

Article title: Budget impact analysis of the introduction of rituximab and trastuzumab intravenous biosimilars to EU-5 markets

Journal: BioDrugs

Authors:

Jang, Minyoung, Celltrion Healthcare, 19, Academy-ro 51, Yeonsu-gu, Incheon, South Korea

Simoens, Steven KU Leuven Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium. ORCID 0000-0002-9512-2005

* Kwon, Taeksang, Celltrion Healthcare, 19, Academy-ro 51, Yeonsu-gu, Incheon, South Korea

*** Corresponding author**

Kwon, Taeksang

Celltrion Healthcare, 19, Academy-ro 51, Yeonsu-gu, Incheon, South Korea

E-mail: Taeksang.Kwon@celltrionhc.com

Funding:

Celltrion Healthcare

Conflict of Interest:

SS is one of the founders of the KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL Fund). SS was involved in a stakeholder roundtable on biologics and biosimilars sponsored by Amgen, Pfizer, and MSD; he has participated in advisory board meetings for Pfizer and Amgen; and he has contributed to studies on biologics and biosimilars for Hospira, Celltrion, Mundipharma, and Pfizer. SS has had speaker engagements for Celltrion, Sandoz and Amgen.

1. Market volume share data for the Originator and the biosimilars (Base Case)

Supplementary Table 1: Market Volume Share Data for MabThera and Truxima (Base Case)

Country	Scenario	Year Indication	Year 1		Year 2		Year 3		Year 4		Year 5	
			IV	SC	IV	SC	IV	SC	IV	SC	IV	SC
UK	MabThera in the world without Truxima	RA, CLL, GPA, MPA	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%
	MabThera in the world with Truxima		50%	0%	8%	0%	4%	0%	1%	0%	0%	0%
	Truxima		50%		92%		96%		99%		100%	
	MabThera in the world without Truxima	NHLd, NHLf	50%	50%	42%	58%	25%	75%	0%	100%	0%	100%
	MabThera in the world with Truxima		27%	45%	6%	38%	3%	38%	0%	38%	0%	38%
	Truxima		27%		56%		59%		61%		62%	
Germany	MabThera in the world without Truxima	RA, CLL, GPA, MPA	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%
	MabThera in the world with Truxima		75%	0%	41%	0%	12%	0%	0%	0%	0%	0%
	Truxima		25%		59%		88%		100%		100%	
	MabThera in the world without Truxima	NHLd, NHLf	75%	25%	75%	25%	75%	25%	75%	25%	75%	25%
	MabThera in the world with Truxima		56%	25%	32%	23%	10%	23%	0%	21%	0%	21%
	Truxima		19%		45%		68%		79%		79%	
France	MabThera in the world without Truxima	RA, CLL, GPA, MPA	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%
	MabThera in the world with Truxima		58%	0%	22%	0%	0%	0%	0%	0%	0%	0%
	Truxima		42%		78%		100%		100%		100%	
	MabThera in the world without Truxima	NHLd, NHLf	42%	58%	32%	68%	21%	79%	11%	89%	1%	99%
	MabThera in the world with Truxima		28%	52%	11%	51%	0%	46%	0%	44%	0%	44%
	Truxima		20%		38%		53%		56%		56%	
Spain	MabThera in the world without Truxima	RA, CLL, GPA, MPA	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%
	MabThera in the world with Truxima		87%	0%	65%	0%	41%	0%	16%	0%	0%	0%
	Truxima		13%		35%		59%		84%		100%	
	MabThera in the world without Truxima	NHLd, NHLf	2%	98%	0%	100%	0%	100%	0%	100%	0%	100%
	MabThera in the world with Truxima		14%	84%	12%	82%	7%	83%	2%	84%	0%	81%
	Truxima		2%		6%		10%		13%		19%	

Country	Scenario	Year	Year 1		Year 2		Year 3		Year 4		Year 5	
		Indication	IV	SC	IV	SC	IV	SC	IV	SC	IV	SC
Italy	MabThera in the world without Truxima	RA, CLL, GPA, MPA	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%
	MabThera in the world with Truxima		75%	0%	16%	0%	0%	0%	0%	0%	0%	0%
	Truxima		25%		84%		100%		100%		100%	
	MabThera in the world without Truxima	NHLd, NHLf	4%	96%	0%	100%	0%	100%	0%	100%	0%	100%
	MabThera in the world with Truxima		9%	88%	2%	85%	0%	75%	0%	75%	0%	75%
	Truxima		3%		12%		25%		25%		25%	

CLL: chronic lymphocytic leukaemia; DLBCL: Diffuse large B-cell lymphoma; EBC: early breast cancer; FL: Follicular lymphoma; GPA: granulomatosis with polyangiitis; Intravenous (IV); MBC: metastatic breast cancer, MGC: metastatic gastric cancer, MPA: microscopic polyangiitis; RA: rheumatoid arthritis; Subcutaneous (SC)

Supplementary Table 2: Market Volume Share Data for Herceptin and Herzuma (Base Case)

Country	Scenario	Year	Year 1		Year 2		Year 3		Year 4		Year 5	
		Indication	IV	SC	IV	SC	IV	SC	IV	SC	IV	SC
UK	Herceptin in the world without Herzuma	EBC, MBC, MGC	29%	71%	29%	71%	29%	71%	29%	71%	29%	71%
	Herceptin in the world with Herzuma		17%	68%	0%	61%	0%	61%	0%	61%	0%	61%
	Herzuma		15%		39%		39%		39%		39%	
Germany	Herceptin in the world without Herzuma	EBC, MBC, MGC	76%	24%	76%	24%	74%	26%	73%	27%	71%	29%
	Herceptin in the world with Herzuma		53%	23%	18%	22%	0%	21%	0%	21%	0%	21%
	Herzuma		24%		60%		79%		79%		79%	
France	Herceptin in the world without Herzuma	EBC, MBC, MGC	39%	61%	36%	64%	34%	66%	31%	69%	29%	71%
	Herceptin in the world with Herzuma		19%	61%	0%	57%	0%	55%	0%	55%	0%	55%
	Herzuma		19%		43%		45%		45%		45%	
Spain	Herceptin in the world without Herzuma	EBC, MBC, MGC	32%	68%	27%	73%	21%	79%	15%	85%	9%	91%
	Herceptin in the world with Herzuma		30%	62%	12%	61%	0%	56%	0%	56%	0%	56%
	Herzuma		8%		27%		44%		44%		44%	
Italy	Herceptin in the world without Herzuma	EBC, MBC, MGC	50%	50%	50%	50%	49%	51%	49%	51%	49%	51%
	Herceptin in the world with Herzuma		39%	46%	17%	42%	1%	42%	0%	42%	0%	42%
	Herzuma		14%		41%		58%		58%		58%	

CLL: chronic lymphocytic leukaemia; DLBCL: Diffuse large B-cell lymphoma; EBC: early breast cancer; FL: Follicular lymphoma; GPA: granulomatosis with polyangiitis; Intravenous (IV); MBC: metastatic breast cancer, MGC: metastatic gastric cancer, MPA: microscopic polyangiitis; RA: rheumatoid arthritis; Subcutaneous (SC)

2. Population Data

Supplementary Table 3. Population and growth rate of the EU-5 countries

Country	Year	Population	Growth rate
UK	2016	65,648,054	0.70% [1]
France	2018	67,186,638	0.30% [2]
Germany	2017	82,792,351	0.30% [3]
Spain	2018	46,698,569	0.45% [4]
Italy	2017	60,589,445	-0.32% [5]

Supplementary Table 4 Incidence of each indication per 1,000 patient-years in the EU-5 countries

Indication	UK	France	Germany	Spain	Italy
RA	0.42 [6]	0.088 [7]	0.4 [8]	0.083 [9]	0.98 [10]
CLL	0.057 [11]	0.0705 [12]	0.067 [13]	0.0635 [14]	0.045 [15]
GPA	0.0283 [16]	0.015 [17]	0.01 [18]	0.0295 [19]	0.0024 [20]
MPA	0.0152 [16]	0.01 [17]	0.0026 [21]	0.0791 [19]	0.001 [22]
NHL*	0.24 [23,24]	0.219 [24]	0.206 [24]	0.16726 [23,24]	0.208 [24]
EBC	1.235 [25]	1.482 [26]	1.35 [27]	0.8406 [28,29]	0.717 [30]
MBC	0.14 [25]	0.08 [31]	0.17 [27]	0.042384 [28,29]	0.08 [30]
MGC	0.081 [25]	0.08 [31]	0.12 [27]	0.14445 [32]	0.211 [30]

**Incidence of each country reported by the WHO IARC was converted to incidence per 1000 patient-years.*

Supplementary Table 5 Eligible patients for MabThera®, Truxima®, and Herceptin®

	Country	UK	France	Germany	Spain	Italy
Intervention	Indication	Eligible patients (%)	Eligible patients (%)	Eligible patients (%)	Eligible patients (%)	Eligible patients (%)
MabThera® IV	RA	10 [33–35]	18 [33,35]	30 [35,36]	10 [33,35]	10 [33,35]
MabThera® SC	CLL	100 [34,35]	45 [35,37]	100 [35]	100 [35]	100 [35]
Truxima®	GPA	100 [34,35]	100 [35]	100 [35]	100 [35]	100 [35]
	MPA	100 [34,35]	100 [35]	100 [35]	100 [35]	100 [35]
	NHLf	49.9 [34,35,37]	54 [17,35]	80 [35,38]	49.9 [35,37]	49.9 [35,37]
	NHLd	100 [34,35]	100 [35]	100 [35]	100 [35]	100 [35]
Herceptin® IV	EBC	17.5 [39–41]	12 [31,39]	19 [39,42]	17.5 [37,39]	17.5 [39,43]
Herceptin® SC	MBC	17.5 [40]	30 [31,39]	19 [39,42]	17.5 [37,39]	17.5 [39,43]
Herzuma®	MGC	25.8 [39,40,44]	18 [31,39]	21 [39,45]	25.8 [39,43]	25.8 [39,44]

Supplementary Table 6 Total eligible patients for Truxima® and Herzuma® in UK

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total
RA patients (IV)	2,189	2,205	2,220	2,236	2,251	11,101
CLL patients (IV)	2,971	2,992	3,013	3,034	3,055	15,065
GPA patients (IV)	1,475	1,486	1,496	1,506	1,517	7,480
MPA patients (IV)	792	798	804	809	815	4,018
NHLf patients (IV/SC)	1,438	1,448	1,458	1,468	1,479	7,291
NHLd patients (IV/SC)	7,428	7,480	7,532	7,585	7,638	37,663
Total eligible patients for Truxima®	8,865	8,929	8,991	9,053	9,117	44,955
EBC patients (IV/SC)	5,710	5,750	5,790	5,831	5,871	28,952
MBC patients (IV/SC)	634	639	643	648	652	3,216
MGC patients (IV/SC)	1,089	1,097	1,105	1,112	1,120	5,523
Total eligible patients for Herzuma®	7,433	7,486	7,538	7,591	7,643	37,691

Supplementary Table 7 Total eligible patients for Truxima® and Herzuma® in France

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total
RA patients (IV)	833	835	838	840	843	4,189
CLL patients (IV)	1,668	1,673	1,678	1,683	1,688	8,390
GPA patients (IV)	788	791	793	796	798	3,966
MPA patients (IV)	526	527	529	530	532	2,644
NHLf patients (IV/SC)	1,955	1,961	1,967	1,973	1,979	9,835
NHLd patients (IV/SC)	5,861	5,879	5,897	5,914	5,932	29,483
Total eligible patients for Truxima®	11,631	11,666	11,702	11,736	11,772	58,507
EBC patients (IV/SC)	4,894	4,908	4,923	4,938	4,953	24,616
MBC patients (IV/SC)	651	653	655	657	659	3,273
MGC patients (IV/SC)	757	759	761	764	766	3,807
Total eligible patients for Herzuma®	6,302	6,320	6,339	6,359	6,378	31,696

Supplementary Table 8 Total eligible patients for Truxima® and Herzuma® in Germany

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total
RA patients (IV)	8,171	8,196	8,220	8,245	8,270	41,102
CLL patients (IV)	4,562	4,576	4,590	4,603	4,617	22,948
GPA patients (IV)	681	683	685	687	689	3,425
MPA patients (IV)	177	178	178	179	179	891
NHLf patients (IV/SC)	3,791	3,803	3,814	3,825	3,837	19,070
NHLd patients (IV/SC)	8,074	8,098	8,122	8,147	8,171	40,612
Total eligible patients for Truxima®	25,456	25,534	25,609	25,686	25,763	128,048
EBC patients (IV/SC)	8,850	8,876	8,903	8,929	8,956	44,514
MBC patients (IV/SC)	1,114	1,118	1,121	1,124	1,128	5,605
MGC patients (IV/SC)	1,716	1,721	1,726	1,731	1,737	8,631
Total eligible patients for Herzuma®	11,680	11,715	11,750	11,784	11,821	58,750

Supplementary Table 9 Total eligible patients for Truxima® and Herzuma® in Spain

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total
RA patients (IV)	320	322	323	325	326	1,616
CLL patients (IV)	2,450	2,461	2,472	2,483	2,494	12,360
GPA patients (IV)	1,138	1,143	1,148	1,154	1,159	5,742
MPA patients (IV)	3,052	3,066	3,079	3,093	3,107	15,397
NHLf patients (IV/SC)	1,103	1,108	1,113	1,118	1,123	5,565
NHLd patients (IV/SC)	4,192	4,211	4,230	4,249	4,268	21,150
Total eligible patients for Truxima®	12,255	12,311	12,365	12,422	12,477	61,830
EBC patients (IV/SC)	2,894	2,907	2,920	2,933	2,947	14,601
MBC patients (IV/SC)	146	147	147	148	149	737
MGC patients (IV/SC)	1,438	1,444	1,451	1,457	1,464	7,254
Total eligible patients for Herzuma®	4,478	4,498	4,518	4,538	4,560	22,592

Supplementary Table 10 Total eligible patients for Truxima® and Herzuma® in Italy

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total
RA patients (IV)	5,120	5,103	5,087	5,071	5,055	25,436
CLL patients (IV)	2,351	2,343	2,336	2,328	2,321	11,679
GPA patients (IV)	125	125	125	124	124	623
MPA patients (IV)	52	52	52	52	52	260
NHLf patients (IV/SC)	941	938	935	932	929	4,675
NHLd patients (IV/SC)	3,772	3,760	3,748	3,736	3,724	18,740
Total eligible patients for Truxima®	12,361	12,321	12,283	12,243	12,205	61,413
EBC patients (IV/SC)	3,369	3,359	3,348	3,337	3,326	16,739
MBC patients (IV/SC)	376	375	374	372	371	1,868
MGC patients (IV/SC)	2,844	2,835	2,826	2,817	2,808	14,130
Total eligible patients for Herzuma®	6,589	6,569	6,548	6,526	6,505	32,737

Supplementary Table 11:SmPC indications for each originator and biosimilars

Originator, Biosimilar	Indication
MabThera IV(1), Truxima (2)	Rheumatoid arthritis
	Chronic lymphocytic leukaemia
	Granulomatosis with polyangiitis
	Microscopic polyangiitis
	Non-Hodgkin lymphoma, follicular
	Non-Hodgkin lymphoma, diffuse large B cell
MabThera SC(3)	Non-Hodgkin lymphoma, follicular
	Non-Hodgkin lymphoma, diffuse large B cell
Herceptin IV(4), Herzuma (5)	Early breast cancer
	Metastatic breast cancer
	Metastatic gastric cancer
Herceptin SC(6)	Early breast cancer
	Metastatic breast cancer
	Metastatic gastric cancer

3. Drug dosage

Supplementary Table 12: Mean dose of MabThera IV/SC and Herceptin IV/SC obtained from the SmPC

Drug	Indication	Mean dose	Dosing
MabThera IV(1), Truxima (2)	RA	2000	<ul style="list-style-type: none"> • 1000mg followed by 1000mg 2 weeks later • Repeat cycle after 24 weeks
	CLL	<ul style="list-style-type: none"> • Loading dose: 375 mg/m² • Maintenance dose: 500 mg/m² 	<ul style="list-style-type: none"> • Week 1 • Weekly (6 weeks)
	GPA	375 mg	Weekly (4 weeks)
	MPA	375 mg	Weekly (4 weeks)
	FL	375 mg	Weekly (8 weeks T1, 6 weeks T2 and 4 weeks T3)
	DLBCL	375 mg	Weekly (8 weeks)
	MabThera SC(3)	FL	1400 mg
	DLBCL	1400 mg	Weekly (8 weeks)
Herceptin IV(4), Herzumab (5)	EBC	<ul style="list-style-type: none"> • Loading dose: 8 mg/kg • Maintenance dose: 6 mg/kg 	<ul style="list-style-type: none"> • Week 1 • Weekly (17 weeks)
	MBC	<ul style="list-style-type: none"> • Loading dose: 8 mg/kg • Maintenance dose: 6 mg/kg 	<ul style="list-style-type: none"> • Week 1 • Weekly (17 weeks)
	MGC	<ul style="list-style-type: none"> • Loading dose: 8 mg/kg • Maintenance dose: 6 mg/kg 	<ul style="list-style-type: none"> • Week 1 • Weekly (17 weeks)
Herceptin SC(6)	EBC	600 mg/kg	Weekly (18 weeks)
	MBC	600 mg/kg	Weekly (18 weeks)
	MGC	600 mg/kg	Weekly (18 weeks)

4. Administration costs for intravenous and subcutaneous MabThera and Herceptin
Supplementary Table 13: Administration tariffs for intravenous and subcutaneous MabThera and Herceptin for the UK

Drug		Intravenous (£)	Subcutaneous (£)	Source
MabThera	Administration tariff in RA and MPA <i>(standard infusion)</i>	351.00	351.00	National Tariff Payment System, HRG HD23J Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 0-2
	Administration tariff in GPA <i>(standard infusion)</i>	423.00	423.00	National Tariff Payment System, HRG JD07K Skin Disorders without Interventions, with CC Score 0-1
	Administration tariff in NHLf and NHLd <i>(standard infusion)</i>	299.00	299.00	National Tariff Payment System, HRG SB13Z, Delivery Tariff
Herceptin	Administration <i>(loading injection)</i>	299.00	299.00	National Tariff Payment System, HTG SB97Z (attendance), SB08Z (Procurement) and SB12Z (Delivery)
	Administration <i>(maintenance injection)</i>	150.00	150.00	National Tariff Payment System, HTG SB97Z (attendance), SB08Z (Procurement) and SB12Z (Delivery)

CLL: chronic lymphocytic leukaemia, EBC: early breast cancer, GPA: granulomatosis with polyangiitis, HRG: Healthcare Resource Group, MBC: metastatic breast cancer, MGC: metastatic gastric cancer, MPA: microscopic polyangiitis, NHLd: Non-Hodgkin Lymphoma, diffuse, NHLf: Non-Hodgkin Lymphoma, follicular, RA: rheumatoid arthritis

Supplementary Table 14: Administration tariffs for intravenous and subcutaneous MabThera and Herceptin for France

Mode of administration	Cost (€)	Source
Intravenous	383.11	ATIH 2019 [46]
Subcutaneous	383.11	ATIH 2019 [46]

ATIH: Agence Technique de l'Information sur l'Hospitalisation

Supplementary Table 15: Administration tariffs for intravenous and subcutaneous MabThera and Herceptin for Germany

Mode of administration	Rituximab administration cost (€)	Trastuzumab administration cost (€)	Source
Intravenous	144.61	105.48	EBM 2018 [47]
Subcutaneous	74.40	88.75	EBM 2018 [47]

EBM: Einheitlicher Bewertungsmaßstab

Supplementary Table 16: Administration tariffs for intravenous and subcutaneous MabThera and Herceptin for Spain

Mode of administration	Cost (€)	Source
Intravenous	478.32	e-Salud, 2017 [48], CPI [49]
Subcutaneous	478.32	e-Salud, 2017 [48], CPI [49]

Supplementary Table 17: Administration tariffs for intravenous and subcutaneous MabThera and Herceptin for Italy

Mode of administration	Cost (€)	Source
Intravenous	45.70	RegioneLombardia, La Giunta 2012 [50], CPI [49]
Subcutaneous	45.70	RegioneLombardia, La Giunta 2012 [50], CPI [49]

5. Price per drug across EU-5

Supplementary Table 18: Price per milligram applied in the model for EU-5 countries

Country	Product	MabThera IV (200 mg pack size)	MabThera IV (500 mg pack size)	MabThera SC	Truxima (200 mg pack size)	Truxima (500 mg pack size)	Herceptin IV	Herceptin SC	Herzuma
UK*	Cost per pack (£)	349.25	873.15	1,344.65	314.33	785.84	407.4	1,263.48	366.66
	Cost per mg (£)	1.75	1.75	0.96	1.57	1.57	2.72	2.11	2.44
Germany	Cost per pack (€)	840.19	2,044.49	2,844.34	700.99	1,761.05	866.4	2,545.21	782.01
	Cost per mg (€)	4.2	4.09	2.03	3.5	3.52	5.78	4.24	5.21
Italy	Cost per pack (€)	916.29	2,290.29	2,914.39	733.03	1,832.23	1,056.93	3,022.82	845.54
	Cost per mg (€)	4.58	4.58	2.08	3.67	3.66	7.05	5.04	5.64
Spain	Cost per pack (€)	567.93	1,342.06	1,896.47	490.68	1,149.47	678.53	1,693.32	585.47
	Cost per mg (€)	2.84	2.68	1.35	2.45	2.3	4.52	2.82	3.9
France	Cost per pack (€)	339.2	848	1,519.81	339.2	848	356.84	1,331.78	356.84
	Cost per pack after discount (€)	305.28	763.2	NA	271.36	678.4	321.16	NA	285.47
	Cost per mg, undiscounted (€)	1.7	1.7	1.09	1.36	1.36	2.38	2.22	1.9

6. Resource Costing for the UK

Supplementary Table 19: HCP time reported for administration and preparation of treatments

	Product	Minutes	Comments
Preparation	MabThera IV		No drug preparation time reported
	MabThera SC		No drug preparation time reported
	Herceptin IV [51]	34.5	Drug preparation completed by pharmacist
	Herceptin SC [51]	0	No drug preparation time reported
Administration*	MabThera IV (<i>standard infusion</i>) [52]	117.9	Scenario where nurse cares for 3.5 patients concurrently (i.e. each patient occupies 29% of their time)
	MabThera IV (<i>rapid infusion</i>) [35,53]	90.0	Scenario where first cycle is given as per standard administration rate then switched to rapid infusion rate on subsequent cycles.
	MabThera SC [52]	48.5	Scenario where nurse cares for 3.5 patients concurrently (i.e. each patient occupies 29% of their time); no change from base case
	Herceptin IV (<i>standard infusion</i>) [51]	58.1	
	Herceptin IV (<i>rapid infusion</i>) [39]	30.0	Scenario where first cycle is given as per standard administration rate then switched to rapid infusion rate on subsequent cycles.
	Herceptin SC [51]	24.6	

HCP: healthcare professional, IV: intravenous, SC: subcutaneous,

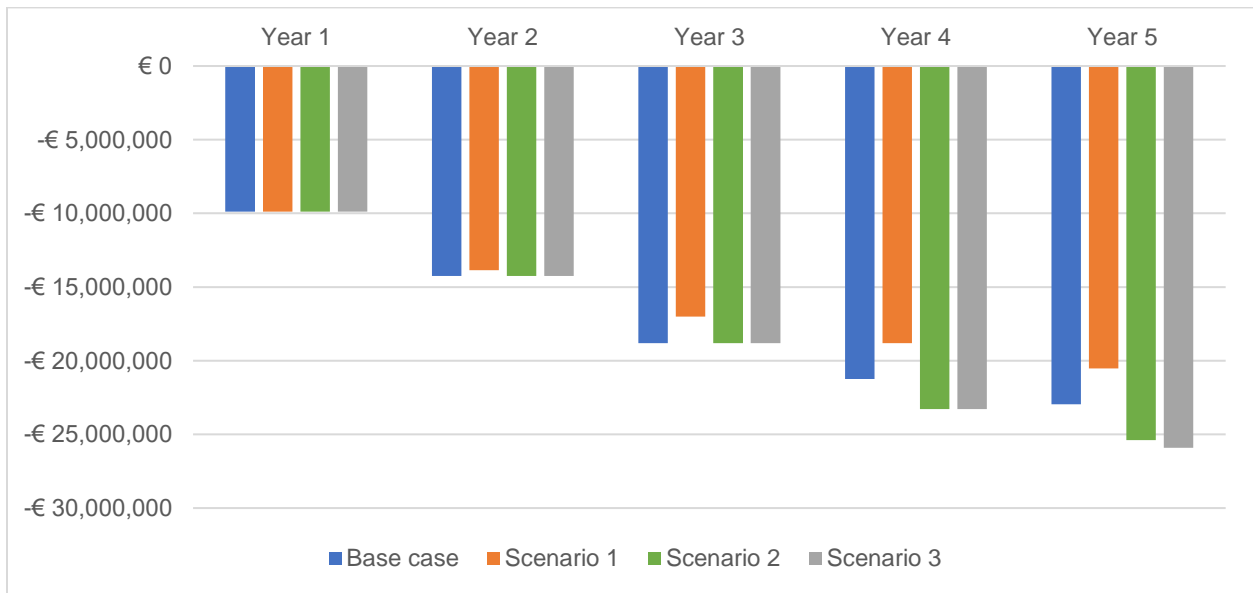
Supplementary Table 20: Resources used for intravenous and subcutaneous MabThera and Herceptin

Drug		Intravenous (£)	Subcutaneous (£)
MabThera	Administration (<i>standard infusion</i>) [52,54]	80.57	33.14
	Administration (<i>rapid infusion</i>) [35,54]	61.50	NA
	Consumables (inflated values) [52]	14.12	1.28
Herceptin	Administration (<i>standard infusion</i>) [51,54]	65.34	16.81
	Administration (<i>rapid infusion</i>) [39,54]	20.50	NA
	Consumables (inflated values) [52]	14.12	1.28

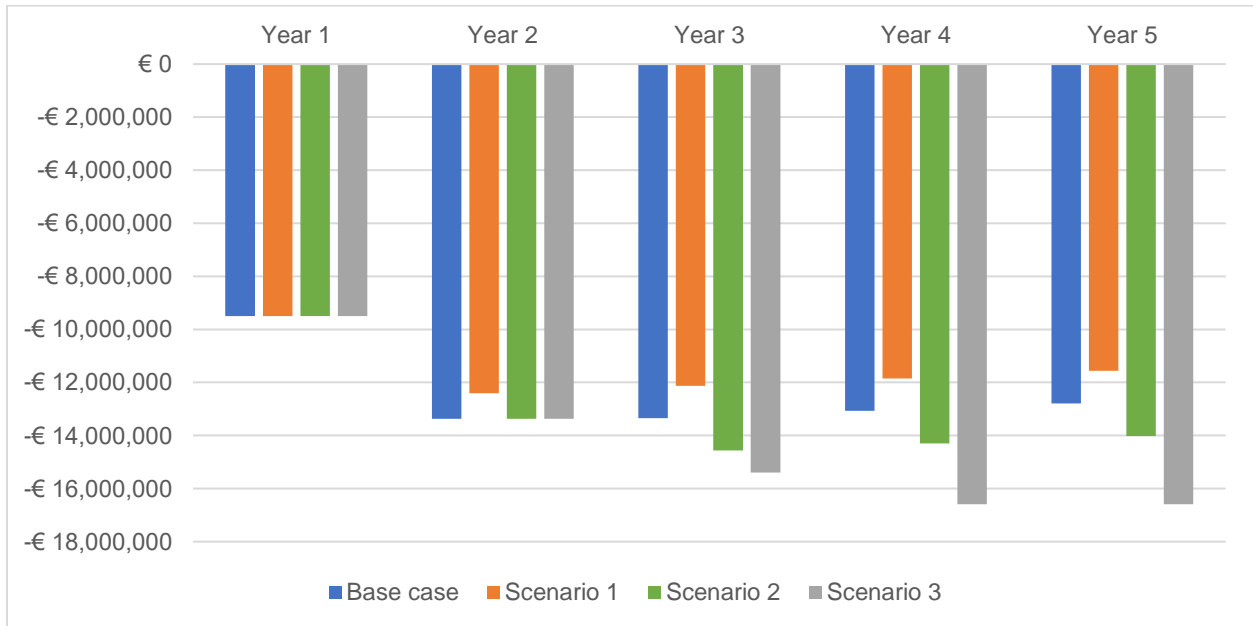
PSSRU: Personal Social Services Research Unit, SmPC: Summary of product characteristics

7. Summary of scenario analyses

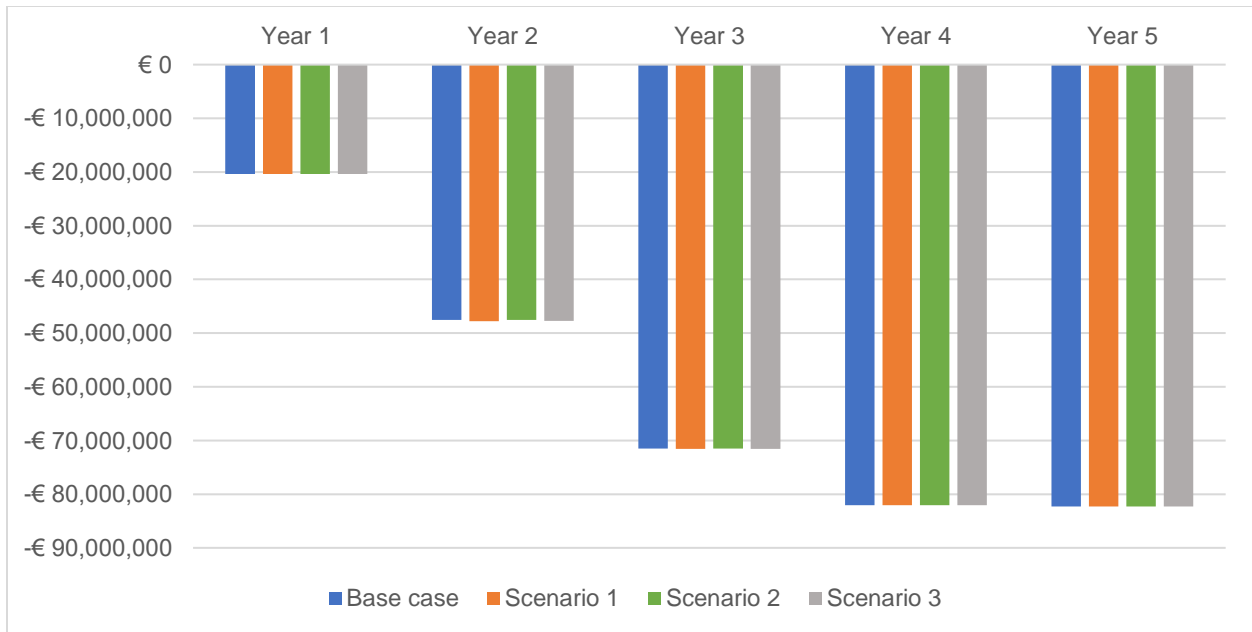
Supplementary Figure 1: Summary of net budget impact results for Truxima (200mg pack size): Base case and scenario 1-3 analyses for France



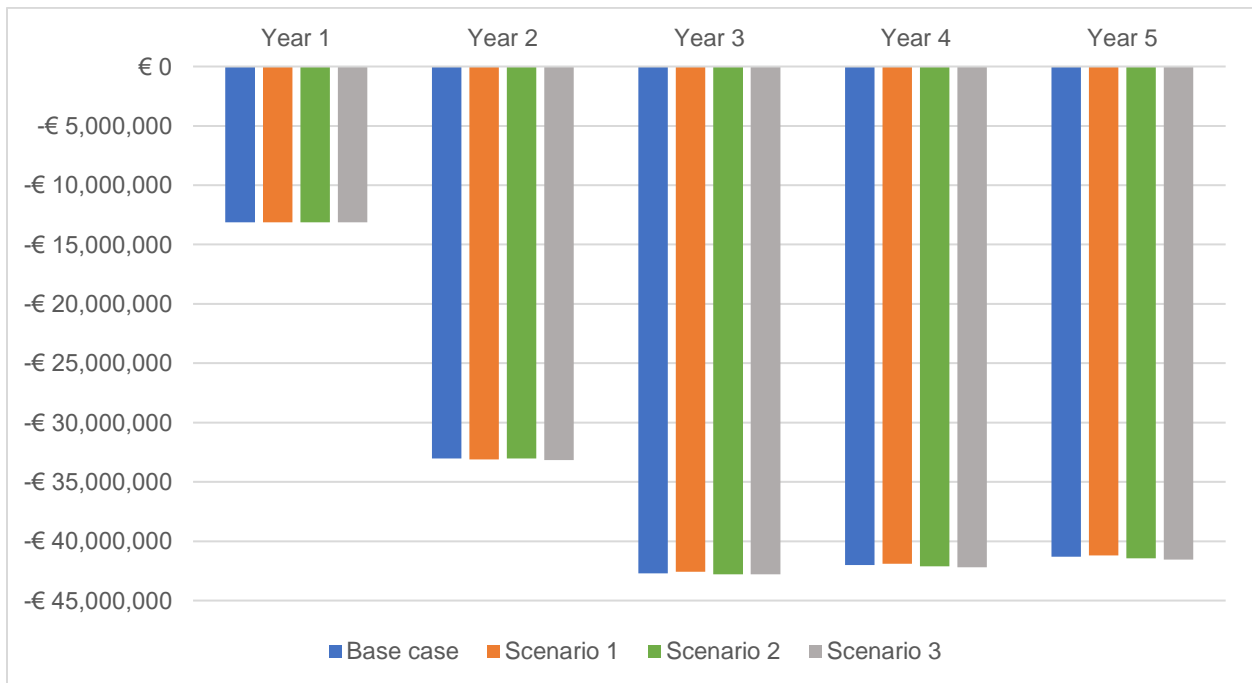
Supplementary Figure 2: Summary of net budget impact results for Herzuma : Base case and scenario 1-3 analyses for France



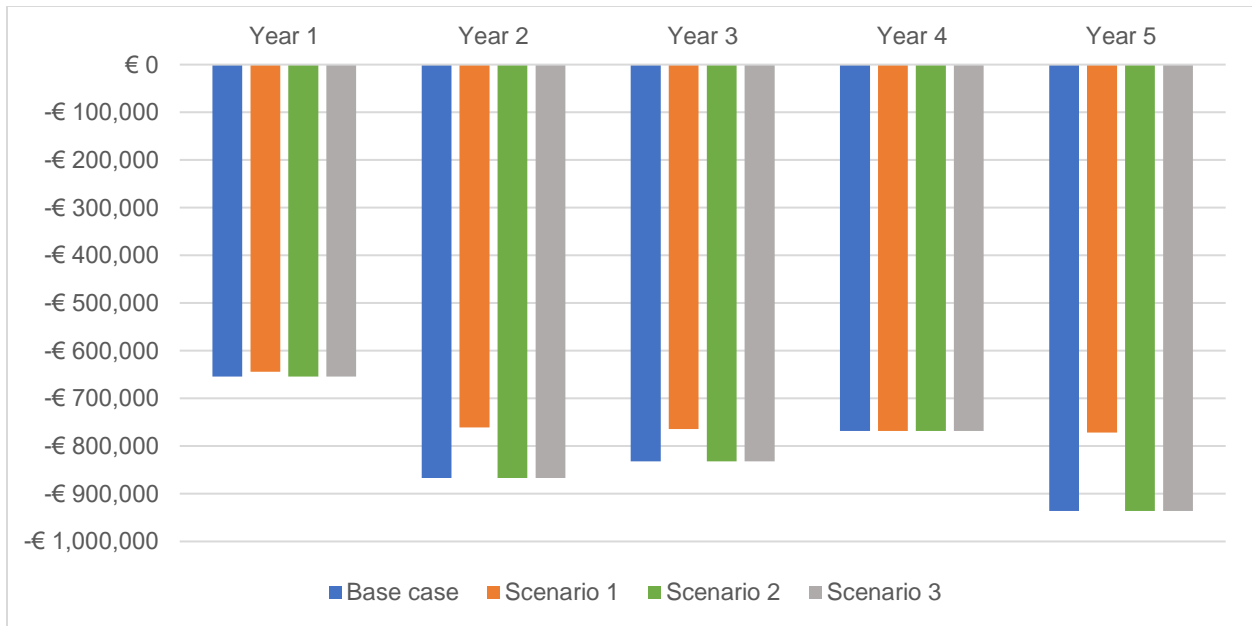
Supplementary Figure 3: Summary of net budget impact results for Truxima (200mg pack size): Base case and scenario 1-3 analyses for Germany



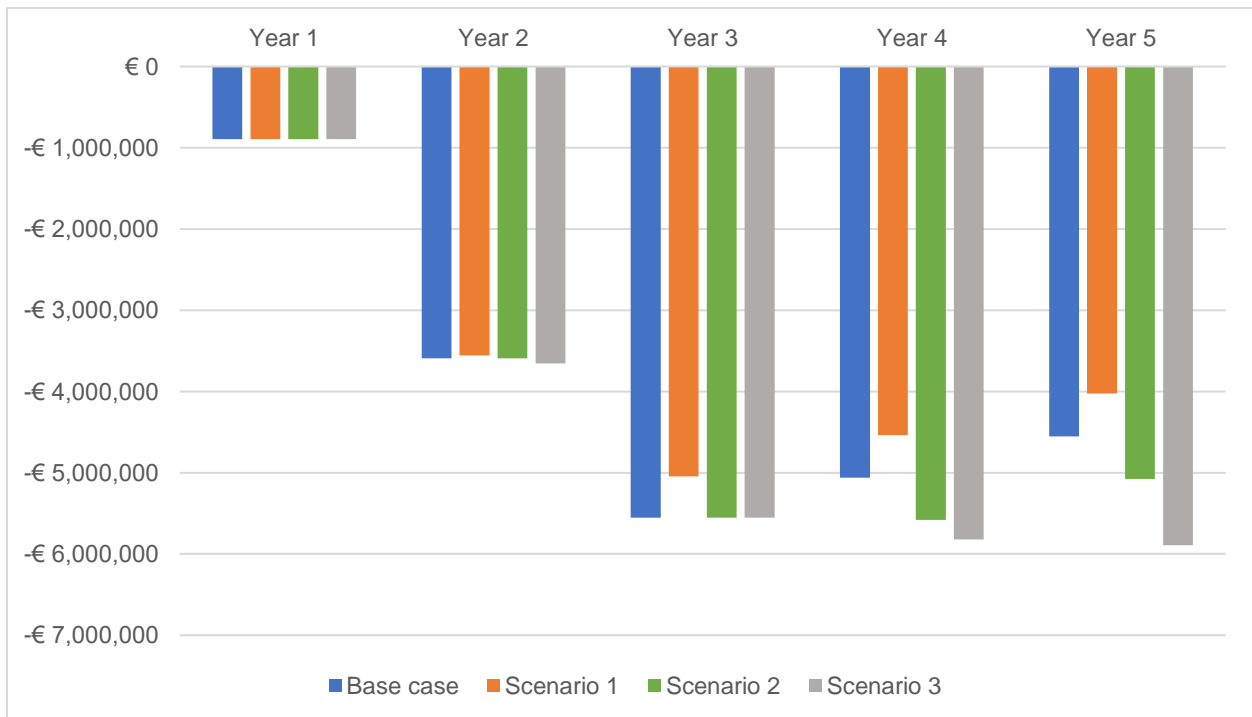
Supplementary Figure 4: Summary of net budget impact results for Herzuma : Base case and scenario 1-3 analyses for Germany



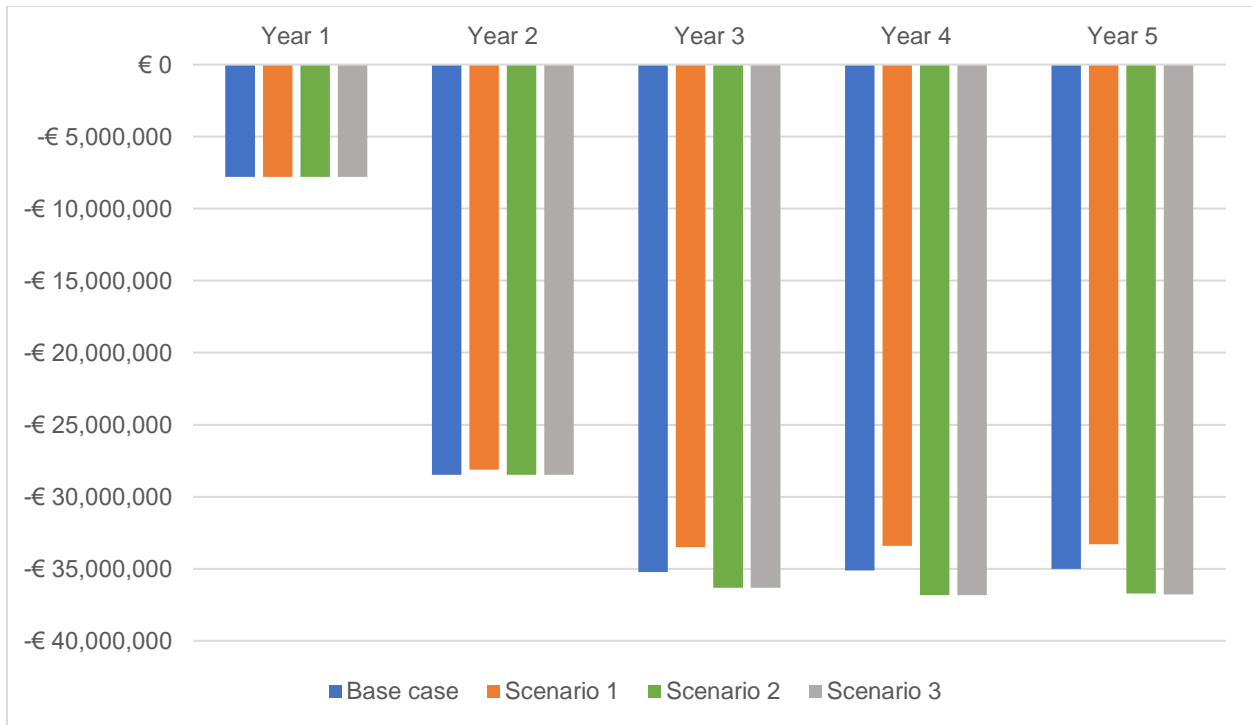
Supplementary Figure 5: Summary of net budget impact results for Truxima (200mg pack size): Base case and scenario 1-3 analyses for Spain



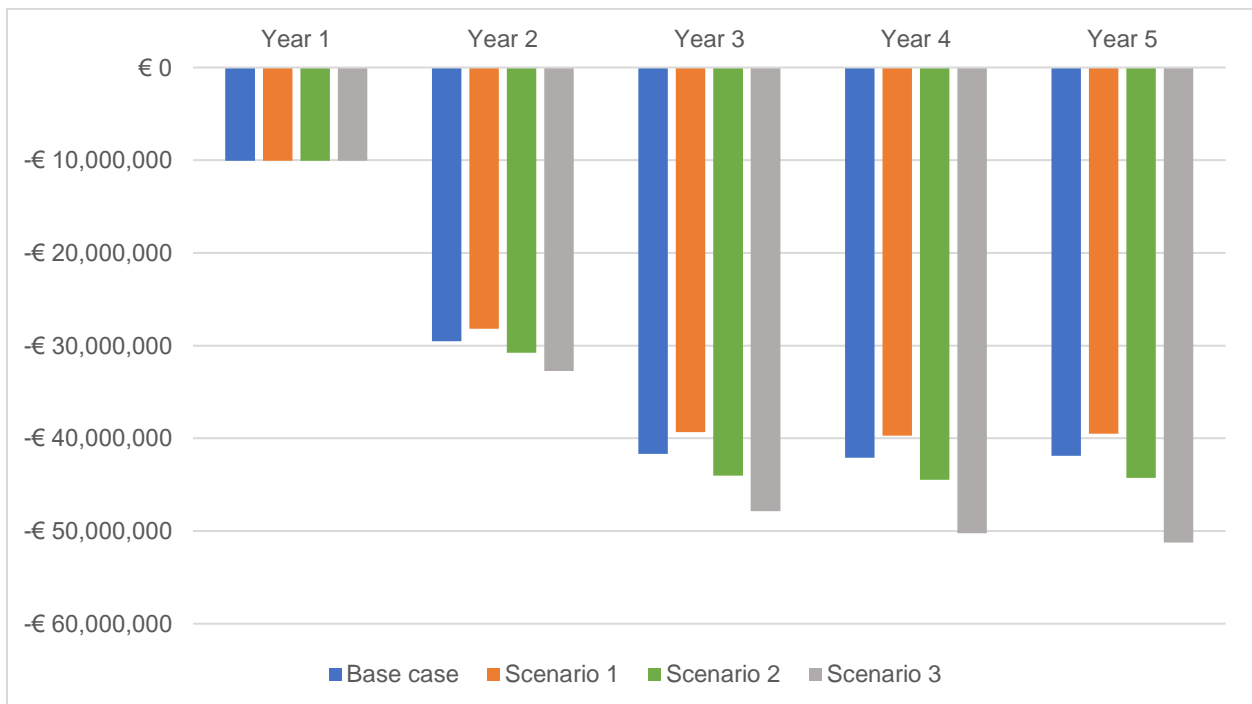
Supplementary Figure 6: Summary of net budget impact results for Herxuma : Base case and scenario 1-3 analyses for Spain



Supplementary Figure 7: Summary of net budget impact results for Truxima (200mg pack size): Base case and scenario 1-3 analyses for Italy

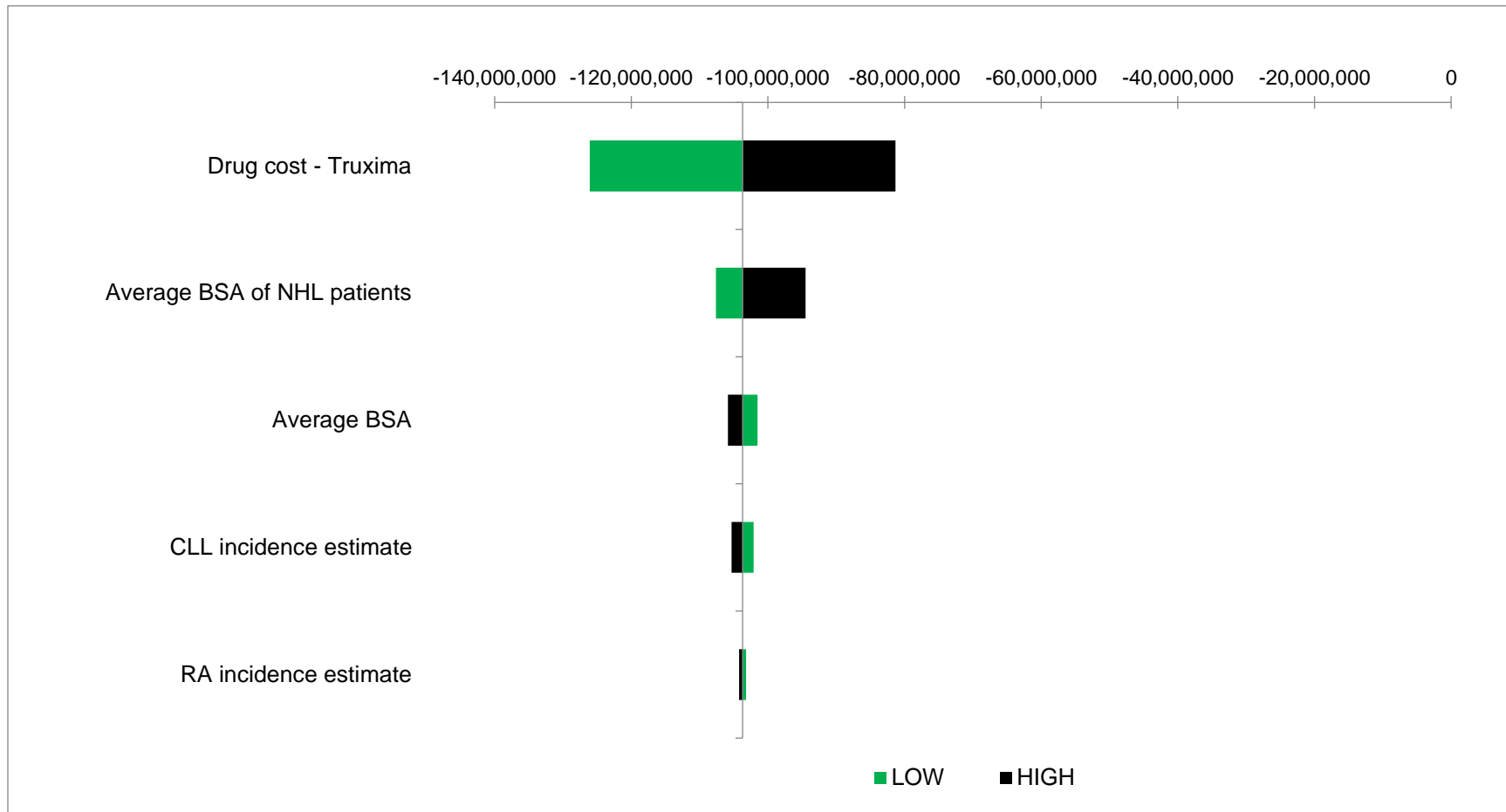


Supplementary Figure 8: Summary of net budget impact results for Herzuma : Base case and scenario 1-3 analyses for Italy



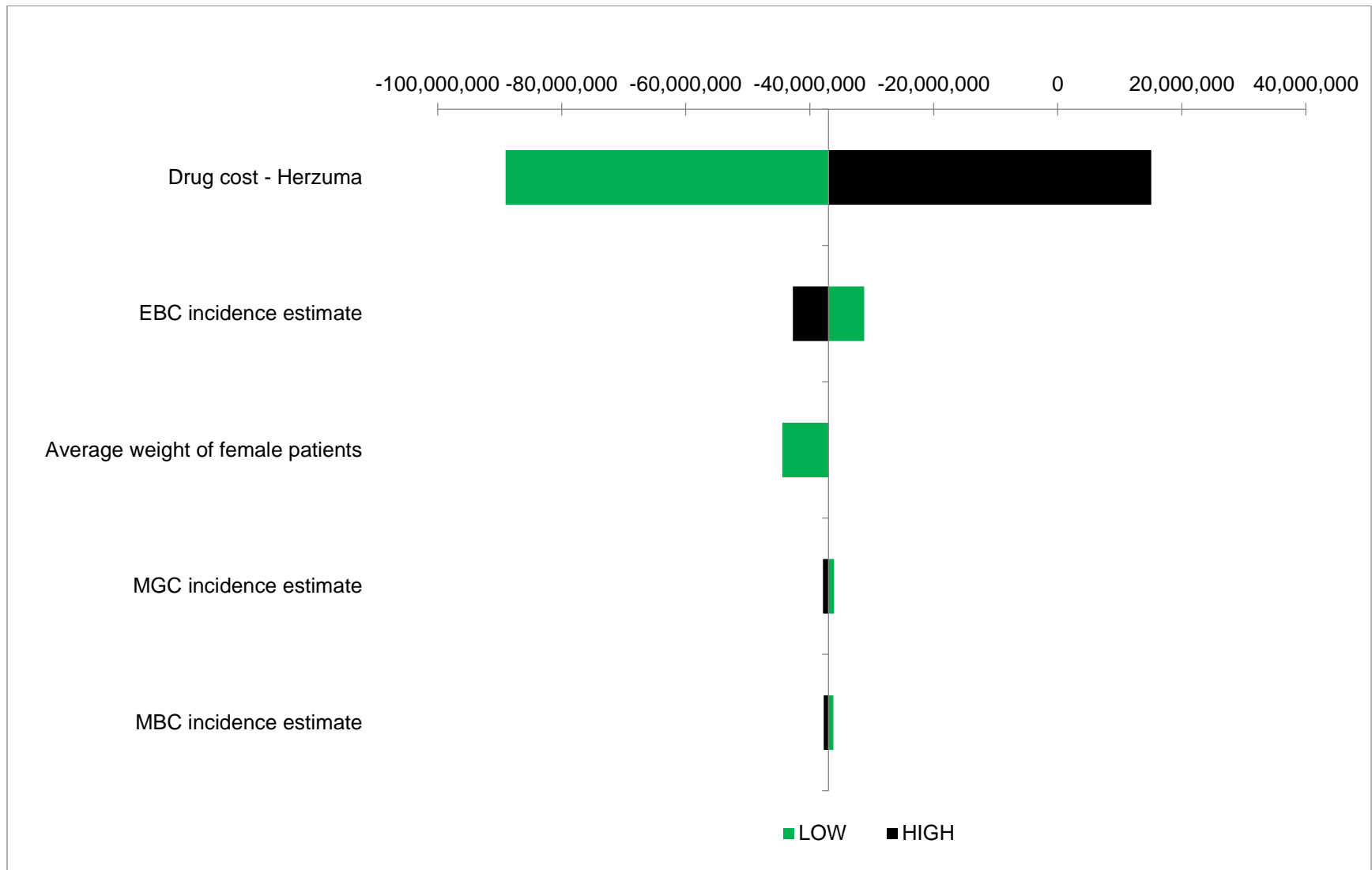
8. Sensitivity analysis

Supplementary Figure 9: Truxima OWSA tornado diagram for France



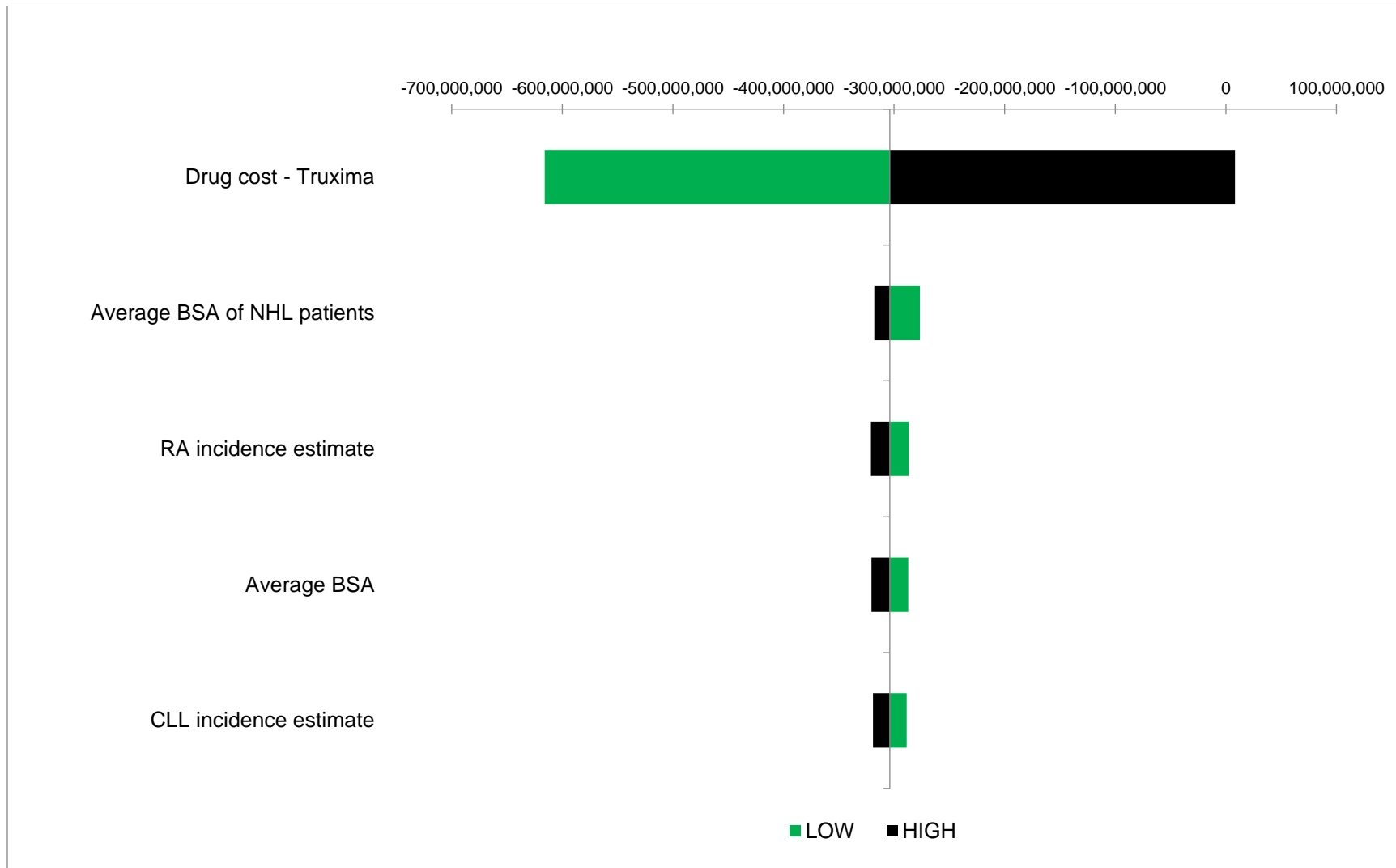
BSA: body surface area, CLL: chronic lymphocytic leukaemia, NHLd: Non-Hodgkin Lymphoma, diffuse, NHLf: Non-Hodgkin Lymphoma, follicular, OWSA: one-way sensitivity analysis, RA: rheumatoid arthritis

Supplementary Figure 10:Herzuma OWSA tornado diagram for France



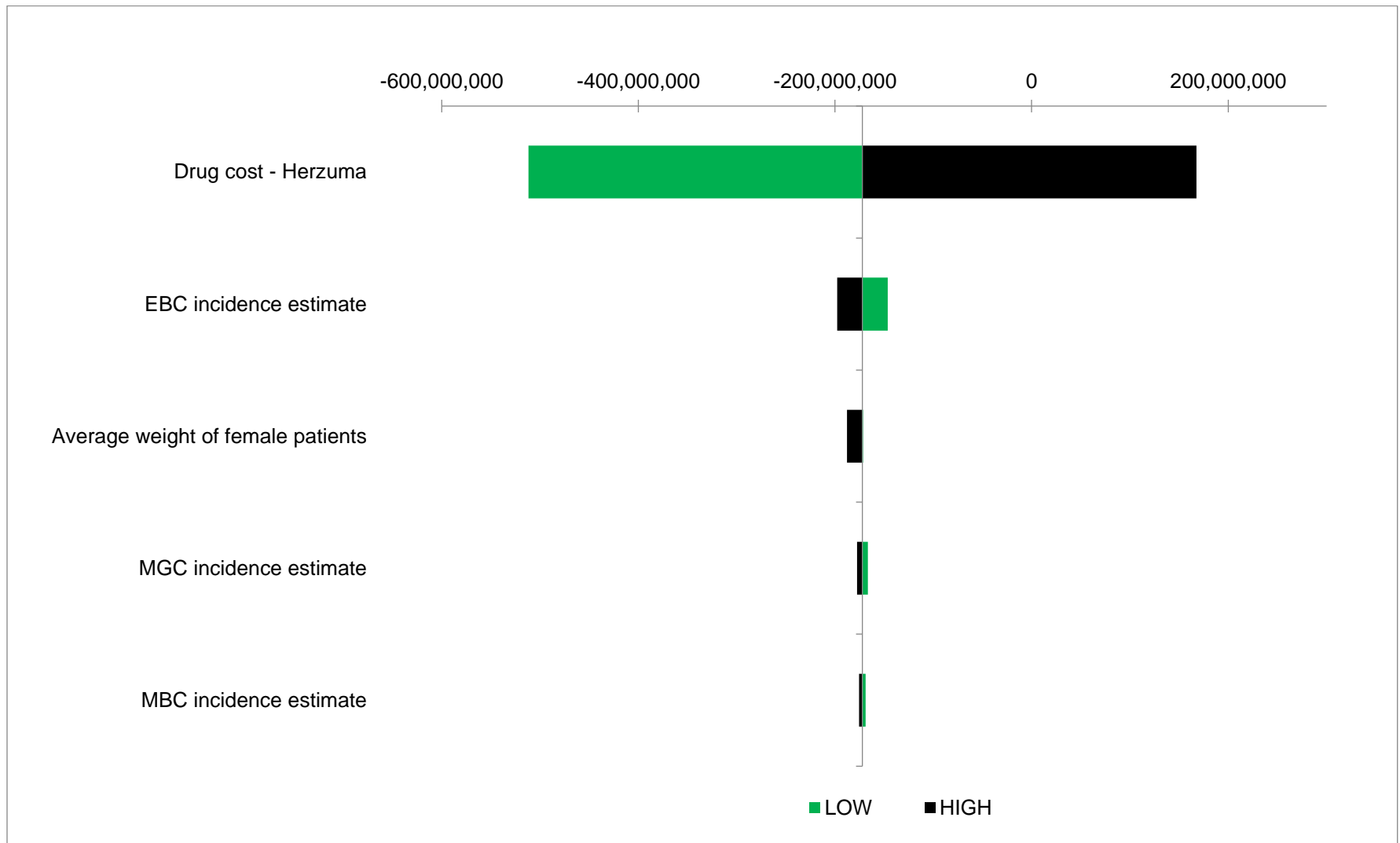
EBC: early breast cancer, GPA: granulomatosis with polyangiitis, MBC: metastatic breast cancer, MGC: metastatic gastric cancer, OWSA: one-way sensitivity analysis

Supplementary Figure 11: Truxima OWSA tornado diagram for Germany



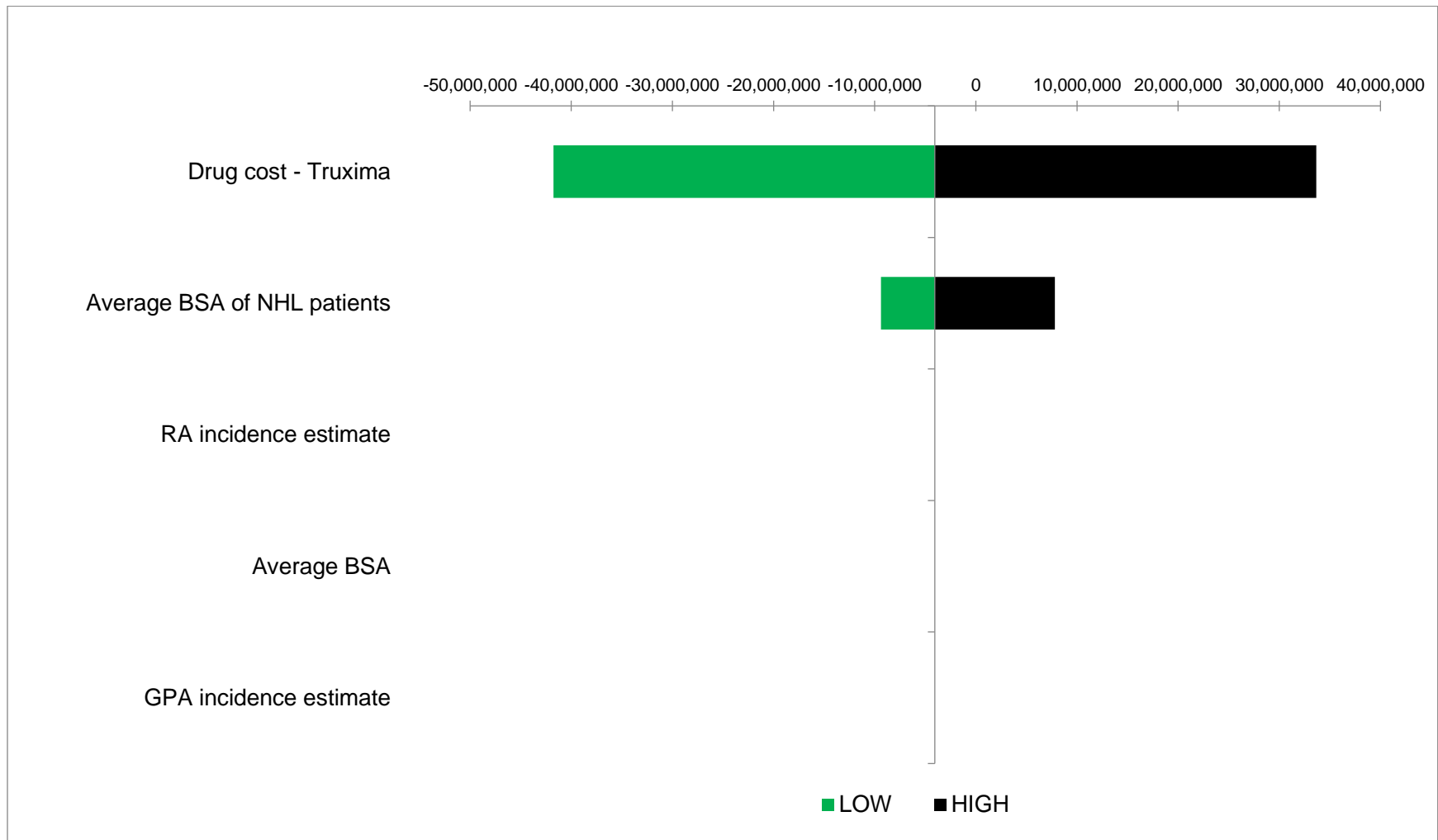
BSA: body surface area, CLL: chronic lymphocytic leukaemia, NHLd: Non-Hodgkin Lymphoma, diffuse, NHLf: Non-Hodgkin Lymphoma, follicular, OWSA: one-way sensitivity analysis, RA: rheumatoid arthritis

Supplementary Figure 12:Herzuma OWSA tornado diagram for Germany



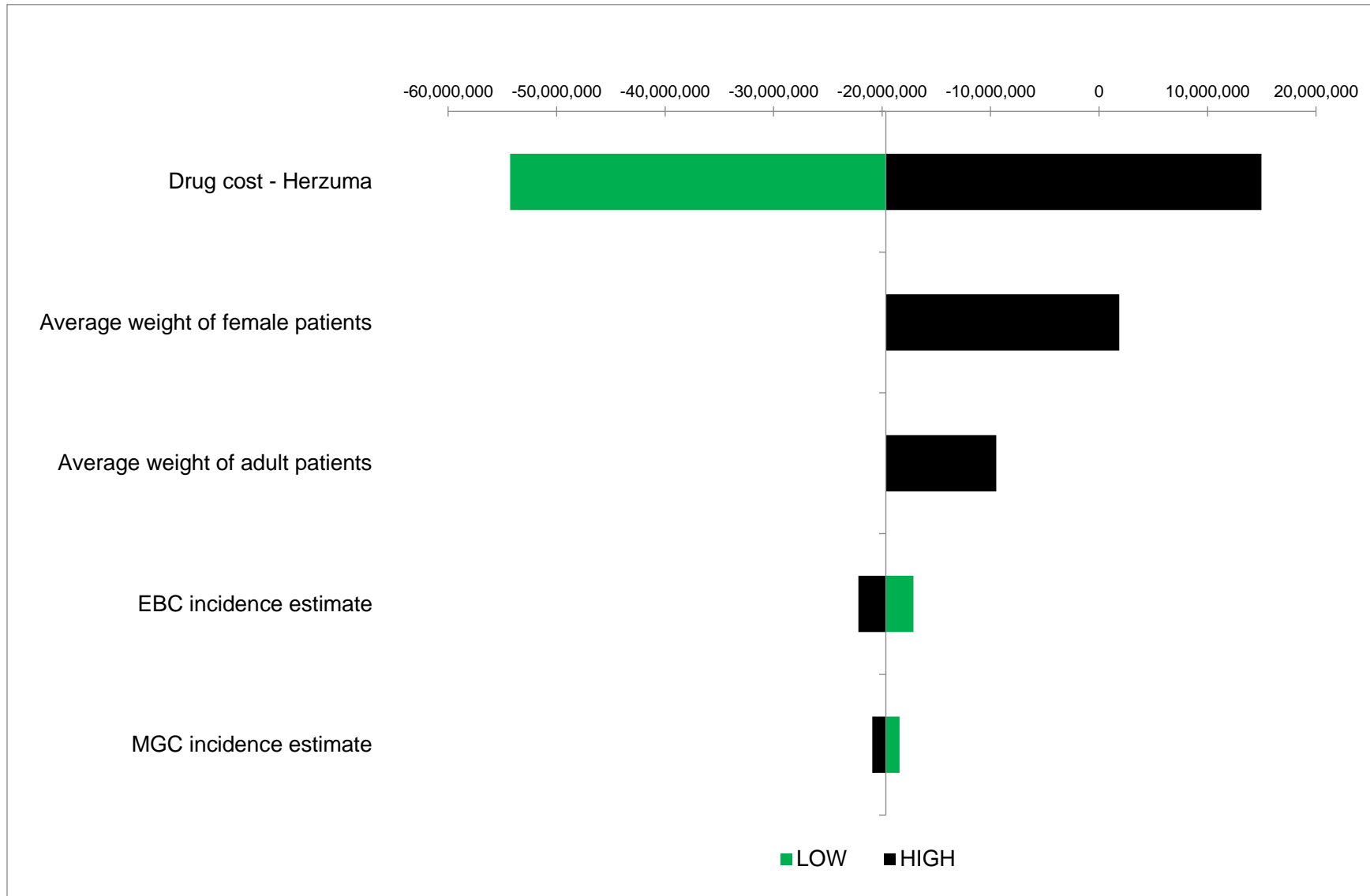
EBC: early breast cancer, GPA: granulomatosis with polyangiitis, MBC: metastatic breast cancer, MGC: metastatic gastric cancer, OWSA: one-way sensitivity analysis

Supplementary Figure 13: Truxima OWSA tornado diagram for Spain



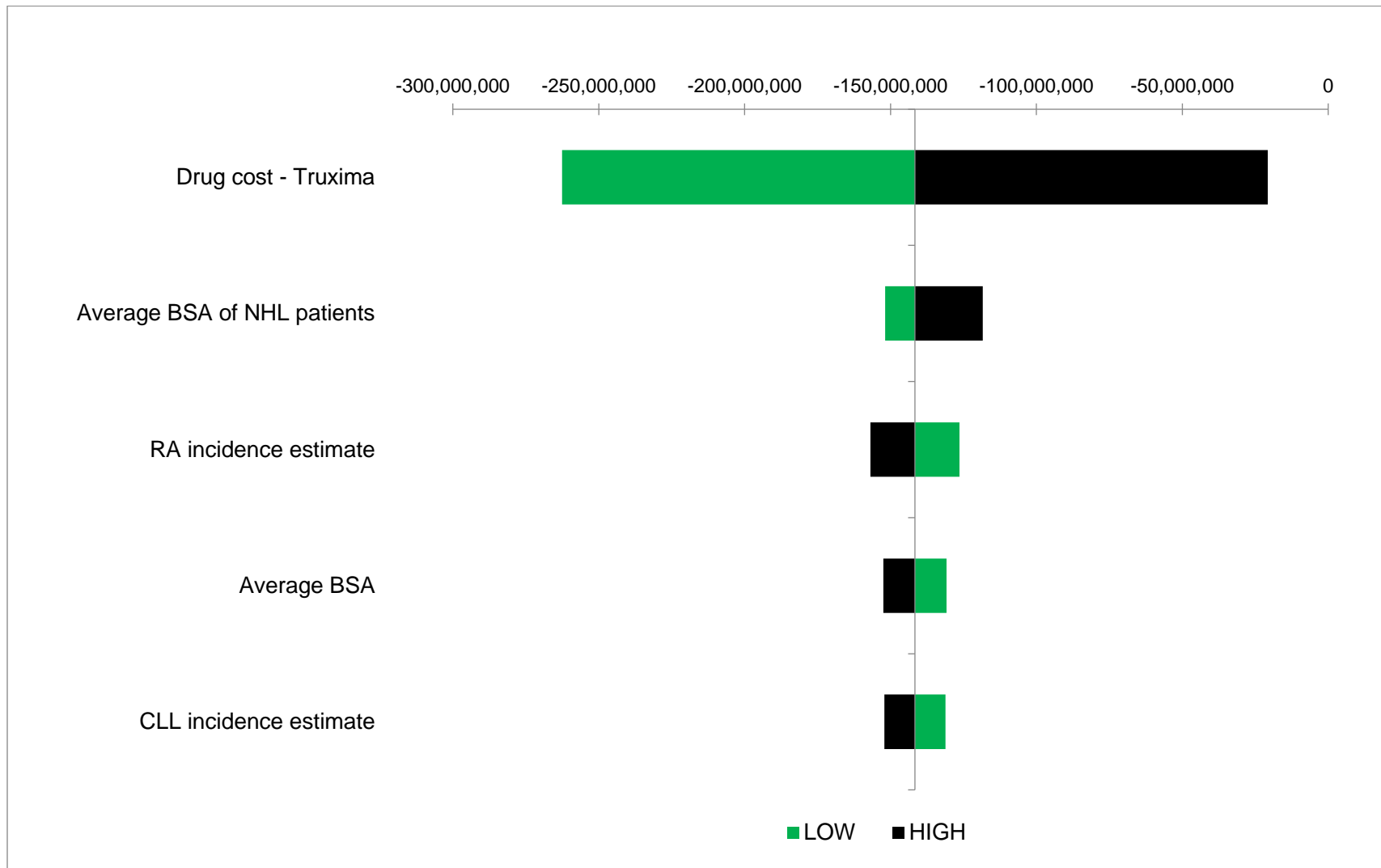
BSA: body surface area, CLL: chronic lymphocytic leukaemia, NHLd: Non-Hodgkin Lymphoma, diffuse, NHLf: Non-Hodgkin Lymphoma, follicular, OWSA: one-way sensitivity analysis, RA: rheumatoid arthritis

Supplementary Figure 14:Herzuma OWSA tornado diagram for Spain



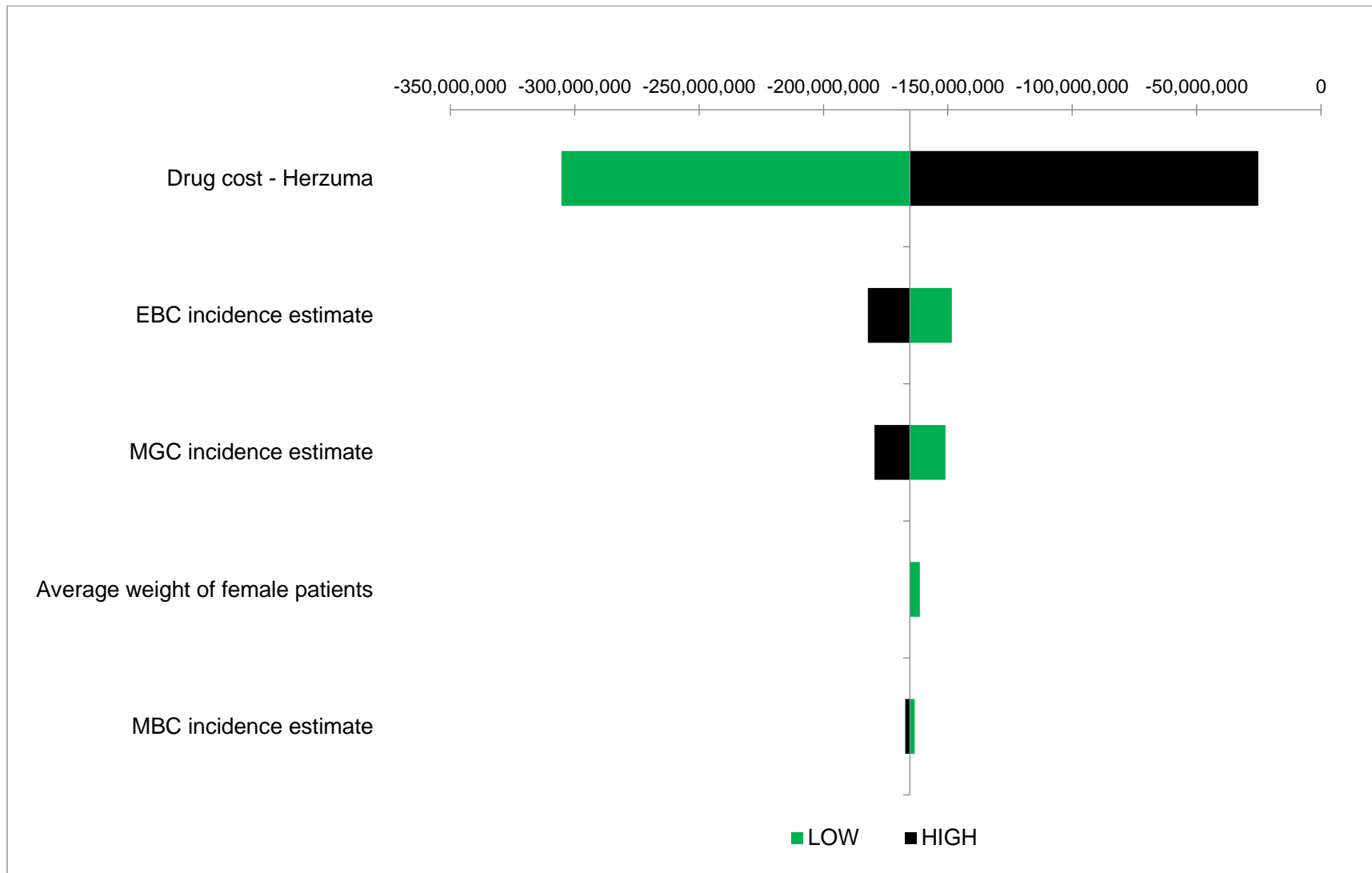
EBC: early breast cancer, GPA: granulomatosis with polyangiitis, MBC: metastatic breast cancer, MGC: metastatic gastric cancer, OWSA: one-way sensitivity analysis

Supplementary Figure 15: Truxima OWSA tornado diagram for Italy



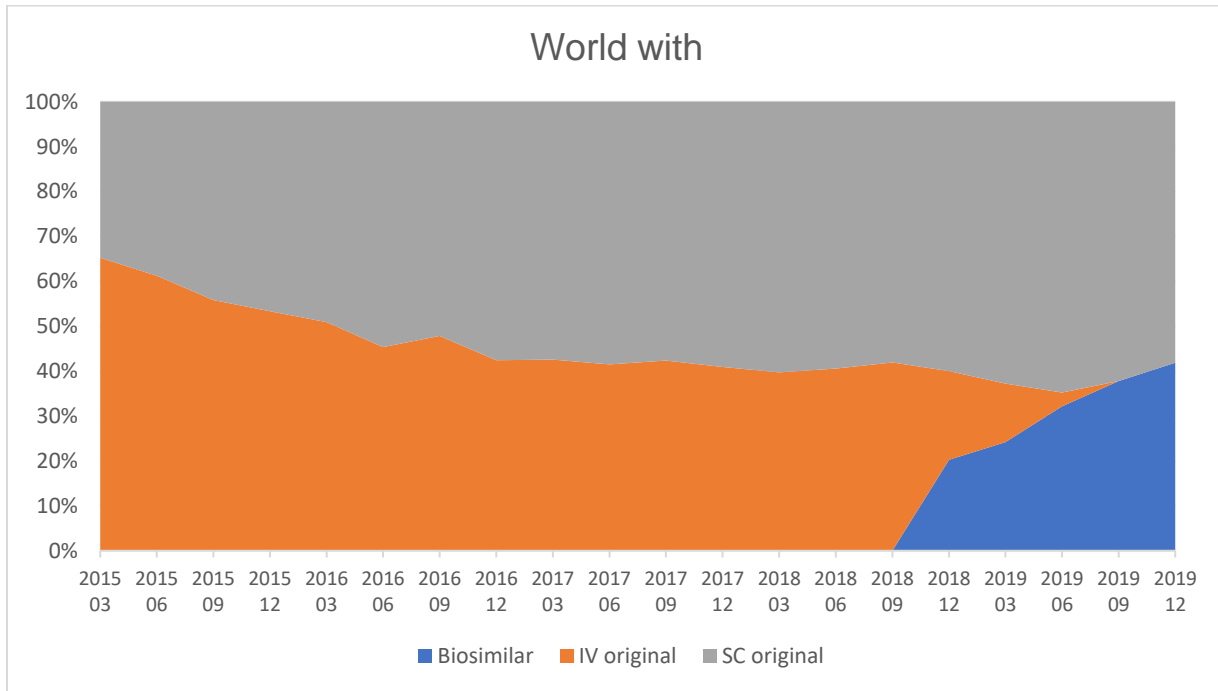
BSA: body surface area, CLL: chronic lymphocytic leukaemia, NHLd: Non-Hodgkin Lymphoma, diffuse, NHLf: Non-Hodgkin Lymphoma, follicular, OWSA: one-way sensitivity analysis, RA: rheumatoid arthritis

Supplementary Figure 16:Herzuma OWSA tornado diagram for Italy

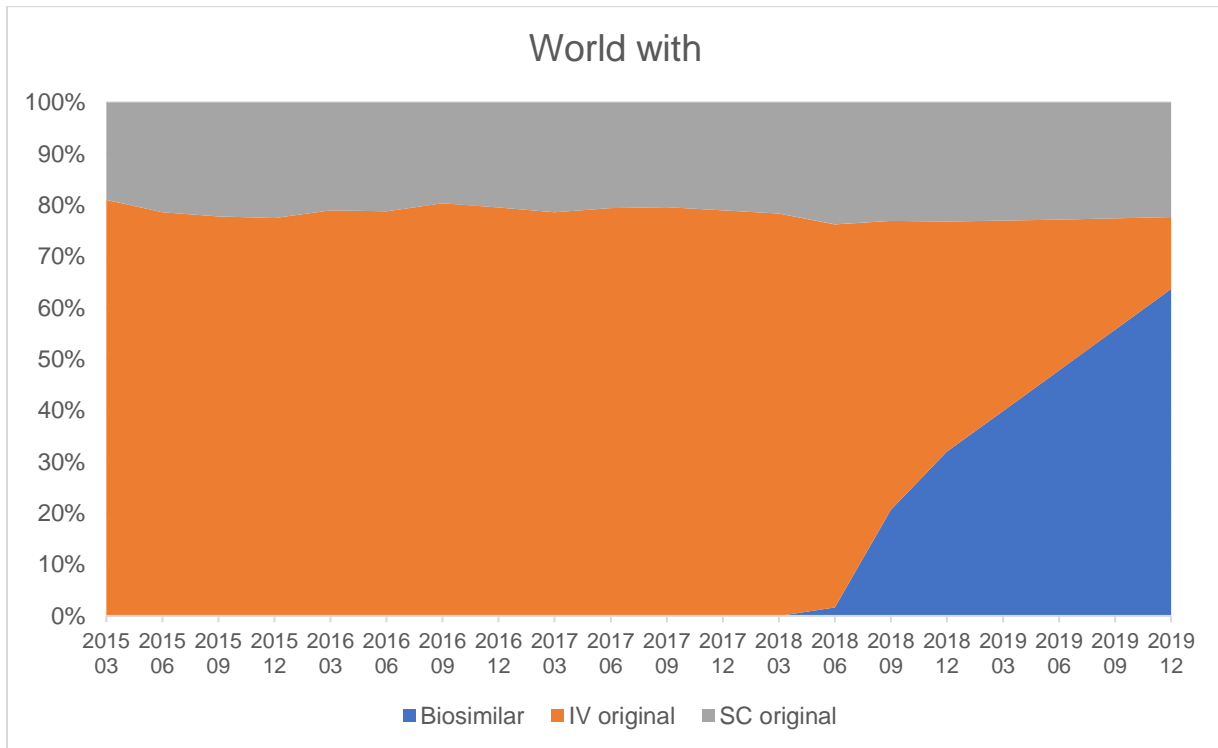


EBC: early breast cancer, GPA: granulomatosis with polyangiitis, MBC: metastatic breast cancer, MGC: metastatic gastric cancer, OWSA: one-way sensitivity analysis

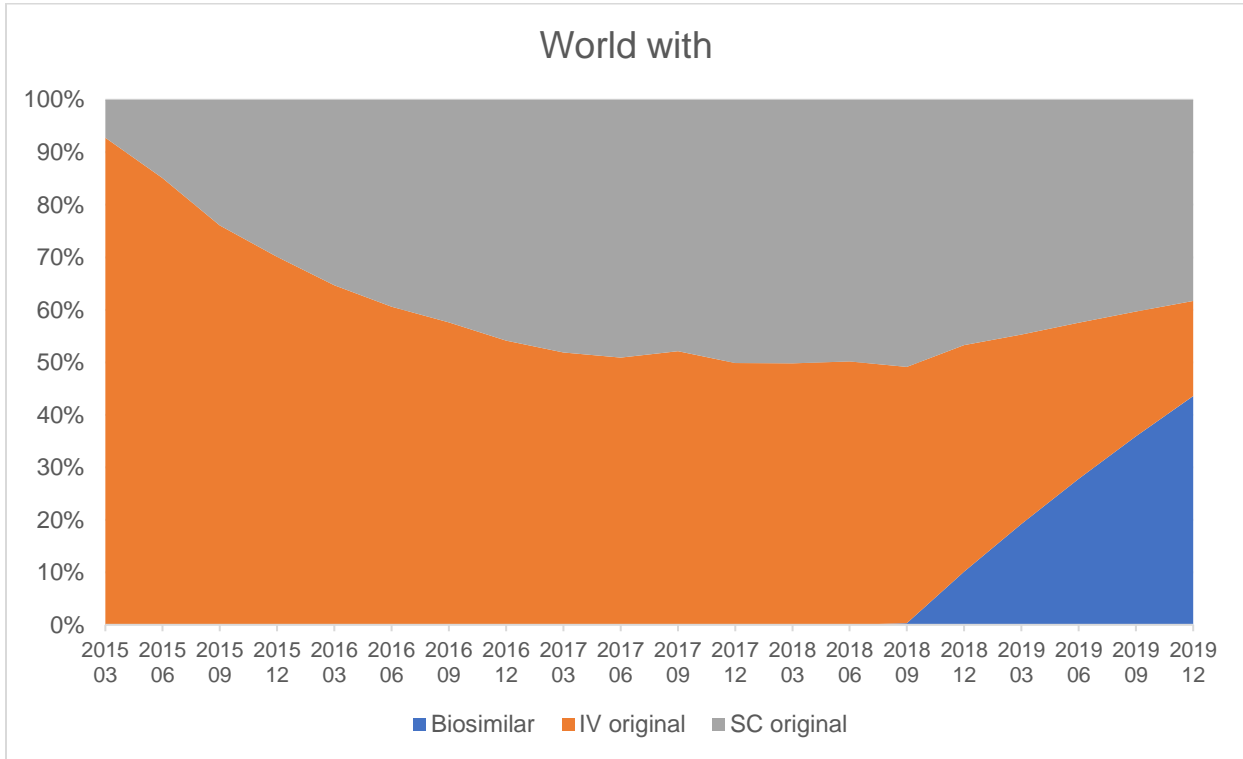
Supplementary Figure 17 Market volume share split between the reference drugs and biosimilars for trastuzumab in France



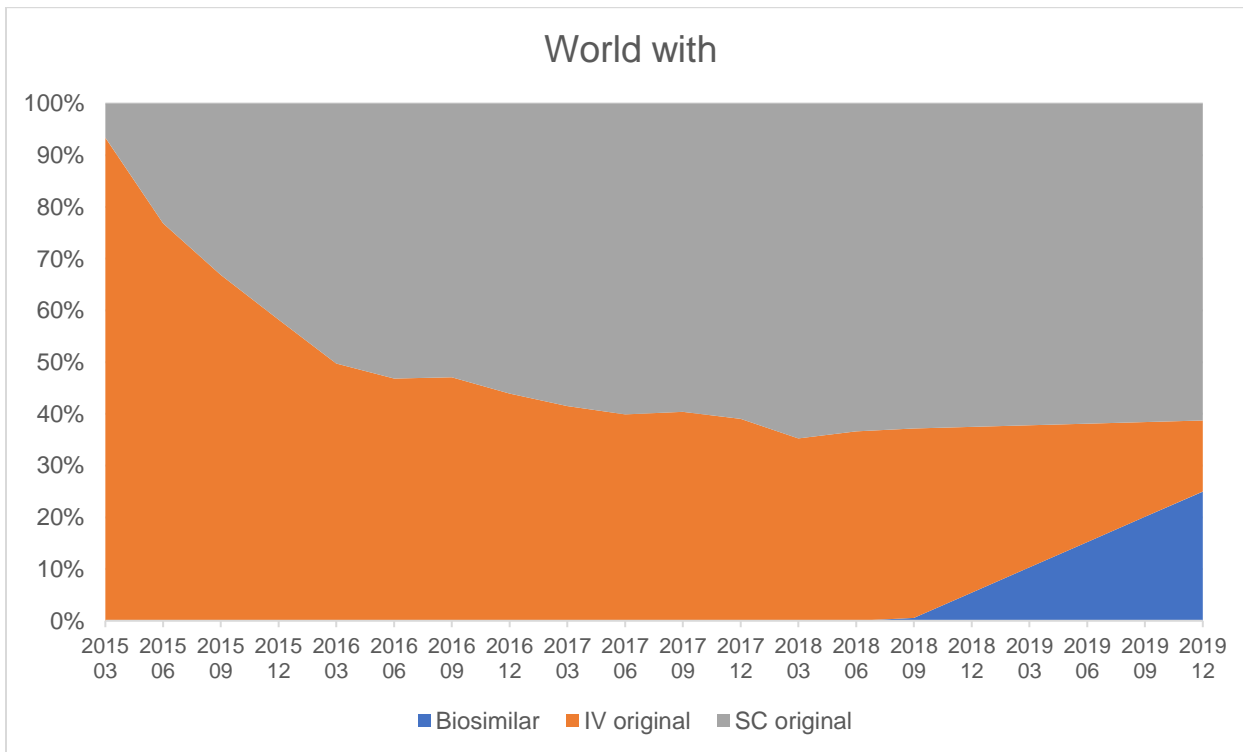
Supplementary Figure 18 Market volume share split between the reference drugs and biosimilars for trastuzumab in Germany



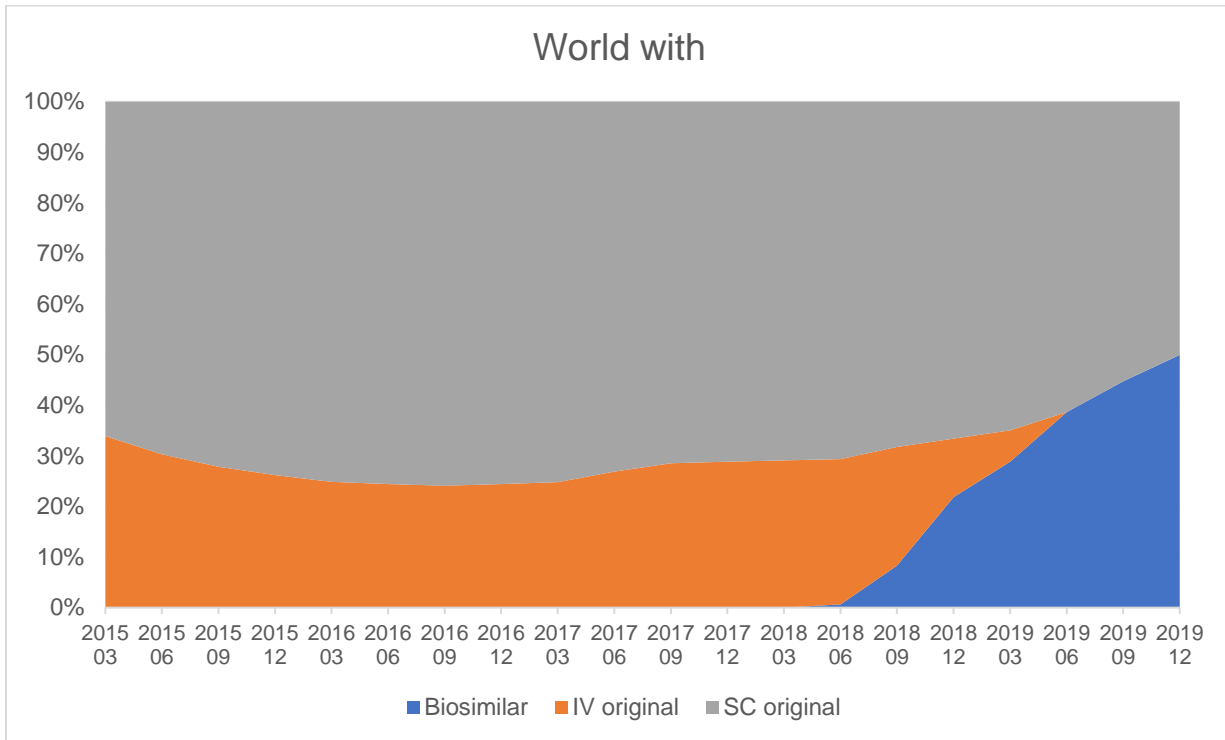
Supplementary Figure 19 Market volume share split between the reference drugs and biosimilars for trastuzumab in Italy



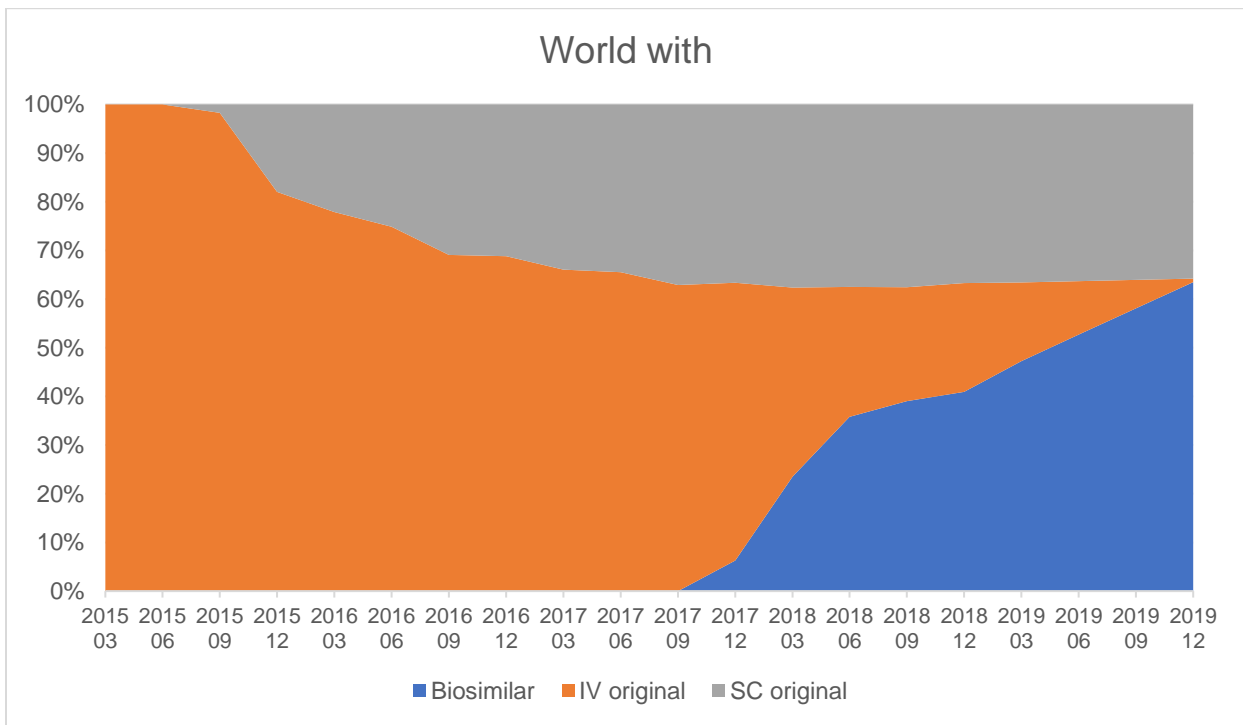
Supplementary Figure 20 Market volume share split between the reference drugs and biosimilars for trastuzumab in Spain



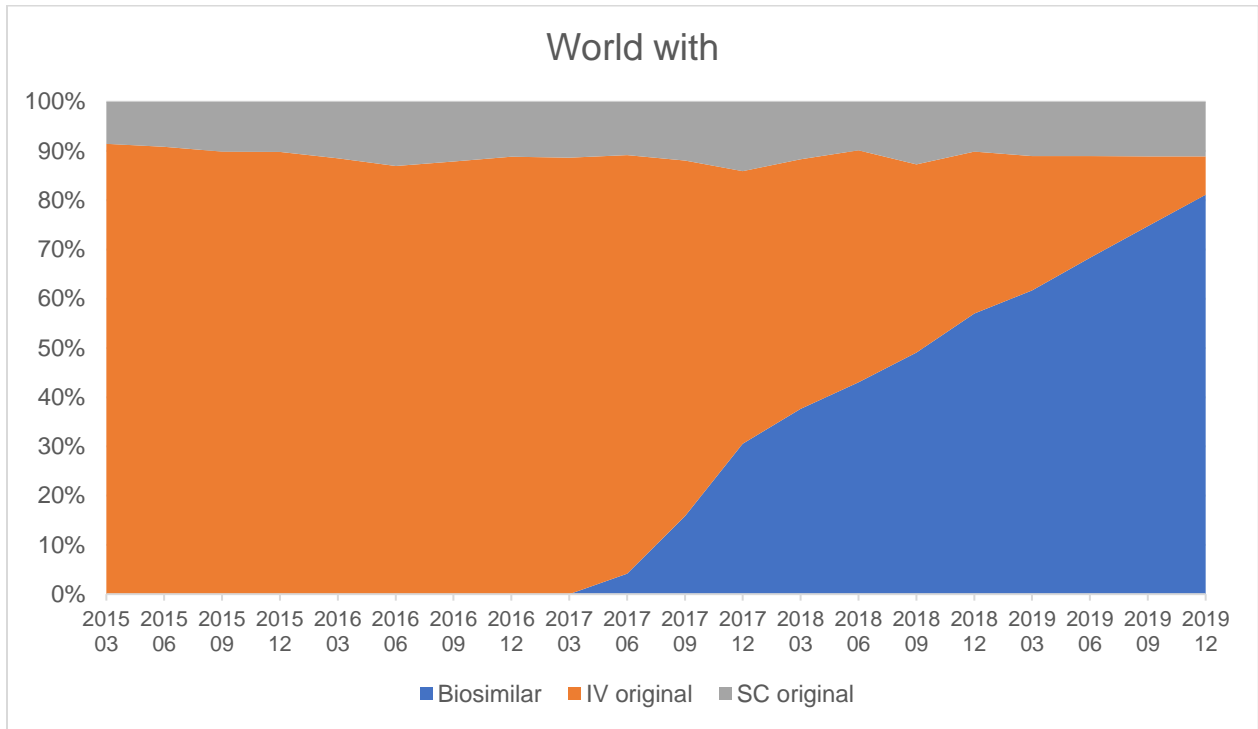
Supplementary Figure 21 Market volume share split between the reference drugs and biosimilars for trastuzumab in the UK



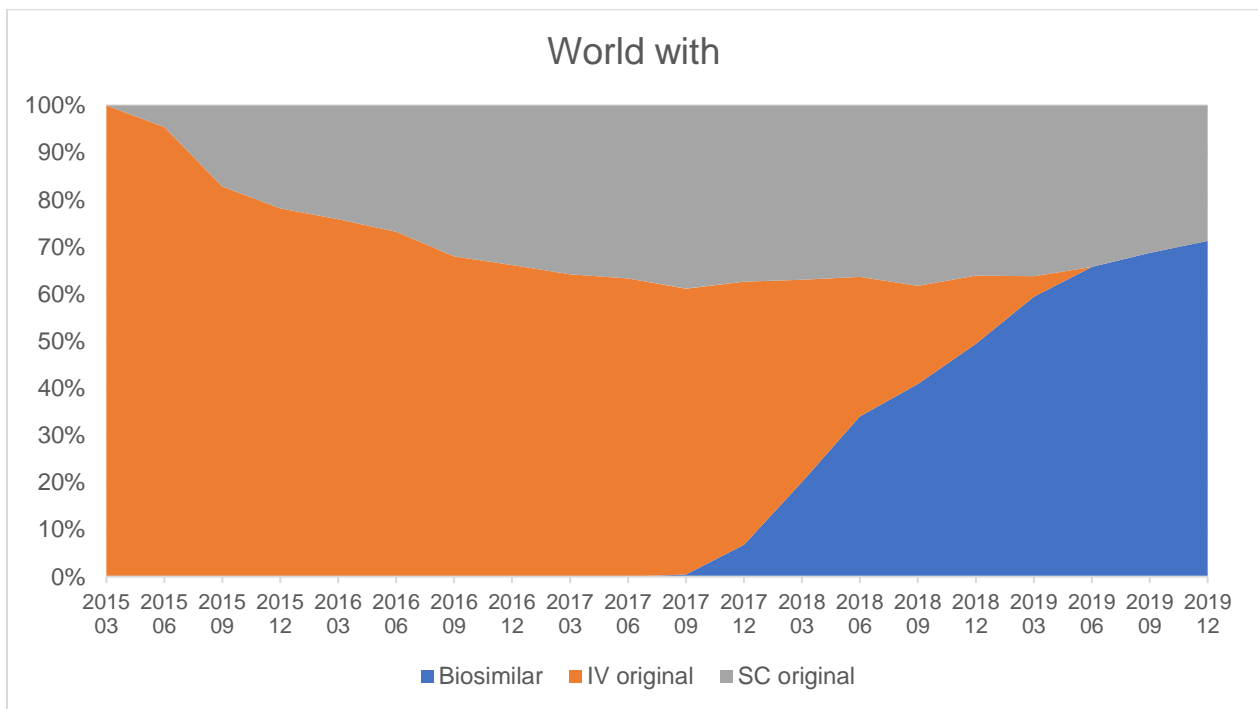
Supplementary Figure 22 Market volume share split between the reference drugs and biosimilars for rituximab in France



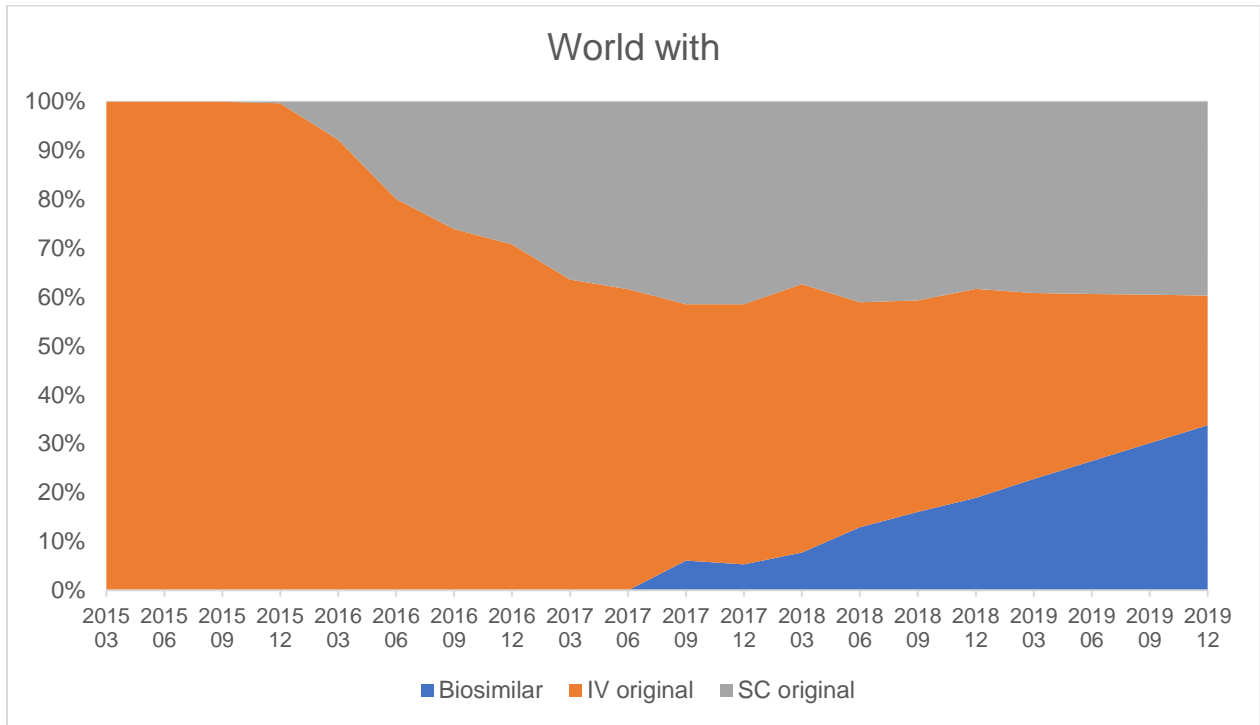
Supplementary Figure 23 Market volume share split between the reference drugs and biosimilars for rituximab in Germany



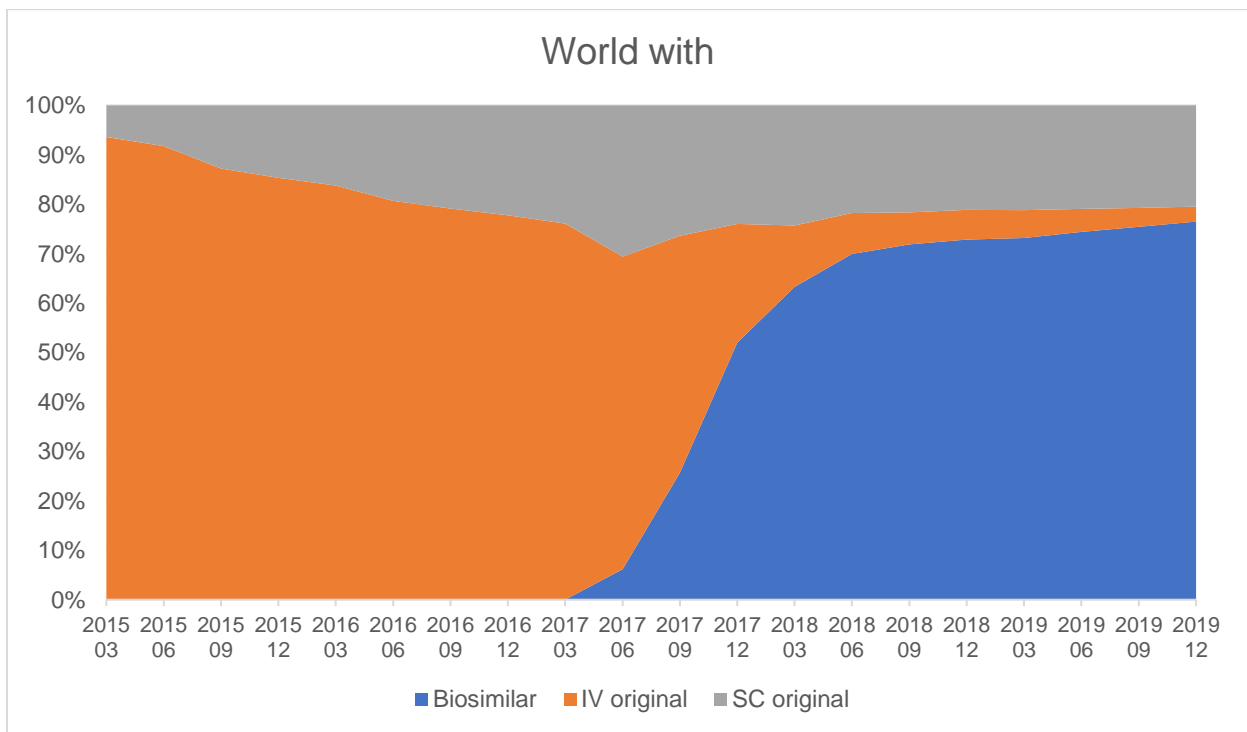
Supplementary Figure 24 Market volume share split between the reference drugs and biosimilars for rituximab in Italy



Supplementary Figure 25 Market volume share split between the reference drugs and biosimilars for rituximab in Spain



Supplementary Figure 26 Market volume share split between the reference drugs and biosimilars for rituximab in Spain



References

1. Office for National Statistics. Overview of the UK Population - ONS [Internet]. 2015 [cited 2020 Nov 26]. Available from: <https://webarchive.nationalarchives.gov.uk/20160105223359/http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/mid-2014/sty---overview-of-the-uk-population.html>
2. Institut national de la statistique et des études économiques. Bilan démographique 2018 [Internet]. [cited 2020 Nov 26]. Available from: <https://www.insee.fr/fr/statistiques/1892086?sommaire=1912926>
3. Bevölkerung in Deutschland: 82,8 Millionen zum Jahresende 2017 [Internet]. Statistisches Bundesamt. [cited 2020 Nov 26]. Available from: https://www.destatis.de/DE/Presse/Pressemitteilungen/2018/09/PD18_347_12411.html
4. Population totale par sexe et âge au 1er janvier 2020, France – Bilan démographique 2019 | Insee [Internet]. [cited 2020 Nov 26]. Available from: <https://www.insee.fr/fr/statistiques/1892086?sommaire=1912926>
5. Popolazione residente al 1° gennaio [Internet]. [cited 2020 Nov 26]. Available from: http://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES1#
6. National Audit Office. Services for people with rheumatoid arthritis 2009 [Internet]. Available from: <https://www.nao.org.uk/wp-content/uploads/2009/07/0809823.pdf>
7. Haute Autorite de Sante. Polyarthrite rhumatoïde : aspects thérapeutiques hors médicaments et chirurgie - aspects médico-sociaux et organisationnels [Internet]. 2007 [cited 2020 Nov 26]. Available from: https://www.has-sante.fr/upload/docs/application/pdf/argumentaire_pr_non_med_071018.pdf
8. Versorgungsforschung in der Rheumatologie [Internet]. springermedizin.de. [cited 2020 Nov 26]. Available from: <https://www.springermedizin.de/versorgungsforschung-in-der-rheumatologie/8387376>
9. Carbonell J, Cobo T, Balsa A, Descalzo MA, Carmona L, SERAP Study Group. The incidence of rheumatoid arthritis in Spain: results from a nationwide primary care registry. *Rheumatology (Oxford)*. 2008;47:1088–92.
10. Benucci M, Cammelli E, Manfredi M, Saviola G, Baiardi P, Mannoni A, et al. Early rheumatoid arthritis in Italy: study of incidence based on a two-level strategy in a sub-area of Florence (Scandicci-Le Signe). *Rheumatol Int*. 2008;28:777–81.
11. Chronic lymphocytic leukaemia (CLL) incidence statistics [Internet]. Cancer Research UK. 2015 [cited 2020 Nov 26]. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence>
12. Monnereau A RL, Maynadié M, Binder-Foucard F, Belot A, Troussard X, Bossard N. Estimation nationale de l'incidence des cancers en France entre 1980 et 2012. 2013.
13. Robert Koch Institut. Krebs in Deutschland für 2013-2014 [Internet]. Available from: <https://www.kup.at/kup/pdf/8742.pdf>

14. Solans M, Osca-Gelis G, Comas R, Roncero JM, Gallardo D, Marcos-Gragera R, et al. Challenges in assessing the real incidence of chronic lymphocytic leukemia: 16 years of epidemiological data from the province of Girona, Spain. *Cancer Causes Control*. 2018;29:379–82.
15. Salvi G. CHRONIC LYMPHOCYTIC LEUKAEMIA: CENSUS OF PATIENTS TREATED IN ITALIAN HAEMATOLOGY UNITS. *Mediterr J Hematol Infect Dis*. 2015;7:e2015056–e2015056.
16. Watts RA, Al-Taiar A, Scott DGI, Macgregor AJ. Prevalence and incidence of Wegener’s granulomatosis in the UK general practice research database. *Arthritis Rheum*. 2009;61:1412–6.
17. Haute Autorite de Sante. MABTHERA 100 mg, solution à diluer pour perfusion Conditionnement B/2 (CIP : 34009 560 600 3 0) MABTHERA 500 mg, solution à diluer pour perfusion Conditionnement B/1 (CIP : 34009 560 602 6 9) [Internet]. 2015 [cited 2020 Nov 26]. Available from: https://www.has-sante.fr/upload/docs/evamed/CT-13904_MABTHERA_PIC_EI_vascularite_Avis2_CT13904.pdf
18. Claus Kroegel. *Klinische Pneumologie: Das Referenzwerk für Klinik und Praxis*. 2013.
19. Catanoso M, Macchioni P, Boiardi L, Manenti L, Tumiati B, Cavazza A, et al. Epidemiology of granulomatosis with polyangiitis (Wegener’s granulomatosis) in Northern Italy: a 15-year population-based study. *Semin Arthritis Rheum*. 2014;44:202–7.
20. Catanoso M, Macchioni P, Boiardi L, Manenti L, Tumiati B, Cavazza A, et al. Epidemiology of granulomatosis with polyangiitis (Wegener’s granulomatosis) in Northern Italy: a 15-year population-based study. *Semin Arthritis Rheum*. 2014;44:202–7.
21. Chung SA, Seo P. Microscopic Polyangiitis. *Rheumatic Disease Clinics*. Elsevier; 2010;36:545–58.
22. Orphanet: Microscopic polyangiitis [Internet]. [cited 2020 Nov 26]. Available from: [https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=IT&data_id=753&Disease\(s\)/group%20of%20diseases=Microscopic-polyangiitis&title=Microscopic-polyangiitis&search=Disease_Search_Simple](https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=IT&data_id=753&Disease(s)/group%20of%20diseases=Microscopic-polyangiitis&title=Microscopic-polyangiitis&search=Disease_Search_Simple)
23. National Institute for Health and Care Excellence. Rituximab for the treatment of recurrent or refractory stage III or IV follicular non-Hodgkin’s lymphoma (Review of TA 37) [Internet]. 2002 [cited 2020 Nov 26]. Available from: <https://www.nice.org.uk/guidance/ta137/documents/follicular-lymphoma-rituximab-final-scope2>
24. Cancer today [Internet]. [cited 2020 Nov 26]. Available from: <http://gco.iarc.fr/today/home>
25. Cancer registration statistics, England - Office for National Statistics [Internet]. [cited 2020 Nov 26]. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2016>
26. Quelques chiffres - Cancer du sein [Internet]. [cited 2020 Nov 26]. Available from: <https://www.e-cancer.fr/Patients-et-proches/Les-cancers/Cancer-du-sein/Quelques-chiffres>
27. Robert Koch Institut. Bericht zum Krebsgeschehen in Deutschland [Internet]. 2016 [cited 2020 Nov 26]. Available from:

https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebsgeschehen/Krebsgeschehen_node.html

28. J G, A A, M C, A M, Jr Q, D R, et al. Cancer incidence in Spain, 2015. *Clin Transl Oncol*. 2017;19:799–825.

29. Baeyens-Fernández JA, Molina-Portillo E, Pollán M, Rodríguez-Barranco M, Del Moral R, Arribas-Mir L, et al. Trends in incidence, mortality and survival in women with breast cancer from 1985 to 2012 in Granada, Spain: a population-based study. *BMC Cancer* [Internet]. 2018 [cited 2020 Nov 26];18. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6090958/>

30. Cancro del seno e della tiroide: un legame stretto | Associazione Italiana Registri Tumori [Internet]. [cited 2020 Nov 26]. Available from: <https://www.registri-tumori.it/cms/contenuto/cancro-del-seno-e-della-tiroide-un-legame-stretto>

31. Haute Autorite de Sante. trastuzumab [Internet]. 2016 [cited 2020 Nov 26]. Available from: https://www.has-sante.fr/upload/docs/evamed/CT-14877_HERCEPTIN_PIC_REEV_Avis2_CT14877.pdf

32. Aragonés N, Izarzugaza MI, Ramos M, Chirlaque MD, Almar E, Martínez C. Trends in oesophago-gastric cancer incidence in Spain: analysis by subsite and histology. *Annals of Oncology*. 2010;21:iii69–75.

33. National Health Service. Upadacitinib for adults with moderate to severe active rheumatoid arthritis after conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) or biologic DMARDs failure. 2017 p. 15.

34. MabThera 1400 mg Solution for Subcutaneous Injection - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Nov 26]. Available from: <https://www.medicines.org.uk/emc/product/5333/smpc>

35. MabThera 100 mg Concentrate for Solution for Infusion - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Nov 26]. Available from: <https://www.medicines.org.uk/emc/product/3801/smpc>

36. Georgi A, Aringer M. Therapiemöglichkeiten nach Nichtansprechen von TNF-Blockern bei rheumatoider Arthritis. :8.

37. Non-Hodgkin lymphoma incidence statistics [Internet]. Cancer Research UK. 2015 [cited 2020 Nov 26]. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence>

38. Federal Joint Committee (G-BA). Obinutuzumab (Gazyvaro®) [Internet]. 2013 [cited 2020 Nov 26]. Available from: https://www.g-ba.de/downloads/92-975-1561/2016-06-13_Modul3_Obinutuzumab.pdf

39. Herceptin 150mg Powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Nov 26]. Available from: <https://www.medicines.org.uk/emc/product/3856/smpc>

40. MabThera 1400 mg Solution for Subcutaneous Injection - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Nov 26]. Available from: <https://www.medicines.org.uk/emc/product/5333/smpc>
41. Documents | Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer | Guidance | NICE [Internet]. NICE; [cited 2020 Nov 26]. Available from: <https://www.nice.org.uk/guidance/ta569/history>
42. Wolff AC, Hammond MEH, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med*. 2007;131:18–43.
43. Saini KS, Azim HA, Metzger-Filho O, Loi S, Sotiriou C, de Azambuja E, et al. Beyond trastuzumab: new treatment options for HER2-positive breast cancer. *Breast*. 2011;20 Suppl 3:S20-27.
44. Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial | Journal of Clinical Oncology [Internet]. [cited 2020 Nov 26]. Available from: https://ascopubs.org/doi/abs/10.1200/jco.2009.27.15_suppl.4556
45. Baretton G, Dietel M, Gaiser T, Kirchner T, Kreipe HH, Quaas A, et al. HER2-Testung beim Magenkarzinom. *Pathologe*. 2016;37:361–6.
46. L'Agence technique de l'information sur l'hospitalisation (ATI). 28Z07Z - Chimiothérapie pour tumeur, en séances [Internet]. 2019 [cited 2020 Nov 26]. Available from: <https://www.aideaucodage.fr/ghm-28z07z>
47. Kassenärztliche Bundesvereinigung. Einheitlicher Bewertungsmaßstab (EBM). 2018.
48. eSalud. eSalud - Información económica del sector sanitario [Internet]. 2017 [cited 2020 Nov 26]. Available from: <http://esalud.oblikue.com/>
49. Prices - Inflation (CPI) - OECD Data [Internet]. [cited 2020 Nov 26]. Available from: [https://data.oecd.org/price/inflation-cpi.htm#indicator-chart%20\(26/02/2019](https://data.oecd.org/price/inflation-cpi.htm#indicator-chart%20(26/02/2019)
50. Regione Lombardia La Giunta. DELIBERAZIONE N° IX / 2946. 2012.
51. Burcombe R, Chan S, Simcock R, Samanta K, Percival F, Barrett-Lee P. Subcutaneous Trastuzumab (Herceptin®): A UK Time and Motion Study in Comparison with Intravenous Formulation for the Treatment of Patients with HER2-Positive Early Breast Cancer. *Advances in Breast Cancer Research*. Scientific Research Publishing; 2013;2:720–6.
52. Rule S, Collins GP, Samanta K. Subcutaneous vs intravenous rituximab in patients with non-Hodgkin lymphoma: a time and motion study in the United Kingdom. *J Med Econ*. 2014;17:459–68.
53. British Oncology Pharmacy Association. BOPA. 2017 [cited 2020 Nov 26]. Available from: <http://www.bopawebsite.org/publications/members-documents>

54. Unit Costs of Health and Social Care 2017 | PSSRU [Internet]. [cited 2020 Nov 26]. Available from: <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/>