for M05.8 Other seropositive rheumatoid arthritis

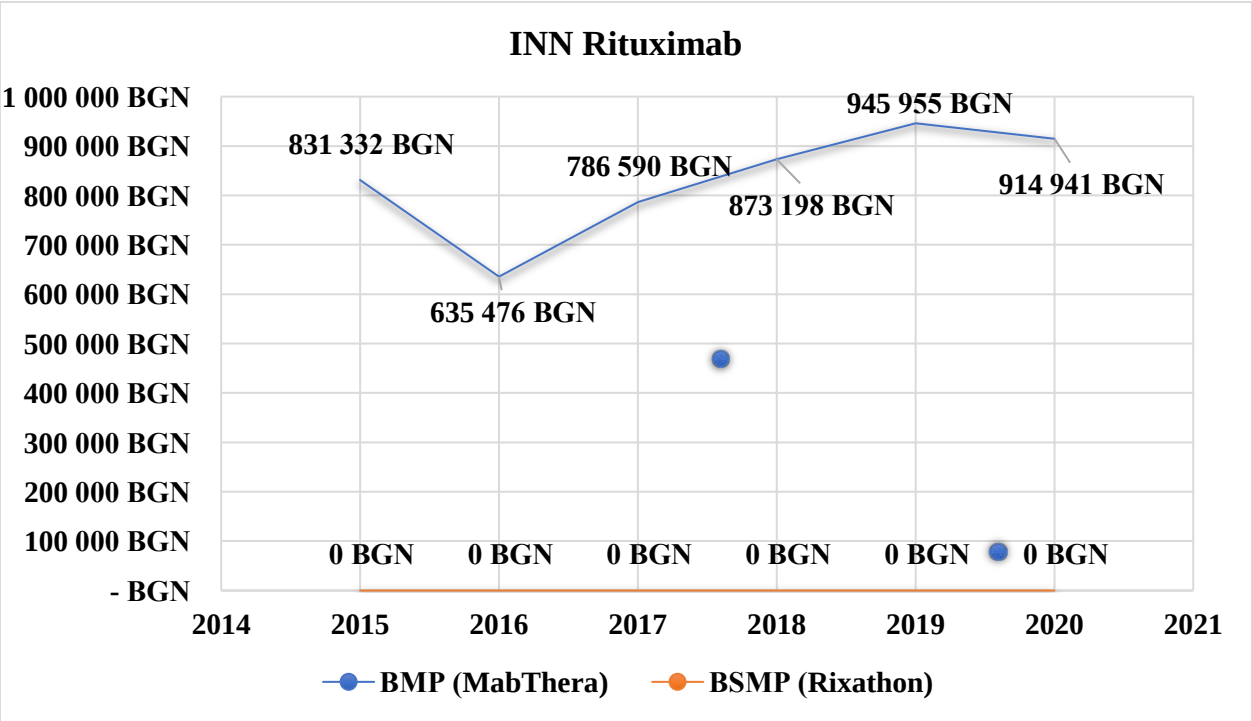

Figure 15. Distribution of BMP and BSMP costs for INN Rituximab for M05.8 Other seropositive rheumatoid arthritis

Rituximab (reference BMP):

Observed mixed trend for the reference biological medicinal product for the INN Rituximab (Figure 15) . With some fluctuations over the years, there is a general increase in its market share in the period 2015 to 2020:

- In the period from 2015 to 2016, its market share decreased by 23.68% from 831 BGN 332 for 635 BGN 476
- In the period from 2016 to 2017, its relative share increased from 635 BGN 476 for 786 BGN 590 and an increase of 23.79%
- In the period from 2017 to 2018, its relative share grew by another 11.39% to 873 BGN 198 and surpasses its levels from 2015 (831 BGN 332)
- In the period from 2018 to 2019, its relative market share marked its third consecutive year of growth with another 8.08% reaching a peak of 945 BGN 955
- In 2020, the relative share of the reference Rituximab decreased by 3.27%.

Despite being included in the INN, BSMP Rixathon does not hold any INN market share Rituximab for M05.8 Other seropositive rheumatoid arthritis according to data from the NHIF.

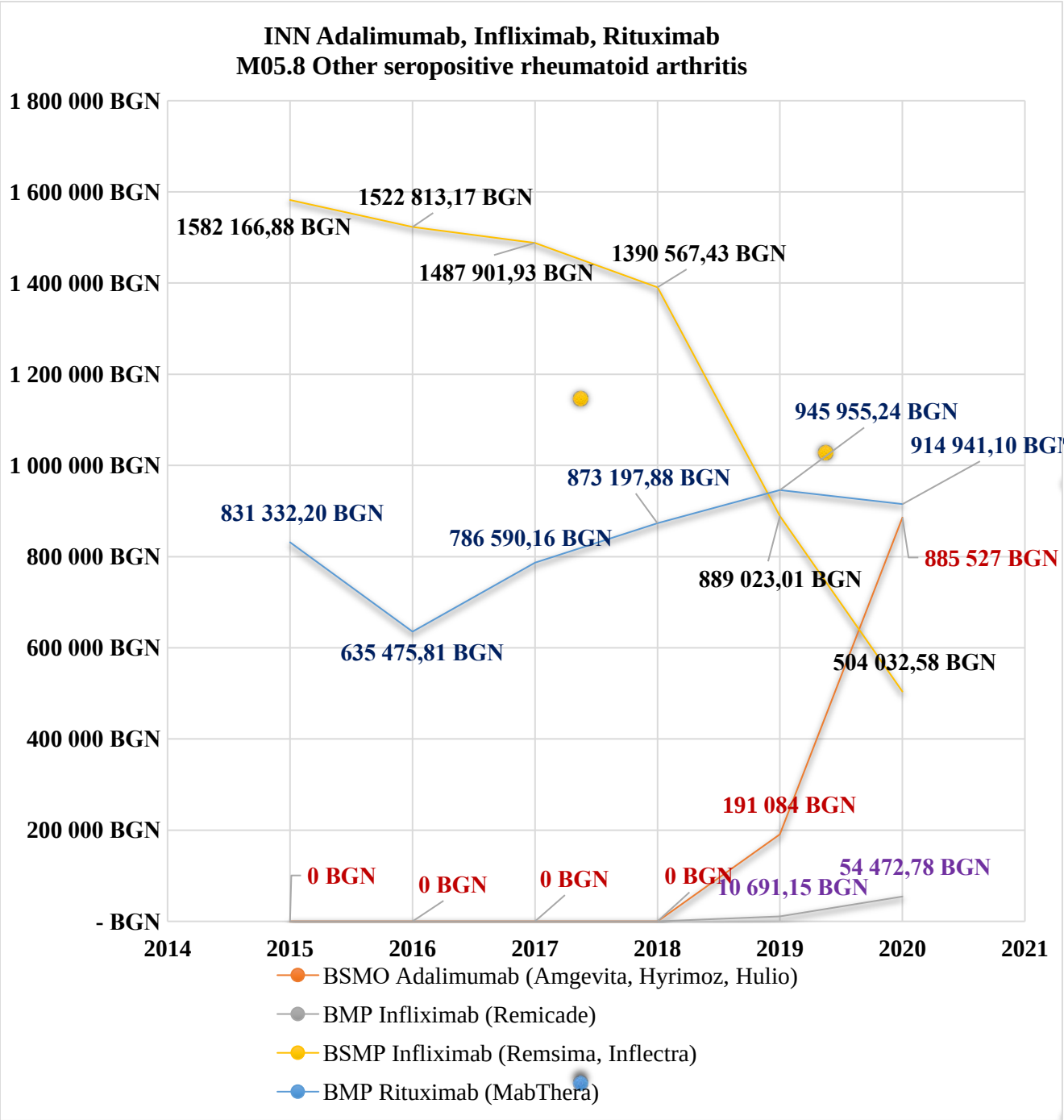

Figure 16. Distribution of BMP and BSMP costs for INN Adalimumab , Infliximab , Rituximab for ICD: M05.8 Other seropositive rheumatoid arthritis

5.1.Results for Task No. 6

The purpose of the conducted study is to identify the main reasons for the low prescribing rate and limited dispensing of biosimilar medicinal products, defining the degree of knowledge and continuity of the specialists prescribing biological and biosimilar medicinal products containing monoclonal antibodies in Bulgaria.

Materials and methods

The study is observational. A questionnaire was prepared to study the knowledge and continuity of specialists prescribing biological and biosimilar medicinal products containing monoclonal antibodies in Bulgaria.
The survey was conducted among doctors specializing in Rheumatology. According to data from the Bulgarian Medical Union, there are doctors in Bulgaria with a recognized specialty "Rheumatology". 37 of them or 33.04% of all doctors with a specialty were included in our study.
Study period - **06/03/2022** to **11/11/2022**
The survey included a total of 17 questions on factors related to the safety profile, interchangeability, substitution and switching in treatment with biological and biosimilar medicinal products.
The study was evaluated using descriptive statistical methods.

Survey results

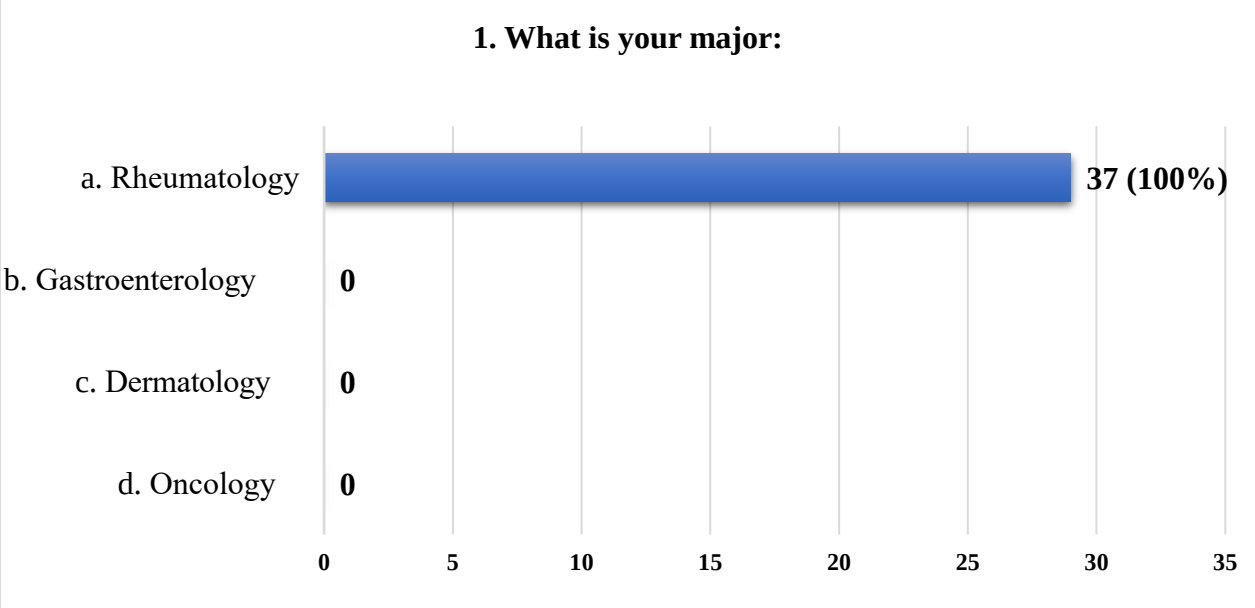

Figure 17. Question No. 1 of the survey - What is your specialty?

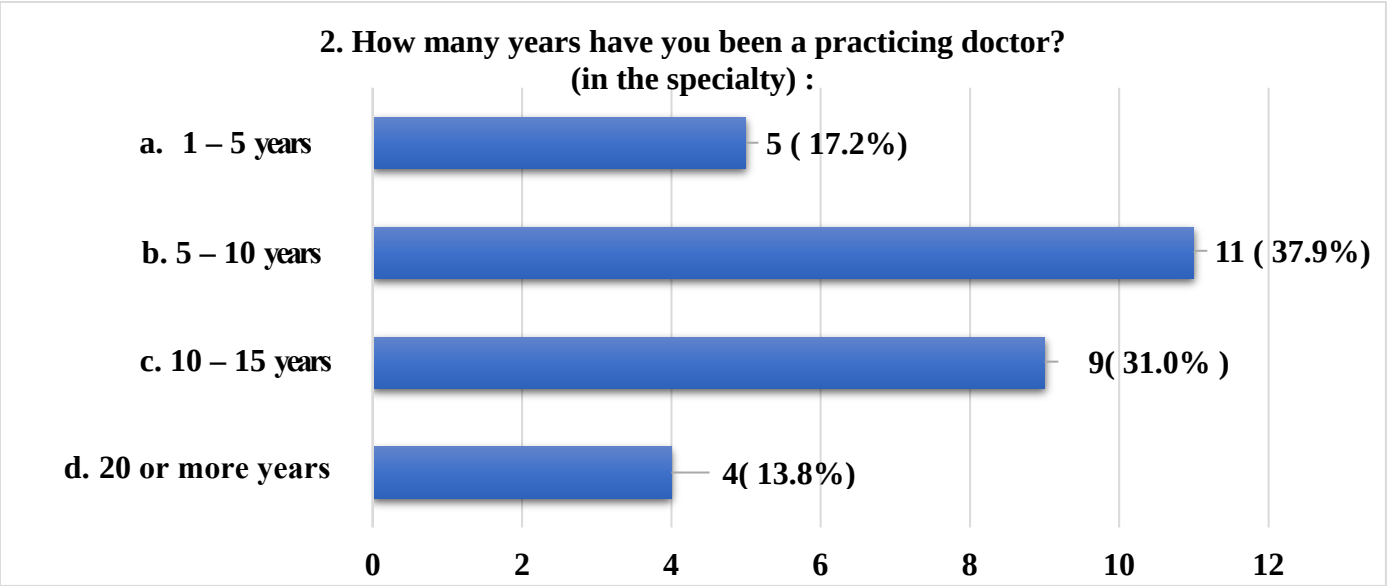

Figure 18. Question No. 2 of the survey - How many years have you been a practicing doctor (in your specialty)?

The representative sample of respondents covered is diverse regarding accumulated years of professional experience. 17.2% of the surveyed medical specialists, some of them have been practicing for 1-5 years, and others - for 10-15 years and more. This information can give us some insight into the level of experience and knowledge of the respondents.

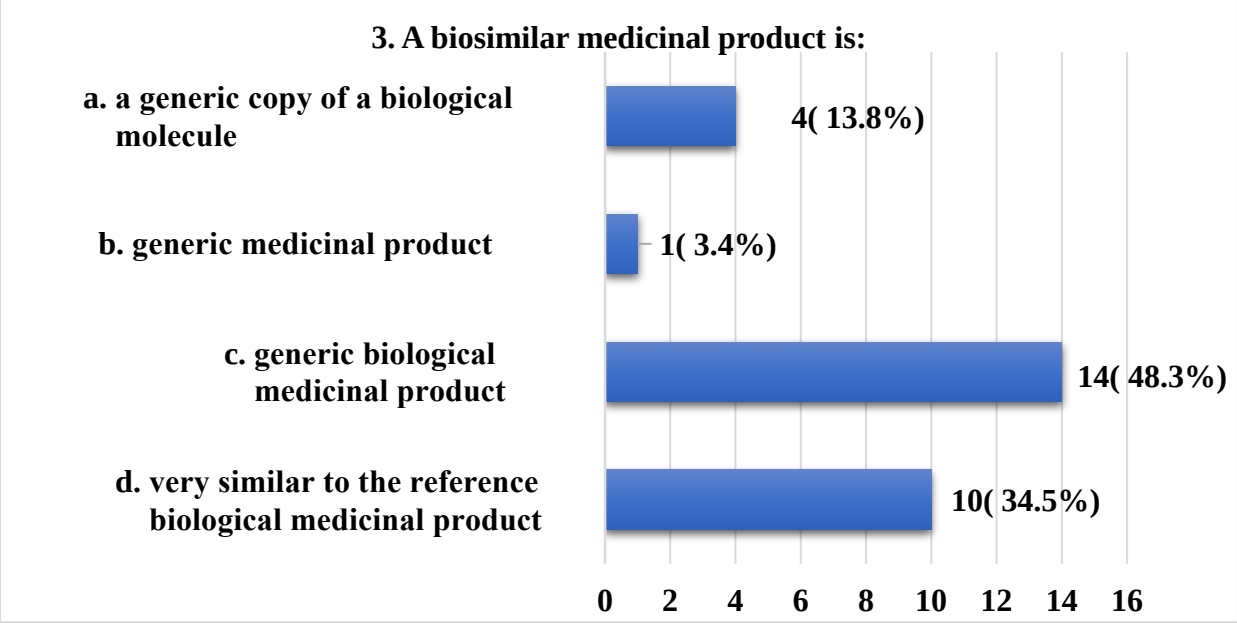

Figure 19. Question No. 3 of the survey - Is a biosimilar medicinal product ?

The answers to Question No. 3 show that **65.5%** of the surveyed medical professionals do not have a completely clear idea about the exact definition of biosimilar medicinal products.

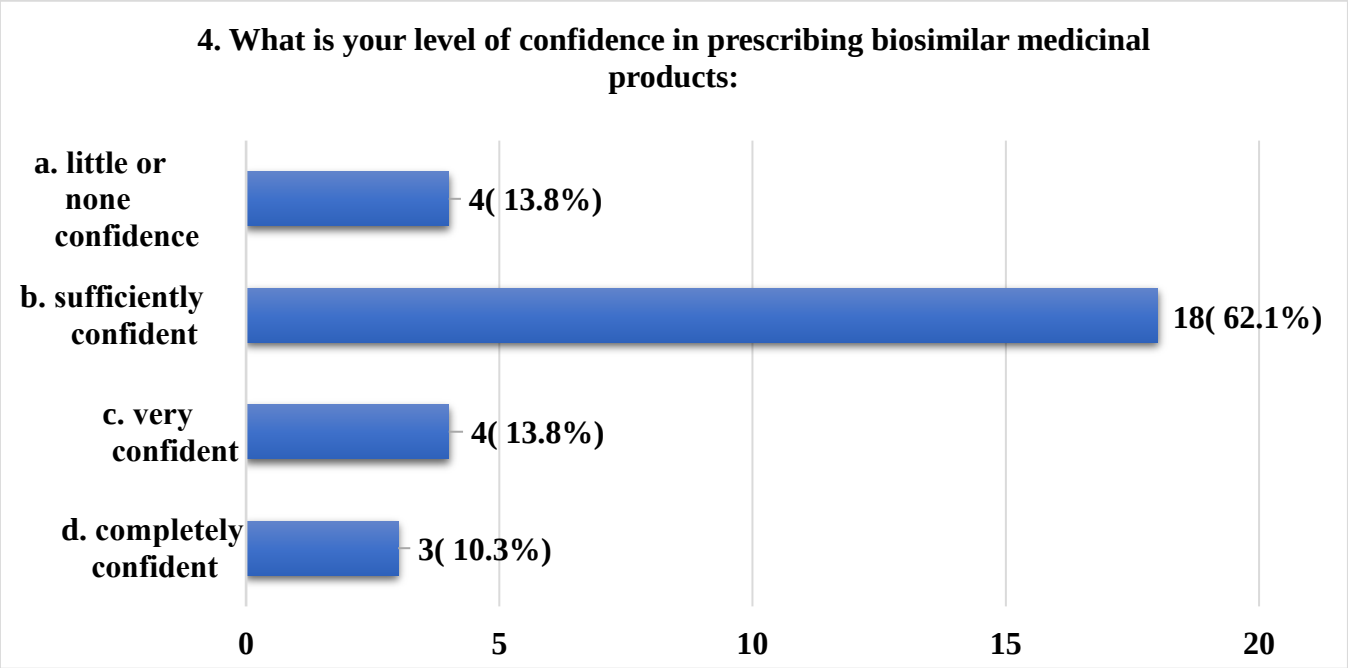

Figure 20. Question No. 4 of the survey - What is your level of confidence in prescribing biosimilar medicinal products?

According to the scientific literature, confidence in prescribing biosimilars is a key factor leading to rational prescribing of biologics and biosimilars. 62.1% of the rheumatologists surveyed shared that they are sufficiently confident, 10% are completely confident, 13.8% are very confident, and the remaining 13.8% state that they do not have any confidence when prescribing biosimilar medicinal products.

48.3% of the surveyed rheumatologists define their knowledge as basic, 20.7% admit that they are not sufficiently familiar with biosimilar medicinal products. In total, this is more than 69% of the surveyed specialists. The answers to question No.5 contradict the answers to question No.4.

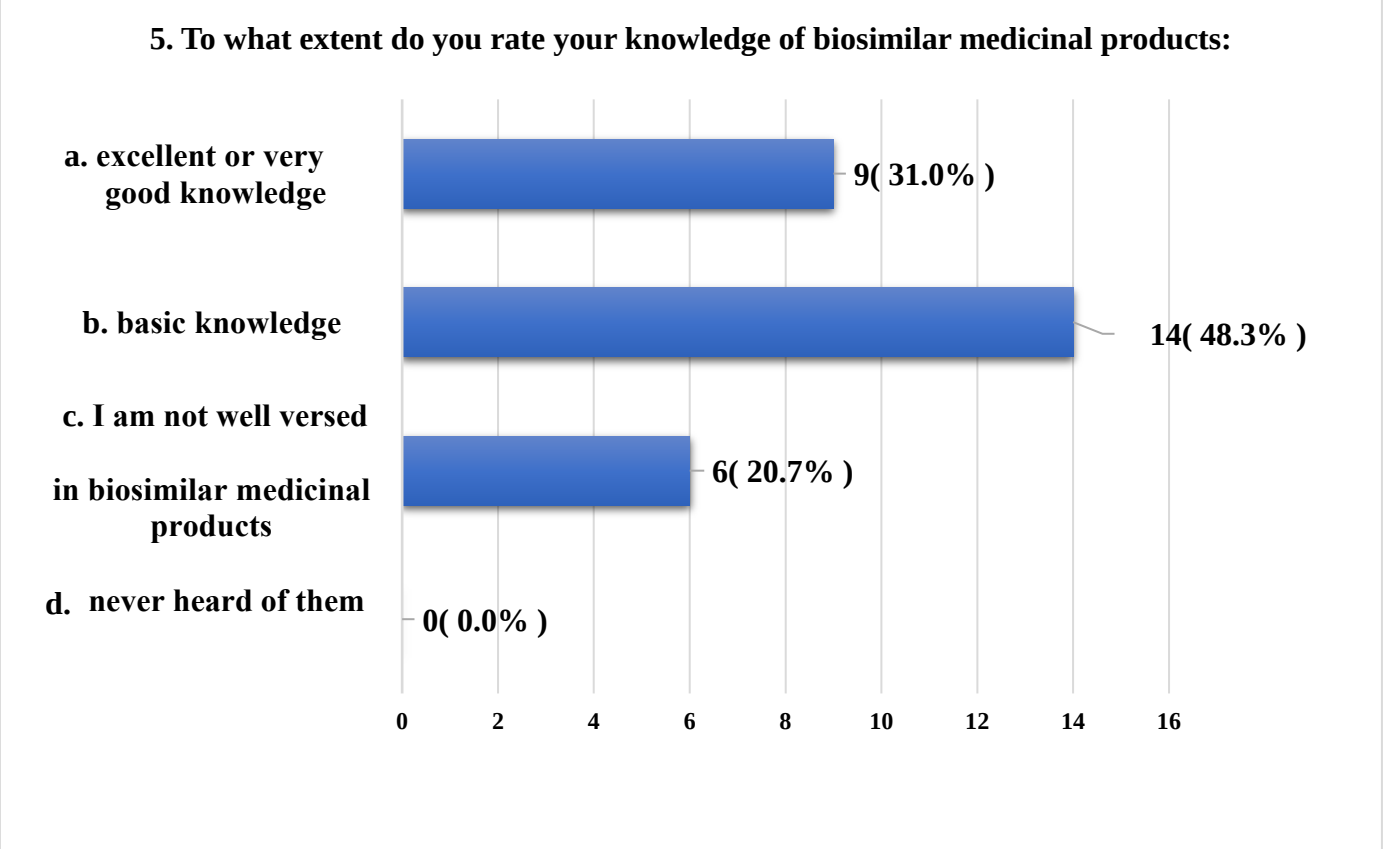

Figure 21. Question No. 5 of the survey - To what extent do you define your knowledge about biosimilar medicinal products?

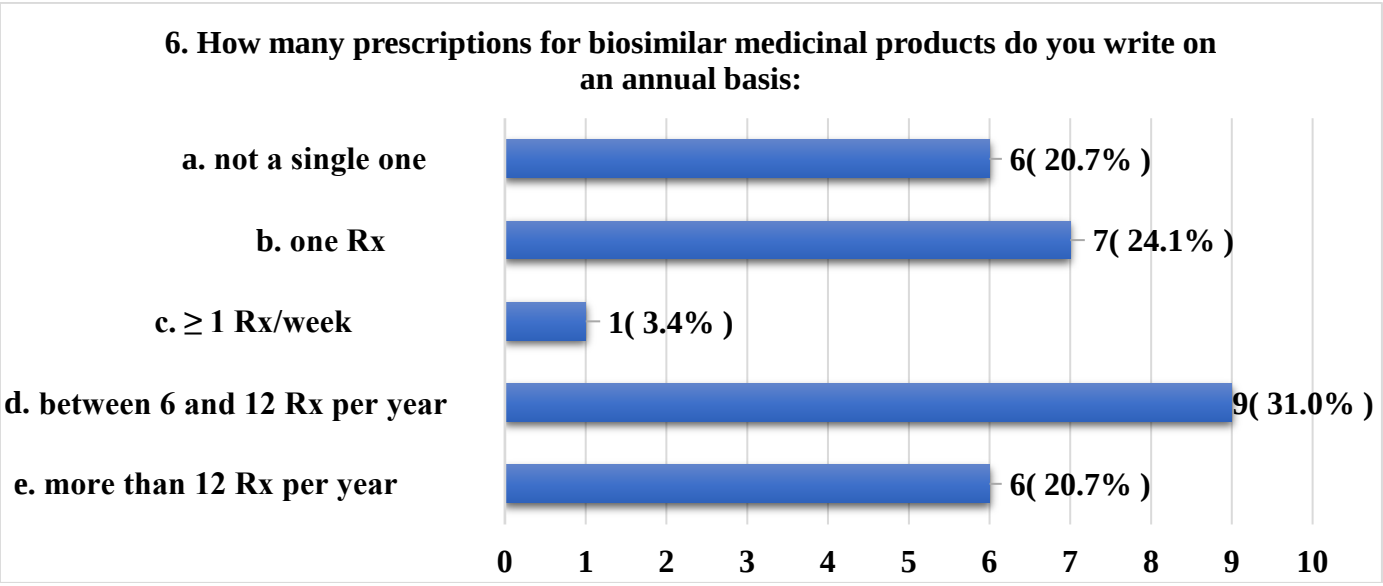

Figure 22. Question No. 6 of the survey - How many prescriptions for biosimilar medicinal products do you write on an annual basis?

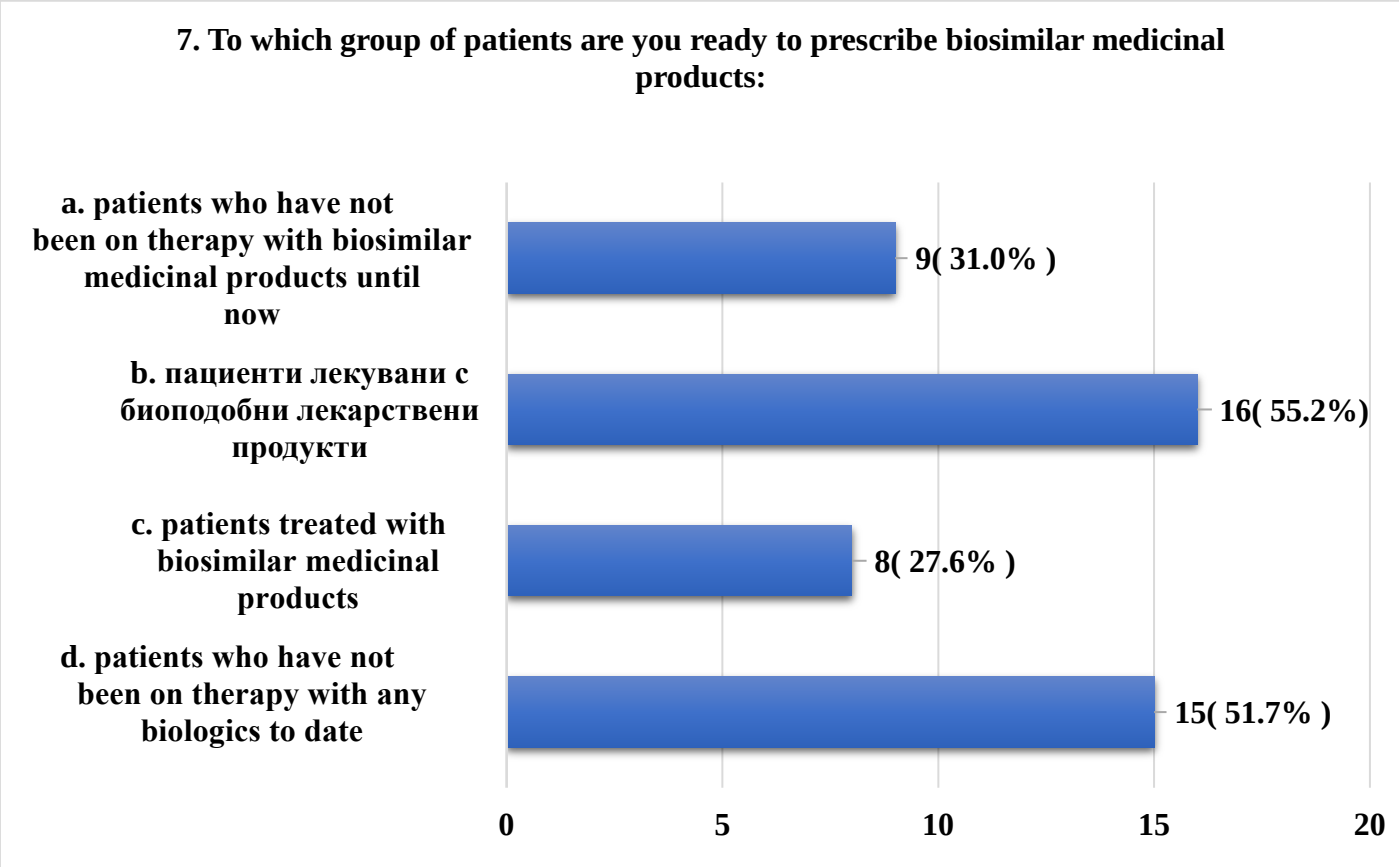

Figure 23. Question No. 7 of the survey - To which group of patients are you ready to prescribe biosimilar medicinal products?

From the obtained results in figure 23, we understand that most rheumatologists in Bulgaria tend to prescribe biosimilar medicinal products to patients who have previously been treated with biosimilar medicinal products (55.2%) or to patients who have not been of therapy with any biological medicinal products (51.7%).

Responses to Question No.8 of the survey provided insight into the prescribing habits of healthcare professionals. Contrary to the results of responses to Question No.7, here rheumatologists openly stated that they prescribe biologics over biosimilars, with 55.2% reporting that they switch patients from biosimilars to biologics therapy.

48.3% stated that they would initiate therapy with biologic medicinal products in patients who had not previously been treated with any biologic medicinal product.

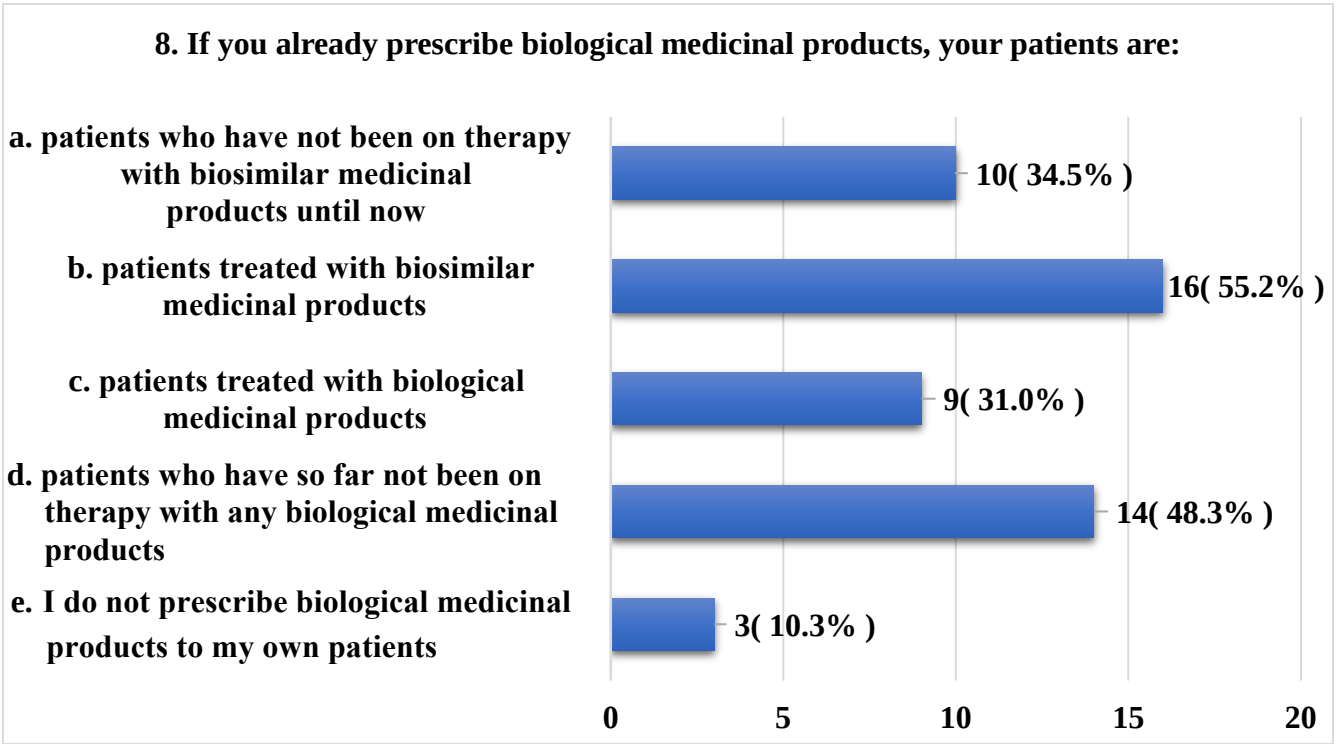

Figure 24. Question No. 8 of the survey - If you already prescribe biological medicinal products, are your patients ?

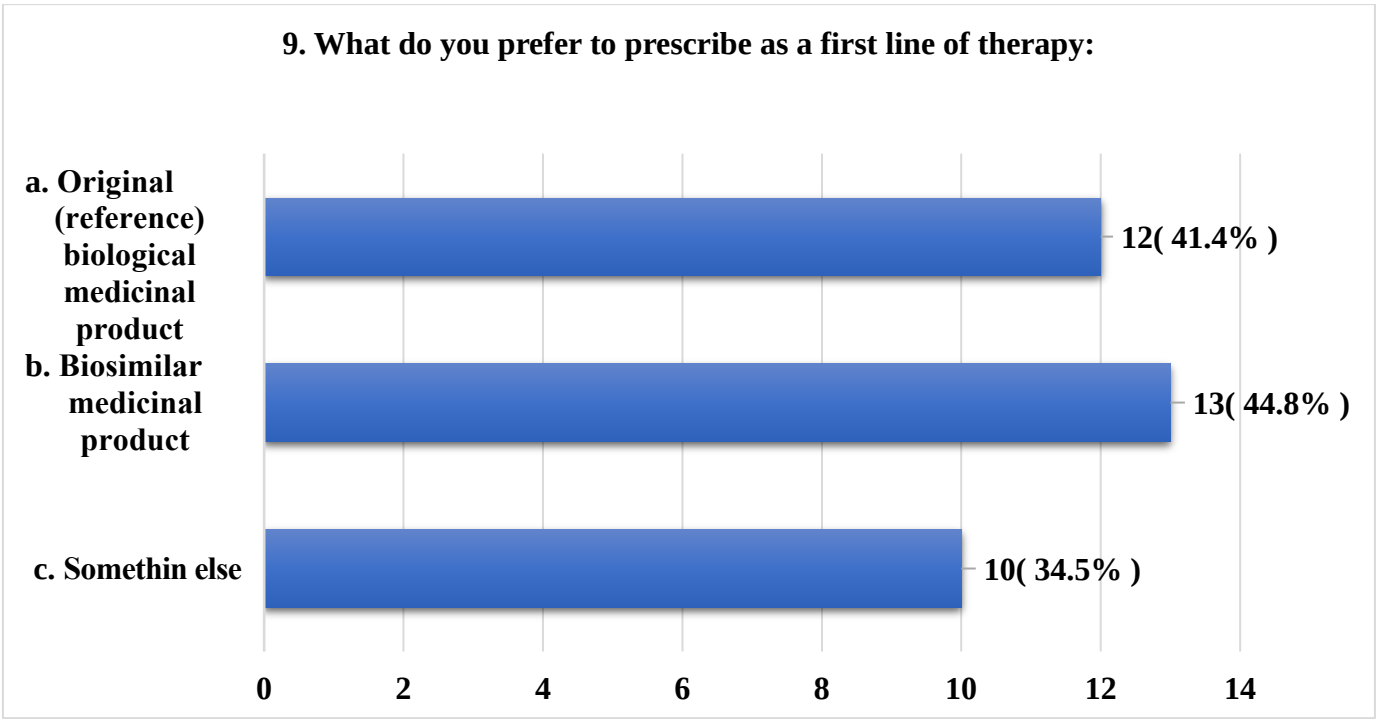

Figure 25. Question No. 9 of the survey - What do you prefer to prescribe as the first line of therapy?

44.8% of the respondents answer to Question No.9 that they prefer to prescribe biosimilar medicinal products as first line therapy. That said, rheumatologists tend to prescribe biosimilars, but it's not yet clear what tips the scales in favor of the biologics they actually prescribe. 41.2% of the respondents stated that they prefer the prescription of biological medicinal products.

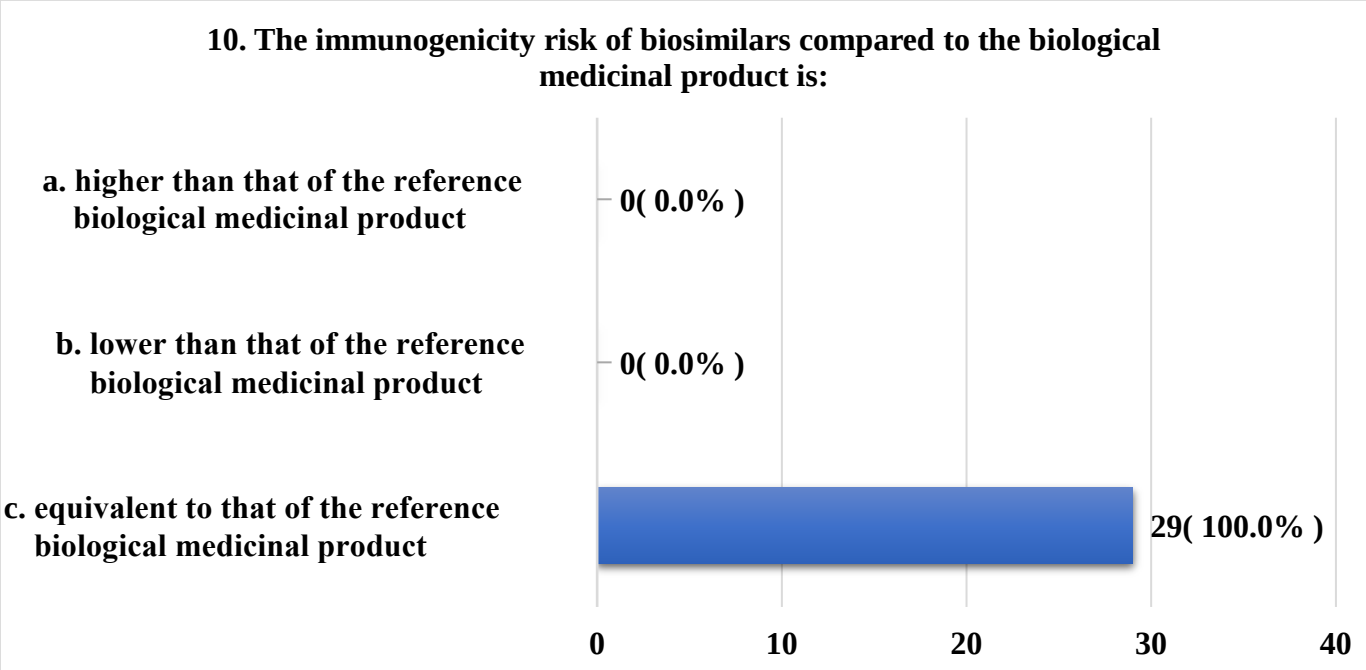

Figure 26. Question No. 10 of the survey - The risk of immunogenicity of biosimilars compared to the biologic medicinal product is ?

Respondents unanimously responded that biosimilar medicinal products have an equivalent risk of immunogenicity to that of the reference biological medicinal product, therefore there should not be an obstacle related to lack of confidence on the part of prescribers of these medicinal products.

79% of the rheumatologists surveyed believe that biosimilar medicinal products are interchangeable with the reference biological medicinal product. This suggests that there is an existing consensus among rheumatologists regarding the interchangeability of biologics and biosimilars.

However, we should note that this answer also contradicts some of the results obtained from the answers to the previous questions, which show that rheumatologists do not always make the decision to replace the therapy, even if they think that the biosimilar medicinal product is interchangeable with the reference one.

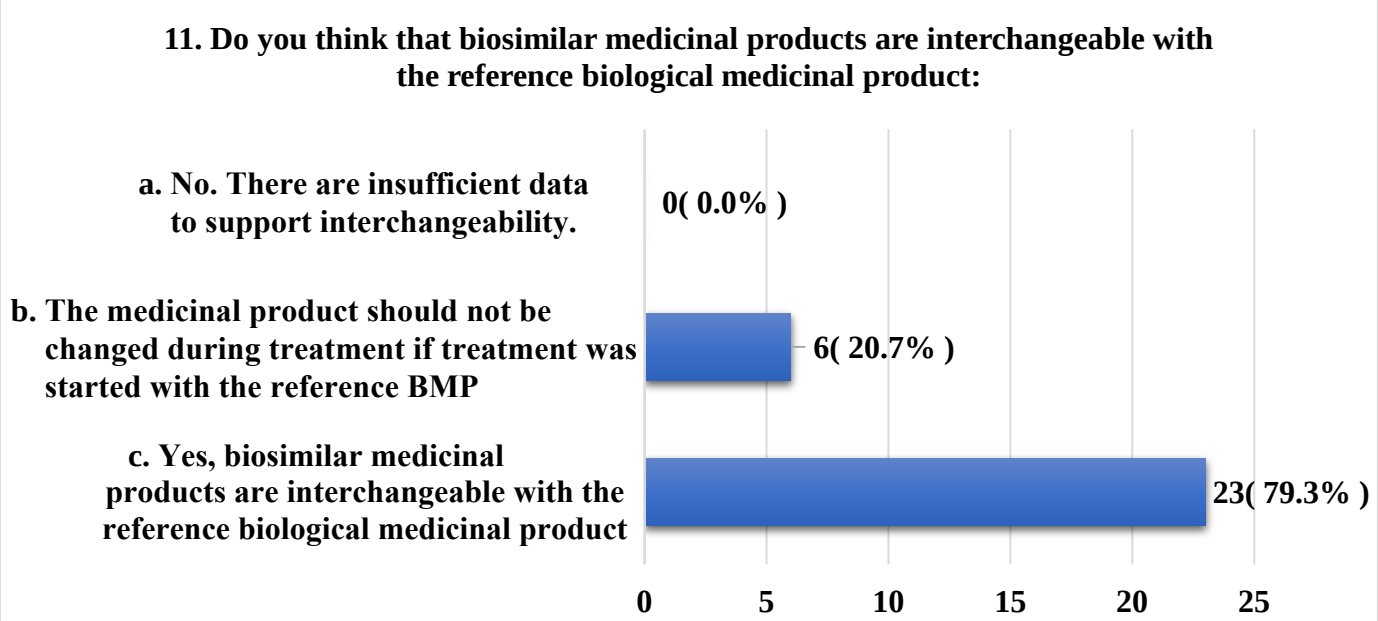

Figure 27. Question No. 11 of the survey - Do you think that biosimilar medicinal products are interchangeable with the reference biological medicinal product?

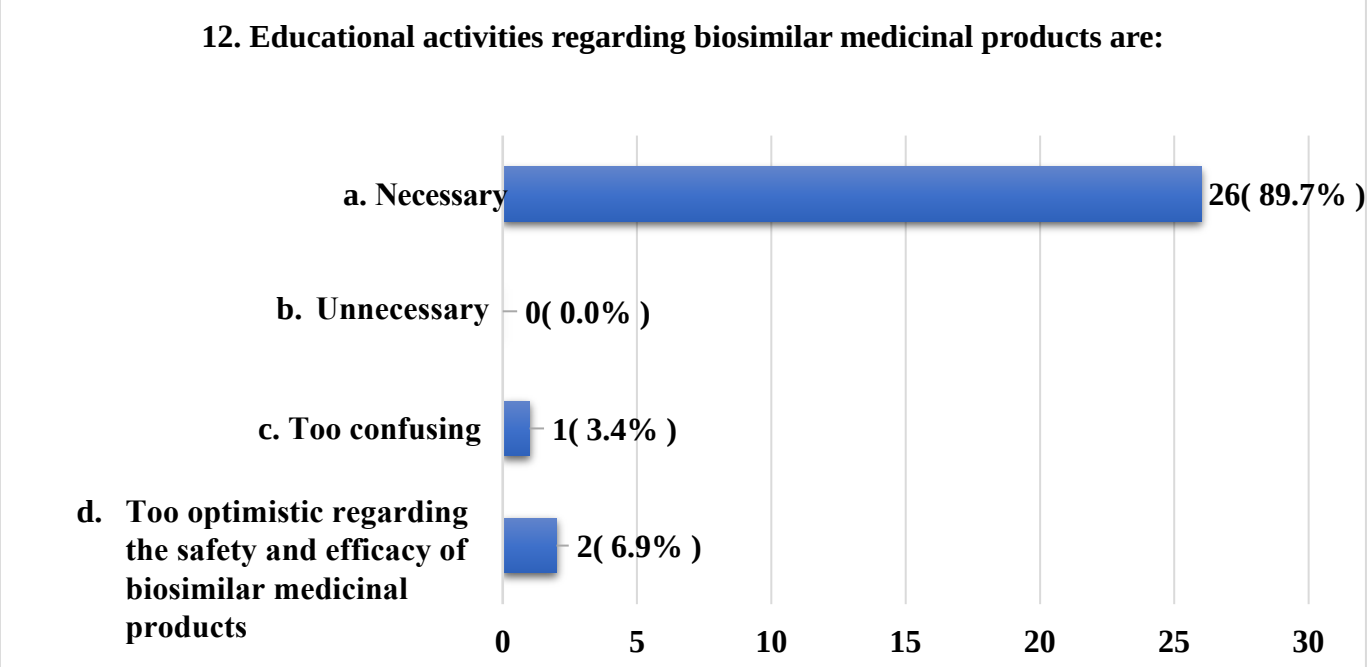

Figure 28. Question No. 12 of the survey - Educational activities regarding biosimilar medicinal products are ?

89.7% of the rheumatologists surveyed consider educational activities related to biosimilar medicinal products necessary.

The survey was also conducted among doctors specializing in Gastroenterology. According to data from the Bulgarian Medical Union, there are 249 doctors in Bulgaria with a recognized "Gastroenterology" specialty. 3 of them or 1.2% of all doctors with a specialty participated in our study. We were able to conduct only a questionnaire survey with a mail survey among gastroenterologists, in contrast to the mixed type (mail survey and face-to-face survey) of the questionnaire survey conducted among rheumatologists. It is difficult for us to determine the exact reason for the refusal of medical professionals to participate. Possible reasons are the type of survey, lack of interest, overload, lack of time, etc. nevertheless, we were left with a feeling of serious dissatisfaction.

V. DISCUSSION OF RESULTS

A medicinal product can only be defined as available if it is authorized for use and has a registered price. The same medicinal product is defined as affordable if it is available and included in a system of reimbursement from public funds.

Under the terms of Bulgaria's membership in the EU, as of January 1, 2007, Bulgarian citizens have a guaranteed availability of high-quality, safe and effective biosimilar medicinal products, equal to other EU citizens. Authorization for the use of biosimilar medicinal products is centralized at the EU level and is ensured by the rules introduced by Directive 2001/83/EC and Regulation (EC) No 726/2004.

In Bulgaria, the time for price registration and inclusion in the reimbursement system is carried out in accordance with the requirements of Directive 89/105/EEC - the terms are 2 to 3 times shorter than those established in the Directive. The average length of time from the RU of a biosimilar medicinal product to its effective reimbursement in Bulgaria is 180 days (6 months). The provision of availability and accessibility is guaranteed and corresponds to the standards established in the EU member states .

The costs of biological treatment (biological and biosimilar drugs) for a five-year period in absolute amount are equal to BGN 716,360,871. The total budget for drug treatment for the same period is BGN 4,350,461,600. The relative share of biological products is 17%, which shows excellent availability, accessibility and usability at a macro level, assessed through budget indicators.

The inclusion of BSMP in the same reimbursement group with BMP leads to the determination of a lower reimbursement amount for payment by the NHIF on the basis of the so-called internal referencing in the relevant INN.

The rule that the price of BSMP cannot exceed 80% of the registered price of the reference biological product leads to a reduction of the total costs of treatment within the budget of the NHIF and provides access to treatment for a larger number of patients.

It would be logical to expect that the expansion of access is due to the entry of BSMP. In practice, this is only a consequence of the effect of reducing the costs of the NHIF for the relevant INN.

Although they fall into a higher price range, reference medicinal products are the preferred means of prescribing, dispensing and treatment. In accordance with the established rules for prescribing and dispensing BMP and BSMP in Bulgaria, prescribing is still by trade name and not by INN. BMP and BSMP are prescribed in a special order by a committee of three doctors with a

recognized specialty in the relevant therapeutic area, and a so-called “Expensive treatment protocol IA'. This type of prescription is valid for 6 months and is also issued under a trade name.

The results obtained by us show that the prescription and dispensing of biosimilar medicinal products is at a negligible low level – only 4.75% of the total prescription estimated through the budgetary costs of the NHIF.

At this stage of the analyses, we could assume that the probable reasons are - the lack of adequate national standards for the substitutability/interchangeability of biological and biosimilar medicinal products with biological and/or biosimilars, prescribing by trade names, conservatism and mistrust of prescribers to t .n. substitute therapies, aggressive drug promotion to medical specialists, etc.

The example of the availability, accessibility and medicinal usability of Infliximab, however, shows another trend - the lack of a reference biological medicinal product on the Bulgarian market leads to the immediate prescription and dispensing of biosimilar medicinal products, and the above-mentioned reasons are completely untenable.

Based on the provided data from the survey among rheumatologists, it appears that the main reasons for the low level of prescribing and limited dispensing of biosimilar drugs among specialists in Bulgaria is the lack of sufficient knowledge and confidence in prescribing these medicinal products, which contributes to limiting the number of the annual prescriptions for biosimilar medicinal products.

The survey also showed that most respondents were willing to prescribe biosimilars to patients who had already been treated with them, but were less likely to prescribe them to patients who had not previously been treated with biosimilars or with other biological medicinal products. This suggests that there may be concern and uncertainty among professionals about the use of biosimilar medicinal products, particularly among patients who have not previously been treated with biologic medicinal products.

The results of the study show that there is a need for more educational materials and resources to support specialists in Bulgaria to improve their knowledge and confidence in prescribing biosimilar medicinal products in order to achieve a more rational medicinal use that will benefit of the patients.

VI. MAIN CONCLUSIONS FROM THE DISSERTATION

CONCLUSIONS

1. Under the conditions of Bulgaria's membership in the EU, Bulgarian citizens have guaranteed availability of quality, safe and effective biological and biosimilar medicinal products, equal to other EU citizens.

2. The average length of time from the RU of biological and biosimilar medicinal products to their effective reimbursement in Bulgaria is 180 days (6 months).

3. There is guaranteed availability of biological and biosimilar medicinal products.

4. Biological products have excellent availability, accessibility and usability at the macro level, assessed through budget indicators.

5. The inclusion of biosimilar products in the reimbursement system leads to a reduction in the total cost of treatment within the NHIF budget and provides access to treatment for a larger number of patients.

6. Although they fall into a higher price range, reference medicinal products are the preferred means of prescribing, dispensing and treatment.

7. The prescription and dispensing of biosimilar medicinal products is at a negligible low level – only 4.75% of the total prescription estimated through the NHIF's budget costs.

8. The example of the availability, accessibility and medicinal usability of Infliximab, however, shows another trend - the lack of a reference biological medicinal product on the Bulgarian market leads to the immediate prescription and dispensing of biosimilar medicinal products.

9. Bulgarian practice lacks uniform and adequate national standards for substitutability and interchangeability of biological and biosimilar medicinal products with biological and/or biosimilars covering all therapeutic areas.

10. Comparative analysis of pharmacotherapeutic guidelines for the treatment of rheumatology and gastroenterology diseases shows a diametrically opposed understanding of the data on quality, safety and efficacy of biosimilar products between the two class groups.

11. The survey showed insufficient knowledge of biosimilars and a lack of confidence in their quality and efficacy.

12. The introduction of new products into clinical practice requires continuous training of medical professionals in the direction of improvement and building knowledge and gaining confidence in prescribing biosimilar medicinal products.

13. The introduction of the criteria of rational drug use in clinical practice should become a mandatory element of the drug policy.

VII . YIELDS

CONTRIBUTIONS OF SCIENTIFIC AND THEORETICAL NATURE AND ORIGINALITY OF THE PhD THESIS

1. A study of medicinal use at the national level is conducted and the availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria are analysed.

2. For the first time, a systematic review of scientific publications was performed according to the PRISMA standard for evaluating the medicinal usability of biosimilar medicinal products containing monoclonal antibodies.

3. For the first time in Bulgaria, the level of knowledge of biosimilars and biological products containing monoclonal antibodies among medical specialists from real practice is measured.

4. The study reveals new theoretical aspects of the processes of pricing and reimbursement of medicinal products in the solidarity insurance systems for health care.

METHODOLOGICAL CONTRIBUTIONS

1. An original protocol and survey design was developed to assess scientific knowledge regarding knowledge of new medicinal products among physicians of various specialties.

CONTRIBUTIONS OF SCIENTIFIC AND APPLIED NATURE

1. The study enriches the knowledge of medical professionals about the practical application and medicinal use of biosimilar medicinal products containing monoclonal antibodies worldwide .

2. The study reveals the impact of biosimilar medicinal products containing monoclonal antibodies on pricing and reimbursement systems.

3. The study shows the existence of scientific and regulatory problems in the validation and application in clinical practice of the pharmacotherapeutic guidelines from the national competent authorities for the treatment of different groups of diseases and their compliance with the guidelines of the scientific medical societies.

CONFIRMATIVE CONTRIBUTIONS

1. The entry of new products into clinical practice requires continuous training of medical specialists in the direction of improving and upgrading knowledge and achieving confidence in prescribing biosimilar medicinal products.

2. The introduction of the criteria of rational drug use in clinical practice should become a mandatory element of the drug policy.

VII. SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION

Publications and reports published in scientific publications, referenced and indexed in world-renowned databases of scientific information

1. Stoyanova S, ***Yordanov E*** , Hristov E, Parvova I, Tzachev H, Petkova V. Availability, Affordability and Drug Utilization of Biosimilar Medicinal Products Containing Monoclonal Antibodies in Bulgaria. (**2021**) Journal of Generic Medicines, Vol. 18(1) 42–50 ISSN: 1741-1343, Online ISSN: 1741-7090 doi: 10.1177/17411343211017627

2. Nachev N, Stoyanova S , Rangelov A, ***Yordanov E*** , Hristov E , Parvova I, Petkova V. Retrospective analysis of drug utilization and rational drug use in treatment of essential arterial hypertension in Bulgaria - generic perception. (**2022**) Journal of Generic Medicines, Vol. 18(2) 88–98. ISSN: 1741-1343, Online ISSN: 1741-7090 https://doi.org/10.1177/17411343211055896

3. ***Yordanov E*** , Parvova I, Hristov E, Petkova V. Evaluation of the drug use of biosimilar medicinal products containing monoclonal antibodies - systematic review. (**2022**) Journal of Generic Medicines, Vol. 18(3) 145–153. ISSN: 1741-1343, Online ISSN: 1741-7090 https://doi.org/10.1177/17411343221076371

Publications and reports published in non-refereed peer-reviewed journals or published in edited collective volumes

1. Cannavale C, De Rosa A, ***Yordanov E*** , Hristov E. Comparative analysis of the pricing and reimbursement systems between Italy and Bulgaria.// National Student Conference on Pharmaceutical and Chemical Sciences, FHF, SU "Kliment Ohridski", Sofia, Bulgaria, 04 -05.04. **2019** ISBN 978-954-07-4639-5 ; ISSN: 2738-8247 Online: https://pharmconference.com/2019/ , REPORT

2. Cannavale C, De Rosa A, Yordanov ***E*** , Hristov E. Comparative analysis of the pricing and reimbursement systems between Italy and Bulgaria.// Seventh congress of pharmacy with international participation, November 21-24, **2019** , Hotel "Rila", k .k. Borovets , Bulgaria. REPORT

3. Stoyanova S, ***Yordanov E*** , Hristov E, Parvova I, Tsachev X, Petkova V. Availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria.// National Student Conference on Pharmaceutical and Chemical Sciences, FHF, SU "Kliment Ohridski", Sofia, Bulgaria, 05-06.10. **2022** ISBN 978-954-07-4639-5; ISSN : 2738-8247 Online : https :// pharmconference . com /2022/ , REPORT

4. Nachev N, Stoyanova S, Rangelov A, ***Yordanov E* ,** Hristov E, Petkova V. A finding of drug usability and rational drug use in the treatment of essential arterial hypertension in Bulgaria.// National Student Conference on Pharmaceutical and Chemical Sciences, FHF, SU "Kliment Ohridski", Sofia, Bulgaria, 05-06.10 . **2022** ISBN 978-954-07-4639-5; ISSN : 2738-8247 Online : https :// pharmconference . com /2022/ , REPORT

5. ***Yordanov E*** , Hristov E, Parvova I, Petkova V. Analysis of the medicinal usability of biosimilar medicinal products containing monoclonal antibodies - a systematic review.// National Student Conference on Pharmaceutical and Chemical Sciences, FHF, SU "Kliment Ohridski", Sofia, Bulgaria, 05-06.10. **2022** ISBN 978-954-07-4639-5; ISSN : 2738-8247 Online : https :// pharmconference . com /2022/ , REPORT

6. Nedelkov N, ***Yordanov E*** , Hristov E, Parvova I. Approaches to interchangeability of biological and biosimilar medicinal products.// National Student Conference on Pharmaceutical and Chemical Sciences, FHF, SU "Kliment Ohridski", Sofia, Bulgaria, 05-06.10. **2022** ISBN 978-954-07-4639-5; ISSN : 2738-8247 Online : https :// pharmconference . com /2022/ , REPORT

7. Mirzoyan M, Tsvetkov M, ***Yordanov E*** , Hristov E. Standards for reporting data from clinical studies and meta-analyses.// First scientific conference for students and doctoral students "PharmaNova" Faculty of Pharmacy, MU - Sofia, Bulgaria, 16-17.12. **2022** REPORT

8. Mileva A, Tsvetkov M, ***Yordanov E*** , Hristov E. Comparative analysis of pricing and reimbursement systems between Germany and Bulgaria.// First scientific conference for students and doctoral students "PharmaNova" Faculty of Pharmacy, MU - Sofia, Bulgaria, 16-17.12. **2022** REPORT

Other:

1. November 21-24, **2019** , Hotel "Rila", city center Borovets , Bulgaria.
   "Best Oral Presentation of a Doctoral Student or Young Scientist" Award.

2. "Alma Mater" **award for the academic year 2019/2020** by order of the Rector **No. RD-27-1596 of 20.11.2020**

3. Emil Hristov , Emanuil Yordanov. **Project 3717/2022.** Comparative analysis of pricing and reimbursement systems between Italy and Bulgaria , Head, Targeted financing from the state budget. FNI SU "St. Kliment Ohridski"