Overview of Biobetters

Intravenous to subcutaneous formulation conversion for patient compliance, healthcare savings, and market differentiation

June 2020

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Executive Summary

What Are Biobetters?

- An improved version of biologic for better efficacy, safety and patient compliance, while reducing the overall burden on healthcare
- An opportunity for innovators to delay biosimilars threat and extend product lifecycle while an opportunity for biosimilar companies to differentiate among competitors and potentially evade litigation
- Intravenous (IV) to subcutaneous (SC) conversion of biologics - A prudent approach for biobetter development for >50% of the ~40 biologics facing patent expiry this decade, and beyond

Current Biobetters Landscape

Clinical Development and Regulatory

- EU is the preferred geography for biobetter development - Clinical development timeline is similar to early approved biosimilars including reservations for indication expansion
- Technology used for biobetter development could impact timelines
- Unclear regulatory guidelines and nascent market contributes to overall skepticism
- Celltrion developed biobetter Remsima SC using biosimilar Remsima as the comparator arm – An initiative to reduce dependence on innovator product for clinical development and approval

Market Uptake

- High patient preference for SC biobetters over IV biologics
- However, lack of clarity regarding uptake as compared to biosimilars due to nascent market

The Way Forward

- Biobetters are likely to follow biosimilar's clinical development trends, supportive of global trials and indication expansion
- A robust formulation technology with pharmaceutically accepted and safe excipients will accelerate clinical development
- Patient convenience and reduced overall healthcare burden will drive SC biobetters' market uptake
- Two key considerations for biobetters strategy are:

1. **Technology selection** – Patented, safe, widely applicable and cost effective technology
   - Bhami Research Lab's high concentration protein formulation technology (HiC) offers an effective solution
2. **Molecule selection** – Key selection criteria are chronic disease, dosing and its frequency, healthcare savings, and competitive landscape

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Introduction To Biobetters

Biobetters are an improved version of an existing biological product, providing clinical efficacy or safety benefits, improve patient compliance through convenience or less frequent dosing, reduce the cost burden, etc.

Advantages

Product Differentiation

- **For Biosimilars Focused Companies** - Differentiate amongst the competitors offering conventional biosimilars, thereby gaining significant market share
- **For Innovator Companies** - More effective/ convenient/ safer product can help extend the product's lifecycle and delay biosimilars threat

IP

- Eligibility for patent protection and market exclusivity similar to an innovator molecule
- Potential evasion of patent dance and litigations, thereby avoid delays in product launch
- Flexibility in adoption of proprietary, differentiated and cost effective formulation and process development technologies, while not channelizing resources to imitate the innovators

Healthcare Savings

- Biobetters can lead to healthcare savings at several levels –
  - Improved efficacy or reduced frequency cuts down the number of doses patients require
  - Conversion from IV infusion to SC formulation eliminates hospitalization cost
  - Moreover, self-administration of the drugs saves the overall costs associated with hospital visits

Challenges

Clinical Development

- Biobetters are considered as new molecules and require a more elaborate clinical development as compared to biosimilars, leading to higher investments

Regulatory landscape

- Lack of well-defined development guidelines for Biobetters as compared to biosimilars, where the regulators provide detailed development guidelines

Market Uptake

- While the Biobetters by the innovators (Neulasta, Aranesp, etc.) have gained a dominating position in the marketplace, there is an uncertainty regarding the market uptake of Biobetters to biosimilars

Source- Secondary Research

Biobetter Strategies

Formulation changes of biologics to a more convenient and cost/time effective drug administration is one of the most prudent ways to develop biobetters

	Examples	Value Addition	Challenges
Structural Changes	Amgen's Neulasta (Pegfigrastim) is a peglyated form of Amgen's Neupogen (Filgrastim) Amgen's Aranesp (Darbepoetin alfa) is a hyperglysolated version of Amgen's Epogen (Epoetin Alpha) Roche's Lucentis (Ranibizumab) is a fragment of Roche's Avastin antibody (Bevacizumab)	Neulasta reduced the dosing frequency from daily injections to once every 3 weeks Aranesp reduced the dose frequency from 3 times every week to once every 2 weeks Lucentis penetrates the eye's retina better than the full antibody and is approved for ophthalmic use	Structural changes are difficult to apply to complex molecules
Formulation Changes	Celltrion's Remsima SC is a subcutaneous form of intravenous Infliximab Remsima (CT-P13, Biosimilar of Remicade) Roche's Herceptin Hycela is a subcutaneous version of Roche's intravenous Herceptin (Trastuzumab) Rybelsus (Novo Nordisk) is an oral formulation of subcutaneous Semaglutide	Remsima SC can be self-administered at home by the patients within few minutes as compared to ~ 2 hours for Infliximab IV infusion Hycela is administered in ~5 minutes instead of 30-90 minutes for IV infusion Oral formulation is the most preferred route of administration	Identify a technology that can enable cost-effective formulation changes conversion for a wide range of molecules with acceptable safe and efficacy profile

Source- Secondary Research

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IV To SC Conversion Of Biologics – Need And Challenges

Need For Formulation Changes	• Currently, 80% of the marketed ~ 130 protein based biologics are administered through IV infusion
	• Each infusion consists of high doses, and thus needs high volume of 10 to 100 ml
	  • Such large volumes require intravenous (IV) administration, with patient tethered to infusion set-up
	  • Such IV can take a long time to infuse (30 mins to 6 hours), often in a hospital or a clinic, and several times a week adding to the facility and administrative costs ($750-2700/cycle in the US)
	• Subcutaneous (SC) administration will be much more convenient for patients, while saving cost associated with hospitalization

Challenges with High Concentration Protein Formulations	Usually, the protein concentrations achieved are in the range of 40-60 mg/mL, with a few exceptions of ~100 mg/mL. The challenges with high concentration formulations are: **Stability:** Aggregation, sub-visible and visible particle formation **Viscosity and Administration:** High viscosity (>30 cP) impacting syringe ability, injection time, functionality of devices, etc. **Limited Current Technologies:** Halozyme, Reform Biologics, Arsia Therapeutics and Excelse Bio have begun to address the need however, with a number of disadvantages: • Not applicable to all proteins; High Cost; Toxicity burden as the excipients do not belong to GRAS (Generally Recognized as Safe) category

Source- Primary Research, Secondary Research, MP Analysis

IV To SC Conversion – Advantages

Market Differentiation	• SC biobetters are patent protected and eligible for market exclusivity • For innovators, conversion of IV to SC potentially delays the competition from biosimilars • For e.g. Herceptin's patent in the EU expired in 2014; Herceptin SC took over more than 50% of the Trastuzumab market in Europe after its launch in 2013, prior to the entry of biosimilars • For a biosimilar company, IV to SC conversion offers marketplace differentiation amongst the peers
Patient Convenience	• SC biobetters avoid frequent visits to the hospitals and patients tethered to infusion set up for hours • >80% of patients preferred Herceptin SC and Rituxan SC in their respective clinical trials • Pre-filled syringe (Inflectra SC), auto injectors (SureClick for Enbrel), Pen Injectors (Humira Pen), etc. further enable self-injection

Cost Savings	• SC formulations reduces or eliminates consumables, facility, administrative costs
	• Our analyses suggests that that **Herceptin Hycela potentially saves > $10,000 per patient per year as compared to IV Herceptin,** leading $2.8 Billion in overall annual savings
	  • **Drug cost**: Herceptin SC costs ~14% more compared to Herceptin IV for average patient weight (~70 kg)
	  • **Consumables Cost:** Consumable costs for IV infusions are ~30X higher than SC administration;
	  • **Facility and Administrative Costs:** Herceptin IV administration would require 2-6 hours of clinical facility chair time as opposed to 15-30 min for Herceptin
	• Self-administered SC formulations completely eliminates all of the above costs, resulting in higher cost savings
	• Moreover, IV biologic formulations either have high volumes to process or additional lyophilization steps. SC biobetters with lower volumes can significantly reduce the cost of manufacturing

Source- Company Reports, Secondary Research, MP Analysis

Subcutaneous Biobetters – Several Factors Resulting In Overall Skepticism

Most pharmaceutical companies are skeptical to take up biobetters owing to unclear regulatory guidelines and uncertainty about market uptake. The aspects contributing to the skepticism are:

- Extensive preclinical and clinical data to establish similarity in PK, non-inferior efficacy and safety, and more so if the excipients are not pharmaceutically accepted, adding to the high cost of development
- Current regulatory guidelines do not allow indication expansion with biobetters without indication-specific clinical trials
- Nascent market contributing to the lack of clarity on the market uptake of biobetters

We analyzed the following three prominent biobetters to understand the status quo and the evolution of biobetters landscape (clinical development, regulatory guidelines and market uptake)

Active Ingredient	Biosimilar	Biobetter
Trastuzumab	Kanjinti (Amgen), Ogivri (Mylan/biocon)	Herceptin SC (Roche)
Rituximab	Truxima (Teva Pharmaceuticals), Ruxience (Pfizer)	Rituxan SC (Roche)
Infiximab	Inflectra/Remsima (Celltrion), Renflexis (Merck)	Remsima SC (Celltrion)

In these analyses we have compare the following parameters between biosimilars and biobetters in the subsequent slides - The number of trials required for FDA & EMA approval, number of patients recruited for each trial, the primary and secondary endpoints, additional trials required for indication expansion, and other regulatory marketplace parameters

Clinical Development Of Subcutaneous Biobetters

Inferences	Examples		
	Early approved biosimilar	Trend	Recently approved biosimilar
The length of phase 1 clinical studies is decreasing for biosimilar approval. A similar trend is expected for biobetters.	Truxima (Rituximab, Teva Pharmaceuticals, 2017*) • Phase 1 primary endpoint - PK up to 24 weeks	↘	Ruxience (Rituximab, Pfizer, 2020*) • PK up to 12 weeks
	Inflectra (Infliximab, Pfizer, 2013*) • Phase 1 primary endpoint-PK up to 22 week	↘	Renflexis (Infliximab, Merck, 2016*) • PK up to 10 weeks
Technology used for biobetter development could impact the length of phase 1 study. Halozyme technology's inherent toxicity prompted longer PK studies. However, with pharmaceutically accepted excipients, phase 1 timelines can be shortened.	Biosimilar		Subcutaneous Biobetter
	Truxima (Rituximab, Teva) • PK up to 24 weeks	↗	Rituximab SC (Halozyme technology) • Phase 1 study primary end point-PK up to 126 weeks
	Remsima (Infliximab, Celltrion) • PK up to 22 weeks	≈	Remsima SC (with pharmaceutically accepted excipients) • Phase 1 study primary end point-PK up to 22 weeks
Phase 2 studies are generally required for approval of biobetters leading to more elaborate clinical development timelines as compared to biosimilars.	No Phase 2 studies required for biosimilar development	≠	Roche did a phase 2 patient preference and efficacy study for ~500 patients upto week 24 for approval of Herceptin SC
The scale of phase 3 biobetter clinical trial for the EMA approval is similar to early approved biosimilars.	Truxima (Rituximab, Teva) • PK, efficacy up to week 24 • ~400 patients	≈	Rituxan SC • Phase 3 primary endpoint - PK, efficacy up to week 24 • Number of patients – ~400
	Ogivri (Trastuzumab, Mylan) • Efficacy up to week 24 • 500 patients	≈	Herceptin SC • Phase 3 primary endpoint-PK, efficacy up to week 24 • Number of patients-~600

Source- Secondary Research, Company Reports, MP Analysis

*EU approval year

Biobetters Regulatory Landscape

Like biosimilars, EU has been a preferred first market for biobetters; regulatory landscape looks similar to early stage biosimilar approval with current reservations in indication expansion.

Inferences	Examples
Currently, there are no regulatory guidelines for biobetters. EMA has approved SC biobetters through line extension; USFDA treats biobetters as a new molecule, making the clinical development longer and more expensive.	Approval of Celltrion's SC biobetters • EMA market authorization extension (based on previous IV product approval) with pivotal phase 3 study in Rheumatoid Arthritis (phase 1 study in IBD to support indication expansion) • Additional phase 3 study is ongoing for Crohn's Disease to support traditional BLA for FDA approval
Like biosimilars, biobetters have seen early acceptance in the EU market. Biobetter companies are exploring the EMA route before proceeding with the USFDA regulatory process.	Herceptin SC - Approved in EU in 2013, US in 2019 • Pivotal phase 1 PK study and a phase 3 efficacy study, <700 patients in total for EU approval • Additional phase 3 safety study with ~1900 patients to support USFDA application
Similar to the early stage biosimilars, biobetters require additional trials for indication expansion with USFDA/EMA.	Remsima SC's clinical development is similar to biosimilar Remsima • Beyond an approval for Rheumatoid Arthritis, Remsima SC is conducting additional clinical trials in Crohn's disease for indication expansion

Source- Company Reports, Secondary Research, MP Analysis

Pricing And Market Uptake For Biobetters

Uptake of subcutaneous biobetters is variable due to the nascent market albeit with high patient preference

Inferences	Examples
Most patients prefer the SC biobetters over IV due to convenience and time saved.	• The PrefHER and PrefMab study showed that >80% of patients preferred Herceptin and Mabthera SC over IV
Market uptake of biobetters is susceptible to change based on the changes in the treatment paradigm	• Herceptin SC saw ~50% penetration within 3 years of launch in EU • Low uptake of Herceptin SC post recent launch in US – Preferred dose of Herceptin is now with Perjeta which is still IV
SC Biobetters are expected to be priced higher than competitor biosimilars owing to the value addition, but overall cost of therapy is anticipated to be significantly lower than originator.	• Celltrion's Remsima SC is expected to be priced lower than originator (Remicade), higher than Infliximab biosimilars in the market • Additional cost savings with Remsima SC's associated with hospitalization
SC biobetters are also expected to compete with other biologics in the same therapy area.	• As per Celltrion, Remsima SC will be addressing a $40 bn opportunity competing not only with Infliximab IV but also with other TNF-α Inhibitors

Source- Company Reports, Secondary Research, MP Analysis

Anticipated Evolution Of Biobetter Landscape

In the coming decade, the regulatory and marketplace landscape will evolve favoring SC biobetters

Clinical Development	• Formulation technology with established safety profile will accelerate clinical development • Phase 2 studies will be required to demonstrate efficacy of the differentiated formulation • Although the number of trials/patients will differ on a case-to case basis, the overall scale of clinical development will reduce over the coming decade • Patient preference studies will be inessential as more SC biobetters come to the market
Regulatory	• Global trials in alignment with most regulatory agencies will be accepted • Indication expansion will be allowed in most cases • With the right formulation technology and robust preclinical data package, an abbreviated approval pathway with a bridging study establishing the PK and efficacy will emerge
Pricing and Market Uptake	• In depth research and strategy is required for choosing the right molecule to minimize the risk of low uptake • Competitive pricing, healthcare savings and patient preference will positively impact biobetters' market uptake • With biosimilars competition expected in the coming decade, biobetters will offer the required differentiation for patient acceptance and market penetration

Source- MP Analysis

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1. BRL's Technology
2. Molecule Selection

High Concentration Formulations – The Way Forward

- There are ~40 biologics facing patent expiry in this decade, many more in the next, there is an opportunity to convert at least 50% of those IV biologics to SC formulation
  - For innovators, differentiated formulation can extend lifecycle of these biologics and delay competition from biosimilars
  - For biosimilar companies, SC biobetters provide market differentiation along with new IP, market exclusivity and potential circumvention of innovators' patent dance
  - Potential to reduce the overall burden on healthcare
- MP group, with its >3 decades of global biopharma experience and deep understanding of the biosimilars/biobetters space can help catalyze your biobetters strategy, especially with two of the most important considerations -
  1. Identifying an appropriate, cost effective formulation platform applicable to a wide range of biologics
  2. Identifying the key molecules for IV to SC conversion
- One such formulation technology is Bhami Research Lab's globally patented, widely applicable and completely safe high concentration protein formulation platform (HiC)
  - BRL is a biotech start-up based out of Mangalore, India, that develops solutions for core challenges in protein therapeutics development

Source- MP Analysis

BRL's High Concentration Protein Formulation Technology

BRL's high concentration, globally patented platform with GRAS category excipients addresses most problems with biologics formulations, enabling IV to SC conversion of a wide range of molecules

Salient features of BRL's technology are:

- Protein conc. >250 mg/ml; viscosity between 20-25 Cp enabling injection even through 29G needle
- Applicable to a range of protein/MAbs
- Stable at 4°C, 25°C and 40°C; no signs of aggregation (6 months stability data available)
- All reagents belong to 'Generally Recognized as Safe' (GRAS) category; no toxicity related to the technology
- pH between 6-7
- Doesn't contain arginine, the most commonly used viscosity reducing agent
    - Appropriate for ophthalmic formulations

Competitive Landscape & Challenges With Current Technologies

BRL's HiC technology has several advantages over existing technologies

Parameters	Arsia Therapeutics	Reform Biologics	Halozyme, Inc.	BRL
Lead Compound	Camphorsulfonic acid derivatives	Caffeine	Hyaluronidase (Approved drug)	Nicotinic Acid + Tryptophan – GRAS ingredient
Amount of excipient Needed	BGG: 93 mg (Protein Conc. 260 mg) – 44% Reduction in Viscosity	BGG: 22 mg (Protein Conc. 280 mg) – 37% Reduction in Viscosity	75 to 150 USP units	16 mg - HGG (Protein Conc. 270 mg) with 75% reduction in Viscosity
Viscosity Reduction	Works on only a limited number of tested proteins	Tested only on BGG. No other data available (50 cP).	Viscosity is not an issue since large volume can be injected	Works on all the tested proteins (7 commercially available biologics)
Stability	100 days at 4°C and 7 days at RT.	No Stability data Available	Stable for 2 years at 4°C	6 months at 4 and 25°C. Further studies on-going
Toxicity	No Toxicological data available.	Serious toxicity was seen ≥ 50 mg/L of blood	Toxicity is rare. Thrombosis or hypersensitivity reaction during injection	These excipients are extensively used in parenteral formulation
Available for partnership	No	No	Yes	Yes
Ophthalmic Use	No	No	No	Yes

In addition to the technologies mentioned above, Excelse Bio and Alteogen have begun addressing the need for HiC formulations. The excipients used by them are not GRAS category-adding to the toxicity burden of the molecules. Moreover, these platforms are not applicable to all proteins.

Source- Company Reports, Secondary Analysis

Indicative

Key Parameters For Strategically Choosing The Ideal Molecule

Parameter	Inclusion Criteria
Route of administration	IV infusion
Treatment type	Chronic treatment (>6 months), Monotherapy (or combination therapy if the entire combination can be converted to subcutaneous delivery)
Dose	> 150mg
Frequency of administration	Once a week to once every 12 weeks
Time required for IV infusion	> 30 min
Originator molecule Revenue	> $ 1 bn annually
Competitive Landscape	At least 4 biosimilars approved/in development - SC biobetters can provide competitive edge

- A few existing subcutaneous formulations can also be considered for high concentration formulations, for e.g.
  - Possibly reduce the dosing frequency (molecules like Etanercept - administered every week)
  - Reduce the injection volume (molecules with high injection volumes such as Omalizumab -2.5 mL or Denosumab-1.7 mL)
- The next slide presents an indicative list of wave 1,2 and 3 molecules that can be considered for biobetter development

Source- Company Reports, Secondary Research, MP Analysis

Indicative

Ideal Molecules For IV To SC Conversion

	Molecule	Originator Molecule	Patent Expiry EU	Patent Expiry US	Therapy Area	Average Dose	Frequency	Time for IV	Global Sales 2019	BS Approved in EU/US	BS in Development
Wave 1	**Rituximab**	Rituxan (Genentech)	2013	2018	Oncology	640 mg	Weekly-every 4 weeks	180-240 min	$ 6.7 bn	3	10
	Trastuzumab	Herceptin (Genentech)	2014	2019	Oncology	420 mg	Every 3 weeks	90 min	$ 6.2 bn	5	8
	Natalizumab	Tysabri (Biogen)	2015	2015	Immunology	300 mg	every 4 weeks	60 min	$ 1.9 bn	-	1*
	Infliximab	Remicade (Jannsen)	2015	2018	Immunology	350 mg	Every 6-8 weeks	120 min	$ 4.4 bn	4	4
	Bevacizumab	Avastin (Genentech)	2022	2019	Oncology	350-1050 mg	every2-3 weeks	30-90 min	$ 7.3 bn	2	8
Wave 2	**Eculizumab**	Soliris (Alexion)	2020	2021	Hematology	1200 mg	every 2 weeks	35 - 120 min	$ 3.9 bn	-	10
	Ado-trastuzumab emtansine	Kadcyla (Genentech)	2023	2026	Oncology	250 mg	every 3 weeks	30-90 min	$ 1.4 bn	-	1*
Wave 3	**Pertuzumab (+Trastuzumab)**	Perjeta (Genentech)	2023	2027	Oncology	420 mg each	every 3 weeks	30-60 min	$ 3.6 bn	-	5

* Even though competition is low, SC biobetters can provide a more convenient option for patients, while evading patent dance

Source- Company reports, Secondary Research

Case Study: Remsima SC - Biobetter Of Biosimilar

An initiative to differentiate among peers using biosimilar as the comparator arm and reducing the overall cost of development

	Case Study	Opportunity for Biosimilar Company
Biosimilar	Remsima/Inflectra (Celltrion), Originator-Remicade (Janssen)	
Biobetter	Remsima SC (Celltrion)	High concentration SC formulation
Development & Approval	• Remsima SC was developed using Remsima as the comparator arm instead of Remicade (Remsima captures ~60% Infliximab sales in EU) • Pivotal phase 3 trial with ~400 Rheumatoid Arthritis patients to evaluate efficacy of infliximab SC vs IV • ~1400 IV doses of Remsima used for the trial- Remsima significantly cheaper than Remicade, saving substantial drug cost for the trials	• Companies can develop biobetters using biosimilars (with high market uptake) as comparator leading to significant cost savings • The cost advantage is even higher if one's own biosimilar is used
Market Opportunity	Celltrion is addressing an opportunity >$40 bn with Remsima SC • Initiating Remsima SC for naive patients • Converting patients on Infliximab IV • Competing with other anti-TNF-α drugs	• SC biobetters can potentially capture a significant market share for the targeted therapy area owing to market differentiation and patient convenience
Pricing Strategy	Remsima SC is priced lower than the originator but higher than biosimilars considering the following advantages: • Time and cost saved with subcutaneous injection as compared to IV infusion • Support tech platform for patient and clinicians to assist with self-injection, nursing interaction and collect data on patient outcomes	• SC biobetters if priced strategically, considering the added value but also keeping in mind the biosimilar competition, could lead to high market penetration

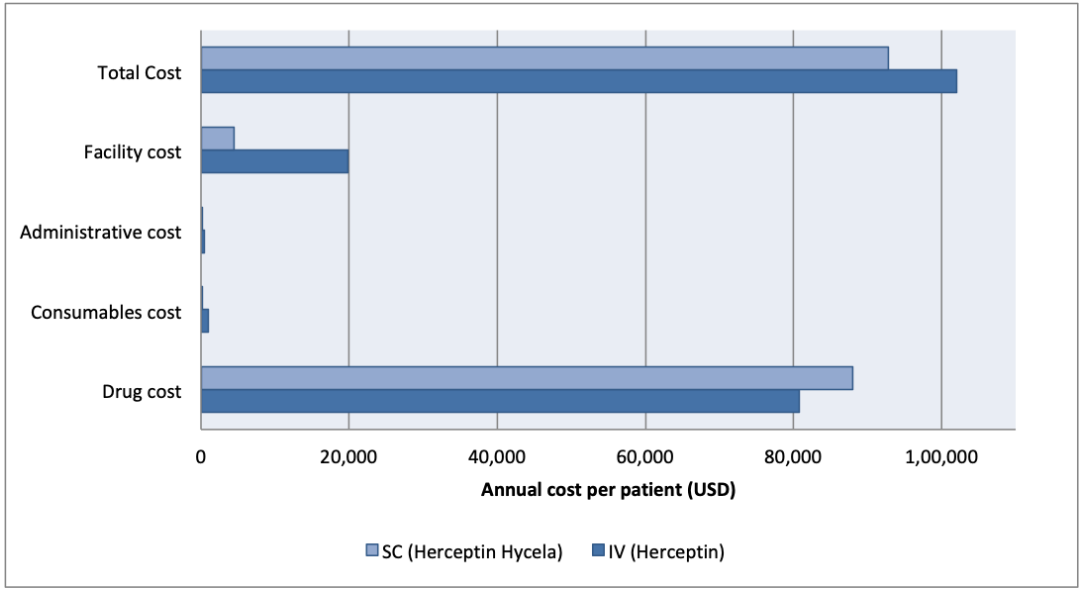
Source- Company Reports, Secondary Research, MP Analysis

Annexure

Significant Cost And Time Saved Subcutaneous Biobetters

One of the most important drawback of IV drug delivery is the cost and time associated with it. We have done a cost analysis (in USD) of Herceptin SC vs Herceptin IV to understand the cost benefit associated with subcutaneous biobetters.

- **Drug cost**
  - Herceptin's average list price is ~ $4300 for a 420 mg single use vial –Dose depends on patient's BSA
  - The loading dose would require two vials of Herceptin for average patient weight (~70 kg), and one for maintenance dose
  - Herceptin Hycela costs ~ $4900 for a single injection
- **Consumables Cost**
  - Herceptin IV infusion would require infusion pumps, saline, IV tubing, Bacteriostatic water, etc. which increases the consumable costs 30 x as compared to subcutaneous delivery
- **Facility and Administrative Costs**
  - Herceptin IV infusion would require 2-6 hours of clinical facility chair time as opposed to 15-30 min for subcutaneous delivery of Herceptin (including the preparation and adverse effect monitoring time)
  - Facility costs are significantly lower for SC delivery due to the time saved.
  - Administrative cost consists of cost associated with preparation, drug administration, monitoring and post administration surveillance. Administrative cost for IV is almost double as compared to SC.



Reduced Burden on Healthcare:

- Overall, Herceptin Hycela could save > $10,000 per patient per year depending on the patient weight
- Each year ~ 1.4 million cases of breast cancer are diagnosed worldwide and 15-20% are HER2 positive
- Herceptin SC has the potential to save $2.8 Billion USD per year as compared to Herceptin IV
- Herceptin Hycela is administered in a clinical facility, biobetters approved for at-home administration present an opportunity to save >$20,000 per patient, per year- compared to IV resulting in significantly reduced burden on the healthcare system

Source- Company Reports, Secondary Research, MP Analysis

Clinical Development Of SC Biobetters- Trastuzumab

	Ogivri		Kajinti		Herceptin SC	
	EU	**US**	**EU**	**US**	**EU**	**US**
Approval Year	2018	2017	2018	2019	2013	2019
Approved Indications	Adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer		Adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer		Adjuvant breast cancer, metastatic breast cancer	
Phase 1						
Number of patients	132		157		66	
Indications	Healthy male volunteers		Healthy male volunteers		Healthy Male Volunteers and HER2 Positive Female Patients	
Primary Endpoint	PK at 10 weeks		PK after a single dose		PK upto 5 months	
Phase 2						
Number of patients					488	
Indications					Breast cancer	
Primary Endpoint					Patient preference at week 24	
Phase 3						
Number of patients	500		725		596	
Indications	Metastatic breast cancer		Breast cancer		Breast cancer	
Primary Endpoint	Efficacy at week 24		Efficacy at 15 weeks		PK, Efficacy at 24 weeks	
Additional Studies						
Number of patients						1864
Indications						Breast cancer
Primary Endpoint						Safety and tolerability for 1 year
Notes						
	Approved later in the EU due to withdrawal of application of Ogivri in 2017 as GMP certificate for the manufacturing site of the product could not be obtained in the time available					
Notes					Line extension application	BLA

Source- Company Reports, Secondary Research

Clinical Development Of SC Biobetters- Rituximab

	Truxima		Ruxience		Rituxan SC	
	EU	**US**	**EU**	**US**	**EU**	**US**
Approval Year	2017	2018	2020	2019	2014, 2016 (CLL)	2017
Approved Indications	NHL, CLL, RA, GPA, MPA, PV	NHL, CLL	NHL, CLL, RA, GPA, MPA, PV	NHL, CLL, GPA, MPA	NHL, DLBCL, CLL	FL, DLBCL, CLL
Phase 1						
Number of patients	154		220		281	
Indications	Rheumatoid Arthritis		Rheumatoid Arthritis		Follicular Lymphoma	
Primary Endpoint	PK upto week 24		PK upto 12 weeks		PK upto 29 months	
Phase 1/2					**Phase 1**	
Number of patients					240	
Indications					Chronic lymphocytic leukemia	
Primary Endpoint					PK at upto 24 weeks	
Phase 3						
Number of patients	384		394		410	
Indications	Rheumatoid Arthritis		Low Tumour Burden Follicular Lymphoma		Follicular Non-hodgkin's lymphoma	
Primary Endpoint	PK, efficacy over 24 weeks		Efficacy at week 26		PK at 21 weeks, efficacy upto week 24	
Additional Studies	**Phase 3**					**Phase 3**
Number of patients	140					572
Indications	Advanced follicular Lymphoma					DLBCL
Primary Endpoint	PK at week 12, efficacy at week 24					Efficacy upto 24 weeks
Additional Studies		**Phase 3**				**Phase 3**
Number of patients		174				743
Indications		Low Tumour Burden Follicular Lymphoma				Follicular Non-hodgkin's lymphoma
Primary Endpoint		Efficacy at 7 months				Patient preference upto 32 weeks
Commercial						
Notes		Seeked approval only in oncology due to patent exclusivity landscape		Not approved in RA due to patent exclusivity terms	EU approval for NHL and DLBCL in 2014 followed by CLL in 2016	

Source- Company Reports, Secondary Research

Clinical Development Of SC Biobetters- Infliximab

	Remsima/ Inflectra		Flixabi/Renflexis		Remsima SC	
	EU	US	EU	US	EU	US
Approval Year	2013	2016	2016	2017	2019	-
Approved Indications	Rheumatoid Arthritis(RA), Ankylosing Spondylitis(AS), Ulcerative Colitis(UC), Crohn's disease(CD), Psoriatic Arthritis(PsA), Psoriasis		Rheumatoid Arthritis(RA), Ankylosing Spondylitis(AS), Ulcerative Colitis(UC), Crohn's disease(CD), Psoriatic Arthritis(PsA), Psoriasis		Rheumatoid Arthritis	Not approved yet
Phase 1						
Number of patients	257		159		38	
Indications	Ankylosing Spondylitis		Healthy volunteers		Healthy volunteers	
Primary Endpoint	PK equivalence at week 22		PK equivalence for 10 weeks		Safety and PK over 12 weeks	
Additional Studies					Phase 1	
Number of patients					218	
Indications					Healthy volunteers	
Primary Endpoint					PK over 12 weeks	
Additional Studies					Phase 1	
Number of patients					170	
Indications					Ulcerative Colitis, Crohn's disease	
Primary Endpoint					PK at week 22	
Phase 3						
Number of patients	617		584		412	
Indications	Rheumatoid Arthritis		Rheumatoid Arthritis		Rheumatoid Arthritis	
Primary Endpoint	PK equivalence at week 30, Efficacy (secondary EP)		Efficacy at week 30		Efficacy at Week 22	
Additional Studies						
Number of patients		220				600
Indications		Crohn's Disease				Crohn's disease
Primary Endpoint		Efficacy at Week 6				Efficacy at week 54
Notes						
Notes	EU approval for all the indications after extrapolation from Rheumatoid Arthritis, Ankylosing Spondylitis studies	Another phase 3 trial involving patients with Crohn's disease for approval for all indications			EU seeking approval for IBD on basis of Phase 1 study	

Source- Company Reports, Secondary Research

Ideal SC Formulation For Differentiated Biosimilars Development

	Molecule	Originator Molecule	Patent Expiry US	Patent Expiry EU	Therapy Area	Average SC Dose	Volume	Frequency	Global Sales 2019 (USD)	BS approved/ Marketed in EU/US	BS In Development
Wave 1	Tocilizumab	Actemra (Genentech)	2015	2017	Immunology	162 mg	0.9 mL	Every 1-2 weeks	$ 2.4 bn	-	3
	Abatacept	Orencia (BMS)	2019	2017	Immunology	125 mg	1 mL	Every week	$ 3 bn	-	-
	Etanercept	Enbrel (Amgen)	2028	2015	Immunology	50 mg	1 mL	Every week	$ 5.2 bn	2	6
	Omalizumab	Xolair (Genentech, Novartis)	2017	2017	Respiratory	150-375 mg	1-2.5 mL	Every2-4 weeks	$ 2 bn	-	2
	Adalimumab	Humira (Abbvie)	2023	2018	Immunology	40 mg	0.8 mL	Every 2 weeks	$ 19.2 bn	7	11
Wave 2	Golimumab	Simponi (Jannsen)	2024	2024	Immunology	50 mg	0.5 mL	Once a month	$ 2.2 bn	-	2
	Ustekinumab	Stelara (Jannsen)	2023	2024	Immunology	45-90 mg	0.5/1 mL	Every 8-12 weeks	$ 6.4 bn	-	4
Wave 3	Denosumab	Xgeva (Amgen)	2025	2025	Oncology	120 mg	1.7 mL	Every 4 weeks	$ 1.9 bn	-	2

Source- Company Reports, Secondary Research

THANK YOU.

We invite you to write to us -

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