Biosimilars Clinical & Regulatory Strategies Encompassing the Needs of East to West

Suzhou, China, 20 November 2014

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Glasgow, UK

Products

- Growth factors
- Monoclonal antibodies
- Hormones

Indications

- Rheumatoid Arthritis
- Oncology
- Haematology
- Neutropenia
- Renal disease
- IVF

Projects include

- EMA and FDA interaction
- Clinical, Nonclinical & Regulatory support for mAbs in EU and USA
- “Buy side” and “sell side” due diligence for US, EU and RoW
- Setting up joint venture between German and Chinese companies
- Detailed development strategic analyses for mAbs
- Supporting major manufacturing change for large biotech

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Content

- Challenges for Global Development & Marketing of Biosimilars
  - The Commercial Drivers
  - Regulatory Obstacles
  - Clinical Challenges
- Suggestion to improve Global Access to Biosimilars
  - Regulatory Harmonization
  - Clinical Trial Strategies
  - Partnering

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Truly Global Biosimilars: A Summary of the Problem

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Is it really possible to have a global biosimilar development programme?

I may not have the complete answer, but I hope to clarify the question and provide some clues…….

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COMMERCIAL DRIVERS, LIKELY MARKET SCENARIO

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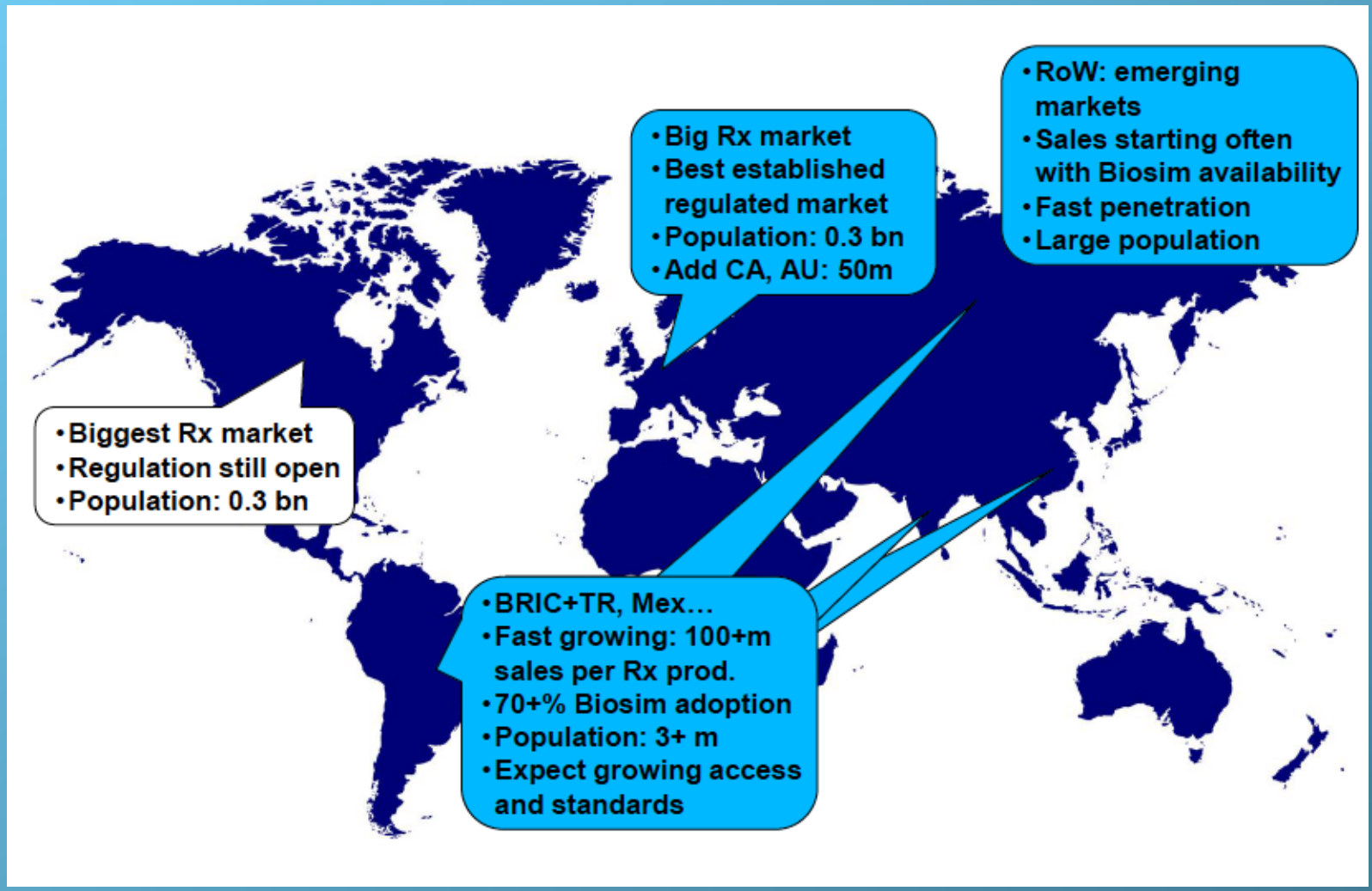
Comparison of the Biosimilars Markets



Until 2020, most ….

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….will be ex-USA

A few words on China

- Pharma Intelligence references **about 40%** of all current biologic sales in China (over 100 products) to be **biosimilars** (but mostly copies).
- This is a large market expected to grow to $2Bn by 2017
- Companies may undertake full development programs in order to gain registration.
- *Recently issued draft Biosimilars regulatory guidance October 2014*

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Biologics are some of the top selling drugs

Drug Name	Company	2013 in bUSD	2012 in bUSD	Change, %	Class
Humira	Abbvie/Abbot	**10.66**	9.27	**14.99**	mAb
Remicade	JNJ, Merck	**8.94**	8.22	**8.76**	mAb
Rituxan/MabThera	Roche, Biogen Idec	8.92	8.65	3.12	mAb
Advair/Seretide	GSK	8.78	8.4	4.52	small mol.
Enbrel	Amgen, Pfizer	**8.33**	7.96	**4.65**	mAb
Lantus/Insulin Glargine	Sanofi	7.85	6.65	18.05	rProtein
Avastin/Bevacizumab	Roche	7.04	6.49	8.47	mAb
Herceptin/Trastuzumab	Roche	6.84	6.62	3.32	mAb
Crestor/Rosuvastatin Cal.	AstraZeneca	5.99	6.62	-9.52	small mol.
Abilify/aripiprazole	Otsuka, BMS	5.27	4.09	28.85	small mol.
Cymbalta/duloxetine	EliLilly,Shionogi	5.19	5.08	2.17	small mol.
Gleevec/imatinib mesylate	Novartis	4.69	4.68	0.21	small mol.
Lyrica/pregabalin	Pfizer	4.6	4.16	10.58	small mol.
Neulasta/pegfilgrastim	Amgen	4.39	4.09	7.33	rProtein
Copaxone	Teva	4.33	4	8.25	polypeptide
Revlimid/lenalidomide	Celgene	4.28	3.77	13.53	small mol.

The Top 8 Biologic Blockbusters had revenue of $63BN in 2013

Brand name	Active ingredient	Type	Class	Treatment	Company	2013 global sales (US$ billion)	Patent expiry EU/US [2]
Humira	adalimumab	Antibody	TNF inhibitor	Arthritis	Abbott/Eisai	10.7	Apr 2018/ Dec 2016
Remicade	infliximab	Antibody	TNF inhibitor	Arthritis	Merck/Mitsubishi	8.9	Aug 2014/ Sep 2018
Rituxan/MabThera	rituximab	Antibody	Anti-CD20	Arthritis, NHL	Roche/Biogen-Idec	8.6	Nov 2013/ Dec 2018
Enbrel	etanercept	Antibody	TNF inhibitor	Arthritis	Amgen/Pfizer/Takeda	8.3	Feb 2015/ Nov 2028
Lantus	insulin glargine	Protein	Insulin receptor	Diabetes	Sanofi	7.8	2014/2014
Avastin	bevacizumab	Antibody	Anti-angiogenesis	Cancer	Roche	7.0	Jan 2022/ Jul 2019
Herceptin	trastuzumab	Antibody	Anti-HER2	Breast cancer	Roche	6.8	Jul 2014/ Jun 2019
Neulasta	pegfilgrastim	Protein	G-CSF	Neutropenia	Amgen	4.4	Aug 2017/ Oct 2015

So, with such massive sales, what's the problem?

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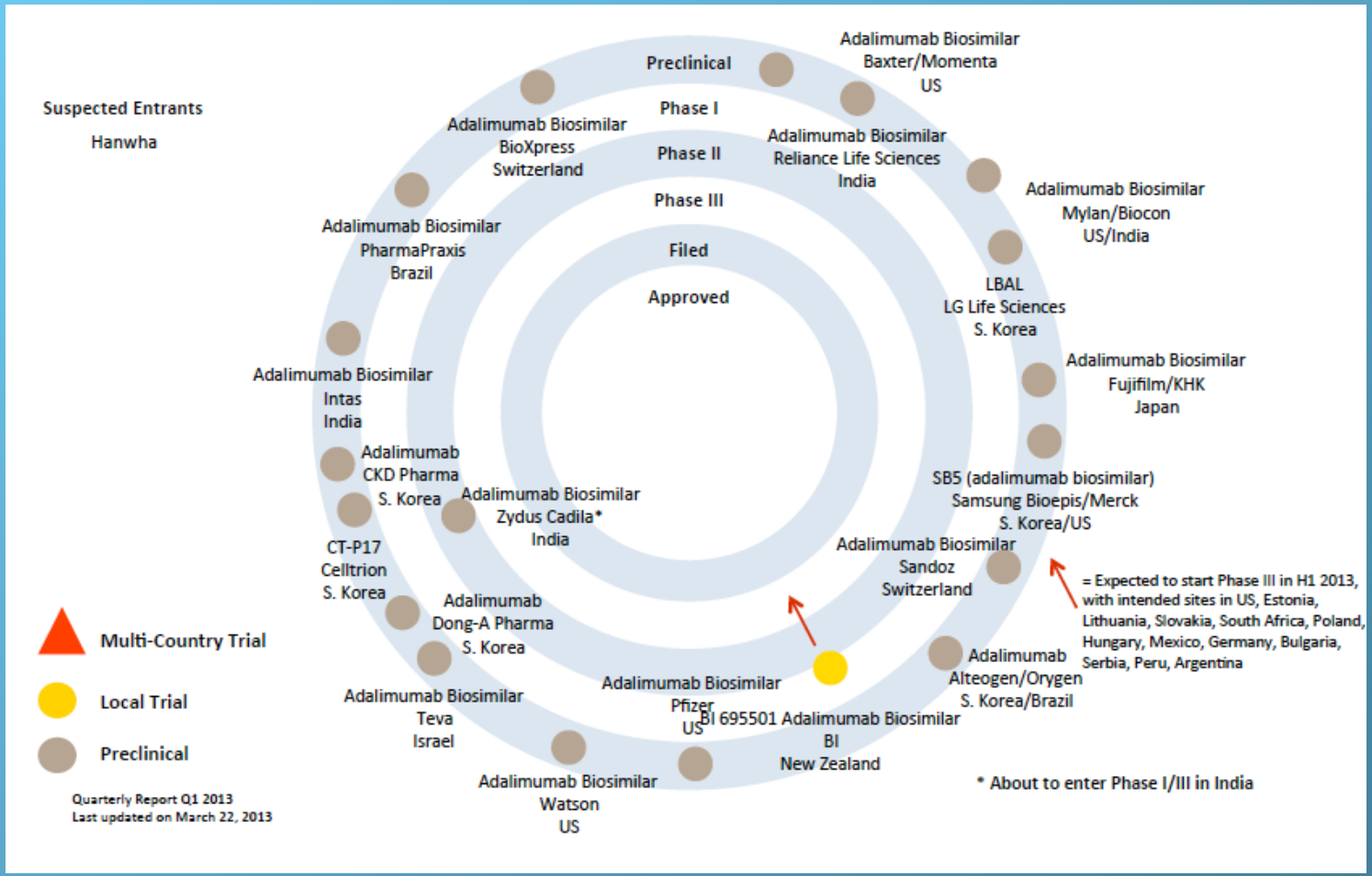
19 Avastin (Bevacizumab) competitors have been identified……

Company	Product code (if available)	Development stage
Actavis; Amgen	NA	Phase 1
Biocad	BCD-021	Phase III
Biocon Corporation	NA	Pre-Clinical
BioXpress	NA	Development (Status Unclear)
Boston Oncology LLC	NA	Pre-Clinical
Celltrion Inc.	CT-P16	Discovery
Dr. Reddy's Laboratories; Merck Serono	NA	Pre-Clinical
Fujifilm Kyowa Kirin Biologics	FKB238	Pre-Clinical
Grupo Insud	NA	Discovery
Harvest Moon Pharmaceuticals USA Inc	NA	Approved for Marketing
Hospira	NA	Discovery
Inbiopro Solutions Pvt Ltd	IBPMOO2BZ	Clinical Development (Phase N/A)
Intas Pharmaceuticals	NA	Discovery
Mabpharma Pvt Ltd (Cipla Ltd)	NA	Discovery
Mabxience; Chemo Sa	mAbx02	Clinical Development (Phase N/A)
Oncobiologics, Inc.	NA	Pre-Clinical
PlantForm Corporation	NA	Pre-Clinical
Reliance Life Sciences Pvt Ltd	R-TPR-023	Phase III
Viropro Inc.	NA	Discovery

And at least as many Adalimumab (Humira) ……



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Avastin (Bevacizumab) competitor scenario

Company	Pre-Clinical	IND	Phase 1 Start	Phase 3 Start	U.S. Launch	Assumed timing to market
Hospira	Q2-2015	Q4-2015	Q1-2016	Q2-2017	Q3-2021	2nd or 3rd
Pfizer	Ongoing	Nov 2013	Q4 2013	Q1 2015	Q4 2019	1st
Amgen	Complete	Filed	Completed	Q3-2015	2019	2nd?

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Costs, Risks and Margins – Assumptions of One Major Player for Avastin

Est. Development cost	**$175M - $225M**	**Preclinical: $20M - $30M** **Phase 1: $15 - $20M** **Phase 3: $120M - $150M** **Registration: $20M**
Probability of Regulatory Success	**60 – 70%**	**Phase 1: 85%** **Phase 3: 85% - 90%** **Registration: 90%** **Assumes commercial scale batches from Ph1**
Biosimilar class peak sales / max for 1 product	**50% / 30% at 5 yrs**	**Class peak sales at 4 yrs. Assumed no. entrants = 4-5**
Biosimilars pricing	**Innovator drops 30% at launch**	**-3% per year to max of -40% vs innovator**
Margin on sales	**60 – 70%**	**Assumes best in class COGS, high titres**

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Conclusions on Commercial / Business Risks

- Competition in markets will be fierce
- Not as risky as novel therapeutics:
  - no drug discovery phase,
  - originator data reassurance, but...
- Risk of not recovering development investment is relatively high – limited number of entrants
- This is due not only to market forces and technical risks, but clinical development risks (time & cost) and global regulatory divergences

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Phase-1 Enabling Comparability Assessment Include Additional Analytical Methodologies

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Nonclinical testing requirements

- In vitro
  - Receptor Binding
  - Functionality testing (biochemical and/or cellular assay)
- In vivo
  - EU: not usually required
  - USA: to be determined. FDA state that normally required but may not be, especially if Ph 1 clinical done elsewhere
  - RoW: Some countries (e.g. India, China) do require tox
    - If study required, most likely in non-human primates and possibly-mouse
  - Immunogenicity study required in China

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CLINICAL & OTHER DEVELOPMENT CONSIDERATIONS

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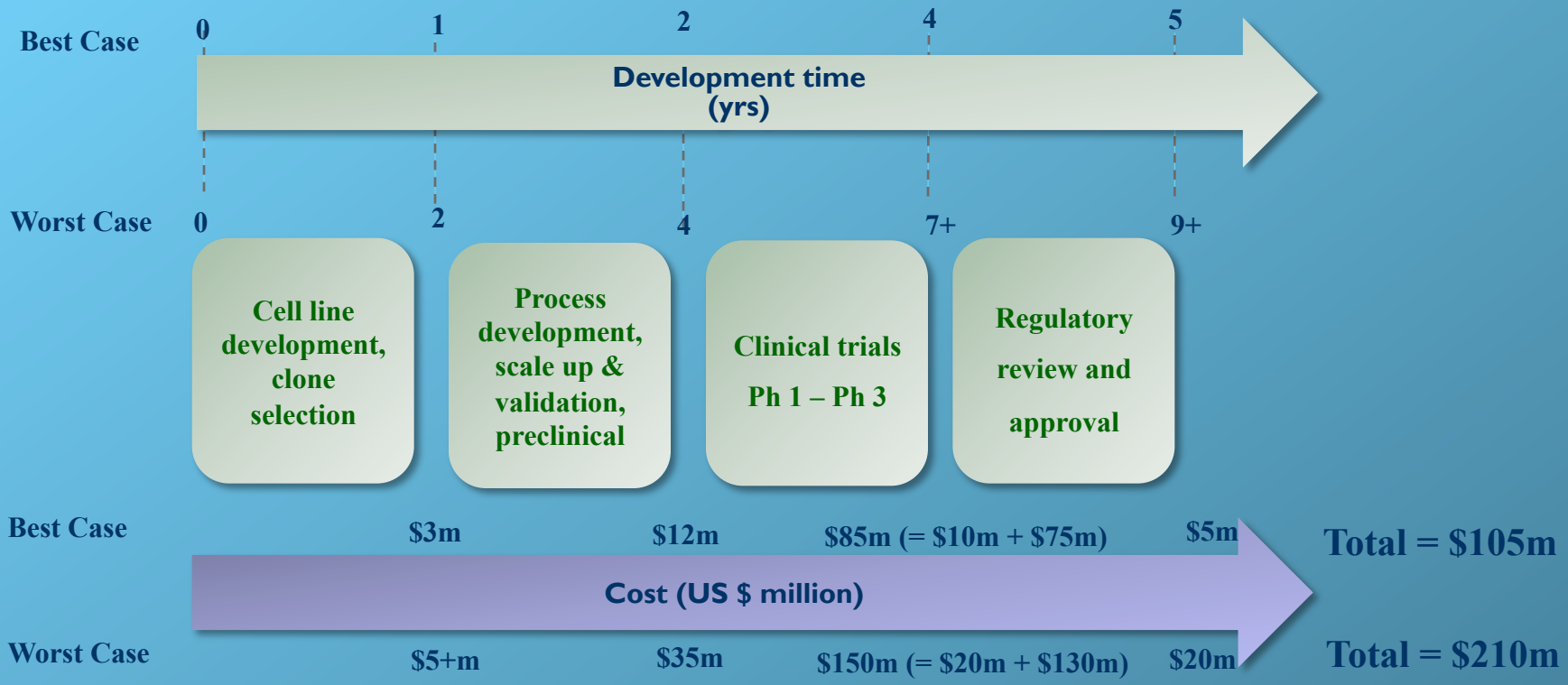
Clinical Phase 3 represents the greatest cost by far*



1. **Product development and comparative analysis:** Creation of cells that reproduce the protein of interest and select most appropriate clone.
2. **Process development scale up and validation:** Scale up of manufacturing, along with improvement of yields. Establishment of processes to ensure good manufacturing practices and reproducibility of the manufacturing process needs to be demonstrated. Demonstration of analytical similarity to the originator ("Reference") drug.
3. **Clinical trials:** Typically, a phase 1 and phase 3 trial, but case-by-case. Some products require more studies. Patient numbers vary. Adaptive designs possible.
4. **Regulatory** Early discussions with EMA (Scientific Advice) and FDA(BIA meeting) essential. Further pre-phase 3 discussions also highly advisable.

* Time and Cost are Product Dependent

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Usually one Phase 1 and one Phase 3 study are required in EU and USA

- Phase 1: 3-arm (Test vs EU vs USA), single dose, PK, safety, immunogenicity and sometimes PD
  - Typically, N = 50-80 volunteers or patients per group
- Phase 3: Efficacy and safety, plus immunogenicity
  - Demonstrate biosimilarity (not efficacy as per originator) in a sensitive indication
  - Patients: typically N = 350 – 750, depends on disease, endpoint
  - Equivalence design: 2-arm study, around 15% margin?
  - Power: up to sponsor, 80% - 90%
  - Immunogenicity: usually to 1 year
- Adaptive design may be acceptable

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EXAMPLES OF FDA & EMA ACCEPTED TRIAL DESIGNS

Anti-TNF (e.g. Humira)

- Licensed for Rheumatoid Arthritis (RA), Crohn's, Ankylosing Spondylitis (AS), Plaque psoriasis (Ppso), psoriatic arthritis
- Acceptable = RA, Ppso. AS??
- RA study for FDA / EMA:
  - N = 450 approx., equivalence, 80% or 90% power
  - 1:1 randomisation
  - 6-month ACR20 1ry endpoint
  - 52 week immunogenicity

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Anti-VEGF (e.g. Avastin)

- Licensed for Cancer of Lung, Bowel, Breast, Ovarian
- Acceptable = Lung, Bowel. Ovarian??
- Lung cancer study example for FDA / EMA
  - N = 700 approx., equivalence, 80% or 90% power
  - 1:1 randomisation
  - ORR as 1ry endpoint but survival data to be collected
  - 52 week immunogenicity

Adaptive Programme and Study Designs: Suitable in some cases but may be more costly and not always more rapid

- Products with oncology and non-oncology indications
  - Phase 1+3 adaptive in RA supported by Phase 1 in lymphoma
- Need to consider logistics of stopping to analyze Phase 1 data in adaptive design
- Will overall sample size be greater due to statistical “hit”
- Is there a risk to whole programme if Phase 1 design not optimum?

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But Phase 3 Drivers - Cost, Time and Quality – may conflict with each other

- Cost / ROI: ?
  - include non-EU, non-US centres

- Time: ?
  - include many centres (100 - 200)
  - Select high recruitment indication

- Quality: ? ?
  - Treatment: patients treated to SoC, local divergences
  - Trial conduct: data must be highest GCP quality

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BIOSIMILARS LEGISLATION WORLDWIDE

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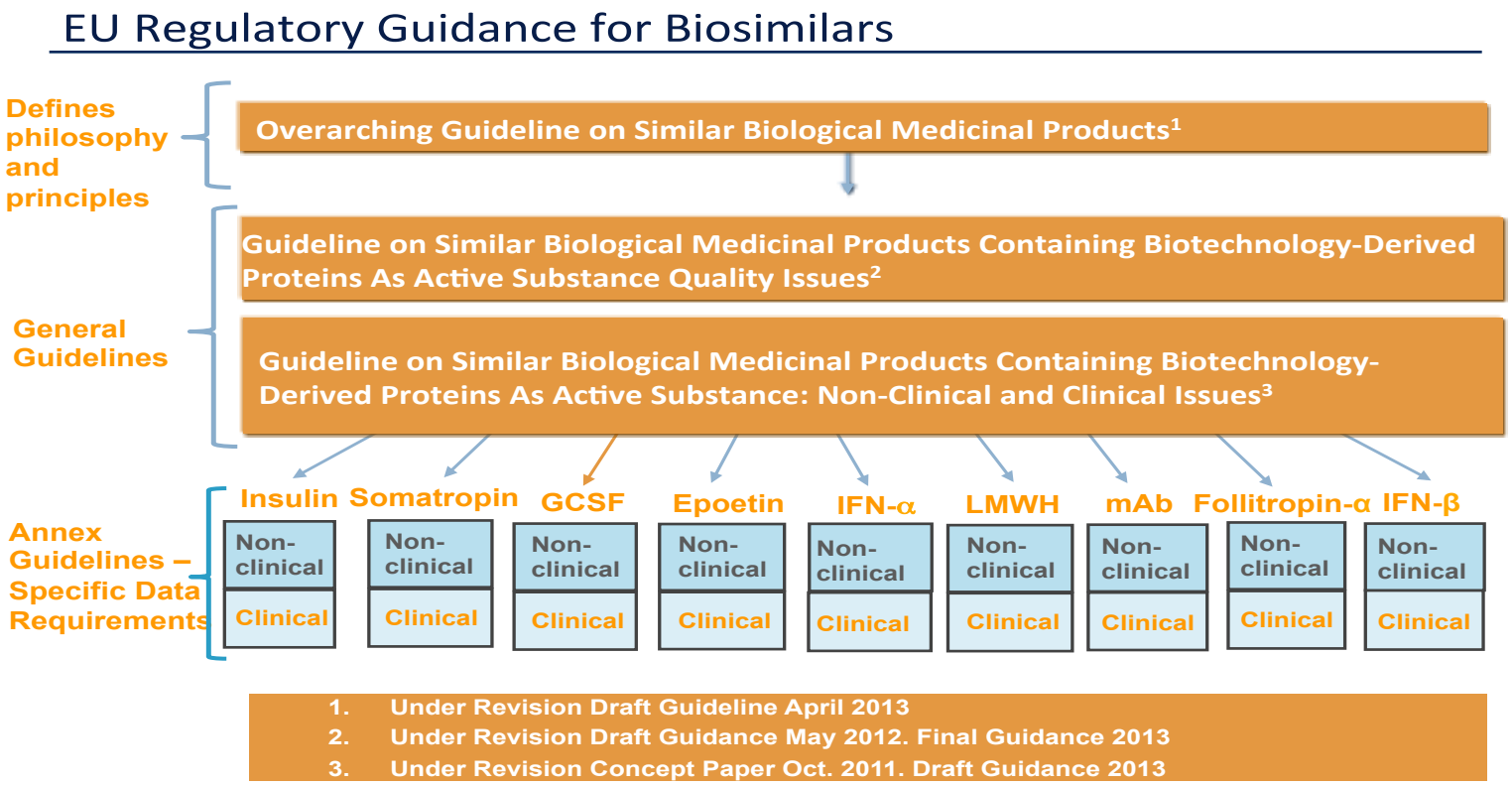
EU Guidance


EU Regulatory Guidance for Biosimilars
Defines philosophy and principles
Overarching Guideline on Similar Biological Medicinal Products[1]
General Guidelines
Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance Quality Issues[2]
Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Non-Clinical and Clinical Issues[3]
Annex Guidelines – Specific Data Requirements
Insulin
Somatropin
GCSF
Epoetin
IFN-α
LMWH
mAb
Follitropin-α
IFN-β
Non-clinical
Clinical
1. Under Revision Draft Guideline April 2013
2. Under Revision Draft Guidance May 2012. Final Guidance 2013
3. Under Revision Concept Paper Oct. 2011. Draft Guidance 2013

Revised overarching guideline

- EMA not responsible for interchangeability of products
- Non-EEA authorised reference product may be OK in some clinical and non-clinical in-vivo studies
  - Authorised by regulatory agency with similar standards as EMA
  - Sponsor to demonstrate non-EEA reference product is comparable to EEA product. Bridging studies?
- Lower levels of impurities or immunogenicity may be OK
- Requirements for clinical studies will depend on robustness of technical characterization, in vitro and in vivo animal studies
- For chemically more simple biologicals, a comparative clinical efficacy study could be avoided.

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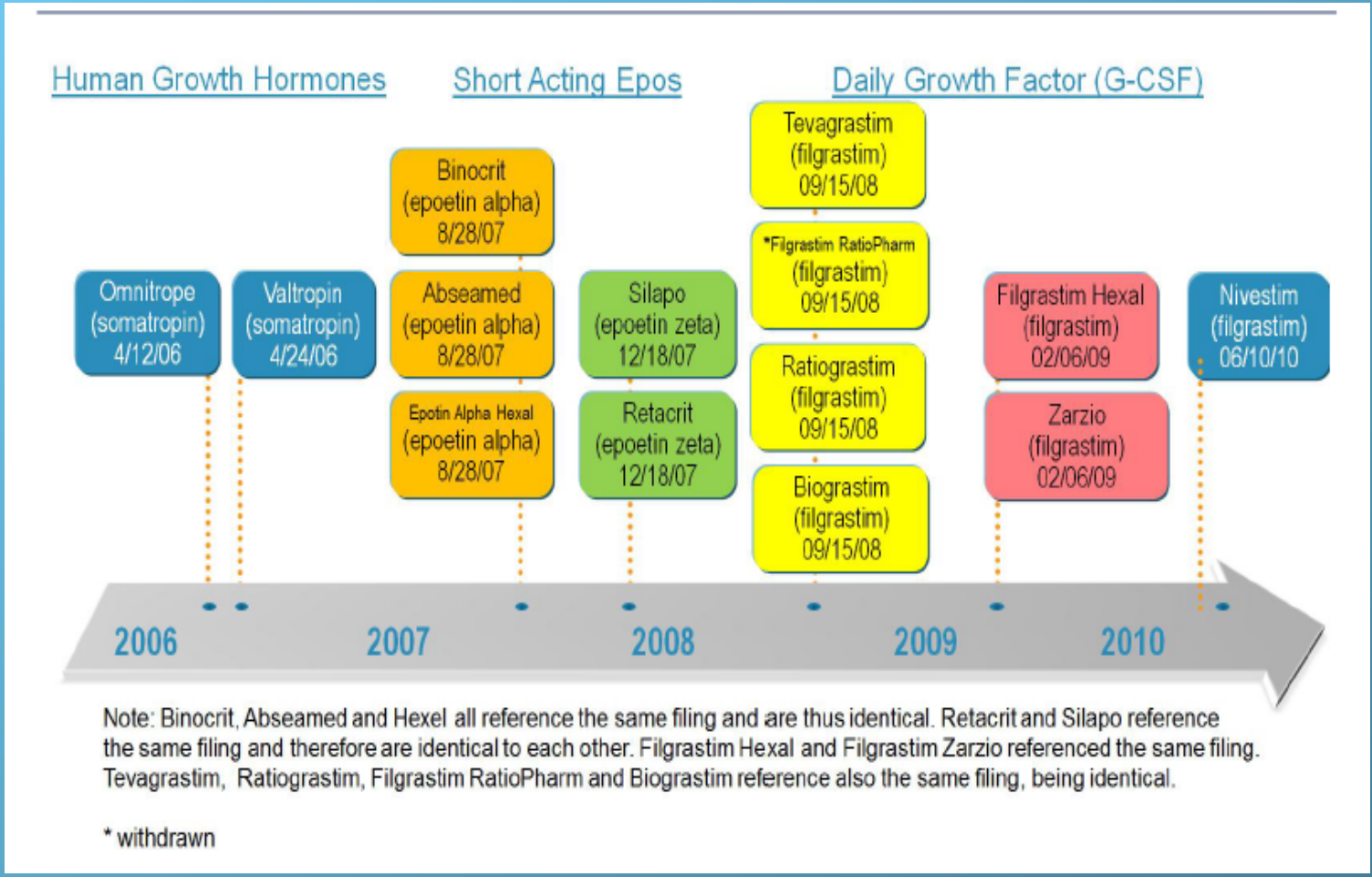
EU approved products to 2013 (except Remsima)



Note: Binocrit, Abseamed and Hexel all reference the same filing and are thus identical. Retacrit and Silapo reference the same filing and therefore are identical to each other. Filgrastim Hexal and Filgrastim Zarzio referenced the same filing. Tevagrastim, Ratiograstim, Filgrastim RatioPharm and Biograstim reference also the same filing, being identical.

* withdrawn

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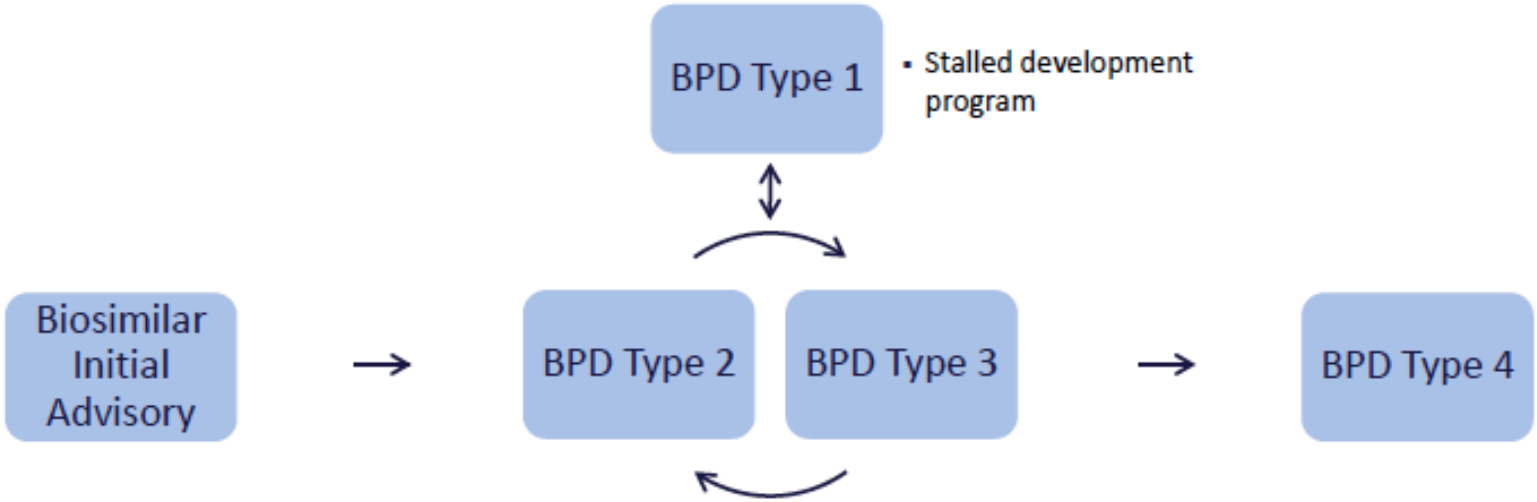
US legislation

- Several years behind EU……
- Biologics Price Competition and Innovation Act, 2009
- The Patient Protection and Affordable Care Act, 2010
  - 351(k) – abbreviated pathway for approval of biosimilars
- BsUFA: Biosimilar User Fee Act
  - "The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Biosimilar User Fee Act of 2012 (BsUFA), authorizes FDA to assess and collect fees for biosimilar biological products from October 2012 through September 2017."

Meetings provide targeted points of interaction to help maximize development program success



Comparison of Regulatory Standards EU vs USA

	EMA	FDA
Quality	Expectation that the biosimilar is highly similar to the innovator Discussion of differences in observed structure Deference to clinical data to prove similarity	Expectation that applicant applies a "fingerprinting" approach to develop a biosimilar that is highly similar. Greater emphasis than EMA on importance of quality data
Nonclinical	Stepping stone to clinical studies, increasingly lower demand for animal toxicology studies	Similar views to EMA, but experience is proving that FDA reviewers are less willing to not require sub-chronic toxicology
Clinical	In essence there is an expectation for A PK/PD study and an efficacy/safety study in one of the approved indications of the innovator. Extrapolation permitted – although not a foregone conclusion Surrogate endpoints permitted – although these are likely to be those deemed "clinically relevant" as opposed to PD markers of activity alone	Essentially similar requirements to the EMA although far more progressive in terms of using novel evaluation of PD markers and modeling.
Safety	Immunogenicity must be evaluated	Similar expectation
RMP	Significant and likely onerous requirements	TBD

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A quick skip through Biosimilars legislation worldwide

- ICH or with well-established regulatory systems
  - Japan (2009 / 2011); Australia (2008 – ref to EMA); Canada (2010 - extensive)
- Asia
  - S. Korea (2009**, ref to EMA**); India (2012 – **tox, multi-dose PK required**, pivotal clinical study can be waived); Malaysia (2009), Russia (none yet); Turkey (2008)
- Latin America
  - Mexico (2010 – biosimilars marketed already); Colombia (2013); Brazil (2010 – **ref to WHO and Canadian legislation**)
- Middle East
  - Egypt (2012 – ref to EMA, WHO, pivotal clinical study can be waived); Saudi Arabia (2010 – ref to WHO, EMA, comprehensive, in vivo study?)

WHO guidance is comprehensive and point of reference

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China – 29 Oct 2014 (draft)

- Comparison principle. **Biosimilar should be compared with the reference drug in the entire R&D progress.**
- Step by step principle. Pharmaceutical, non-clinical, and clinical study should be conducted step by step.
- Consistency principle. The sample tested in the study should be from same source and same batch. The methods and techniques used in biosimilar development should be same with the reference drug.
- Similarity principle. Results of the biosimilar in each study stage should be similar with the reference drug**. If the difference is too big in one step, the test drug will be treated as innovative drug.**
- Choose of reference drug and the test drug. Reference drug used in pharmaceutical, non-clinical, and clinical study should be the same batch. Biosimilar in research should also from the same source. If drugs are from different batch, or the manufacture process, scale, place are changed, the impact on quality of drugs should be evaluated.
- This guideline covers recombinant protein products. According to CFDA's Provisions for Drug Registration Annex 3, biologics are classified in to 15 types. Phase I, II, III clinical trials are needed for type 1-12 biologics, while only phase III clinical trials are needed for type 13-15 biologics.

ANALYSIS OF REGULATORY AND CLINICAL OBSTACLES TO GLOBAL PRODUCTS …….. AND POSSIBLE SOLUTIONS

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Clinical Data & Reference Product

- EMA and FDA accept "foreign" clinical data
  - Not so in countries such as China, Russia, others
  - Phase 3 studies are multinational for recruitment needs
    - Major cohorts to satisfy local requirements?
    - Small supportive local studies that also support marketing in country of origin? Conduct with strategic partner?
- Reference product for comparison
  - EMA & FDA accept use of other ICH region product in Phase 3 study if analytics, functionality and phase 1 OK
    - WHO, Trade Associations to press non-ICH countries?

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Other divergences

- Drug sourcing
  - Difficult and costly to source Reference Product **AND** to know manufacturing site
  - EMA and FDA accept use of regional multi-sourcing in Phase 3
- Nonclinical studies
  - EMA normally does not want animal tox studies
  - FDA sitting on fence to see Phase 1 data
  - Other countries including China and India require tox

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OTHER STRATEGIES TO ACHIEVE GLOBAL COVERAGE

Some Global Partnerships

SANDOZ
A healthy decision

First mover

When world largest generics meets largest bio-CMO

TEVA Lonza

Strategic partnerships

MERCK

PAREXEL
Expertise that makes the Difference

Hanwha

Agreement on Insulin

Pfizer Biocon

Focus on Biobetters

AMGEN Roche

AstraZeneca

Strategic partnership

SAMSUNG QUINTILES

CELLTRION

From CMO to Biosimilars

Boehringer Ingelheim

The newest comer

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Three Partnership models

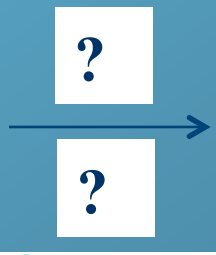
Local market rights model: Company A contributes to product development costs of Company B in exchange for one or few local market rights

Typical: Both companies can be small. Company A is 1. In an Emerging Market. Or 2. Is a Generics company. Company A has no technology, has cash, but has no involvement in development.

Major market share model: Company A contributes to product development costs of Company B. Share of markets globally by companies.

Typical: Both companies can be medium-large. Company A is 1. No biologics history. Or 2. Is a major Generics player. Company A may already have a biosimilars portfolio

Business Strategy change model: Company A acquires full market rights to Company B products. B manufactures, A may help later development.



Typical: Company A is large. Company B is specialized in Biosimilars. Similar to known "biotech" deal. Company B may have novel product platform.

Where are we now?

- True, fully, globally acceptable phase 3 studies are unlikely in near to mid-term future due to:
  - Regulatory barriers and “regulatory evolution” differences worldwide
  - Patient recruitment / site selection requirements driven by major markets; licensed indication and SoC differences
- Some gains could be achieved by:
  - Over-powered studies with major local cohorts might help
  - Use of smaller local studies with dual purpose (market support)
  - Prioritizing lobbying for “regulatory evolution” in major non-ICH markets
  - Lobbying to harmonize regulations on specific issues including in vivo tox studies, use of local Reference Product

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The development strategy needs to adress several challenges

As the biosimilars market continues to evolve, we will need to continually address a set of strategic challenges:

Specifically a focus needs to be:

- Optimizing clinical development strategy to ensure speed to market without sacrificing quality
- Navigating regulatory complexities to adapt as pathways and guidelines are still evolving
- Minimizing the risk of exposure to competitive biosimilars

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Truly Global Biosimilars: A Summary of the Problem

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BACK UPS

Amgen Phase 3 Plaque Psoriasis

- This randomized, double-blind, active-controlled study (study number 20120263) evaluated safety and efficacy of ABP 501 compared to adalimumab **in 350 adult patients** with moderate-to-severe plaque PsO. There were 174 patients in the ABP 501 group and 173 patients in the adalimumab group treated.
- The **primary endpoint,** PASI percent improvement, was evaluated **at week 16.** At week 16, patients with a PASI 50 or above response will remain on study for up to 52 weeks.
- Patients continuing on study beyond week 16 were re-randomized in a blinded fashion such that all patients initially randomized to ABP 501 continued to receive ABP 501 and those on adalimumab either continued on adalimumab or switched to ABP 501 in a 1:1 fashion. Patients will continue on treatment until week 48.
- The **final efficacy** assessments will be conducted at **week 50** and the study will end at week 52.

"At week 16, the PASI percent improvement from baseline was within the prespecified equivalence margin ……. Safety and immunogenicity ……were comparable."

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Amgen Phase 3 RA study (ongoing)

- This is a double blind, safety and efficacy study versus EU reference Humira in moderate to severe RA patients.
- This study is being run in EU and in other countries (USA, Canada, Russia, Argentina, Mexico).
- It will recruit **500 patients**, with about half in EU (more specifically EEA) spread **over 70 sites**.
- The study is planned to run for 2 years.
- It is interesting that the Amgen phase 3 study uses EU reference product and, because it includes US sites, it will almost certainly be the pivotal study for US registration.

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Remsima (infliximab)
1st Biosimilar mAb approved in EU 2013

Topic area: Clinical topics by disease *Topic: 13. Rheumatoid arthritis - anti-TNF therapy* FRI0143

A randomized, double-blind, phase 3 study demonstrates clinical equivalence of CT-P13 to infliximab when co-administered with methotrexate in patients with active rheumatoid arthritis

D.Yoo[1]*, P.Miranda[2], M.Piotrowski[3], E.Ramiterre[4], V.Kovalenko[5], N.Prodanovic[6], M.Tee[7], S.Gutierrez-Ureña[8], R.Jimenez[9], O.Zamani[10], S.Lee[11], H.Kim[12], W.Park[13], U.Müller-Ladner[14]

[1]Hanyang University Medical Center, Seoul, Korea, Republic Of, [2]Centro de Estudios Reumatologicos, Santiago, Chile, [3]REUMED, Lubin, Poland, [4]Brokenshire Memorial Hospital, Davao City, Philippines, [5]National Scientific Center, Kiev, Ukraine, [6]Clinical Center Banja Luka, Banja Luka, Bosnia and Herzegovina, [7]Medical Center Manila, Manila, Philippines, [8]Antiguo Hospital Civil de Guadalajara, Guadalajara, Mexico, [9]Centro de Estudios Investigaciones Clinicas, Vina del Mar, Chile, [10]Rheuma Zentrum Favoriten, Vienna, Austria, [11]University of New Mexico, Albuquerque, United States, [12]CELLTRION Inc., Incheon, Korea, Republic Of, [13]Inha University Hospital, Incheon, Korea, Republic Of, [14]Kerckhoff-Klinik GmbH, Bad Nauheim, Germany

Background

- CT-P13 was developed as a biosimilar to infliximab, and has been tested in accordance with European Medicines Agency (EMA) and World Health Organization (WHO) guidance for biosimilar medicines[1,2]
- This randomized, double-blind, multicenter, parallel-group, prospective phase 3 study was conducted to compare the clinical efficacy and safety of CT-P13 with those of infliximab in patients with active RA

Objectives

- Primary objective: to demonstrate CT-P13 equivalence to infliximab up to Week 30, in terms of ACR20 response rate
- Secondary objectives: to evaluate long-term efficacy, pharmacokinetics,pharmacodynamics, and overall safety of CT-P13 in comparison with infliximab up to Week 54
  - This poster only presents data for secondary objectives assessed to Week 30

Methods

- Key inclusion criteria were identical to a pivotal phase III trial for infliximab reference product:[3] swollen joint ≥ 6; tender joints ≥ 6, and at least two of the following: morning stiffness lasting ≥ 45 mins, ESR ≥ 28 mm/h, CRP ≥ 2.0 mg/dL
- Patients were randomized in a 1:1 ratio to receive either CT-P13 or infliximab (both administered as a single 3 mg/kg i.v. dose), coadministered with methotrexate (12.5–25 mg/week) and folic acid (≥5 mg/week) [Figure 1]
- Patients were premedicated with an antihistamine (chlorpheniramine 2–4 mg or equivalent dose of equivalent antihistamine) 30–60 minutes prior to the start of each study infusion at the investigator's discretion.
- Statistical analysis for the primary endpoint is outlined in Table 1

Table 1. Statistical assumptions

Sample size	584
Enrolled population, no	617*
Target population, no	468
Primary endpoint	ACR20 (at week 30)
Statistical assumptions	• Equivalence margin: ±15% • Response rate (ACR20): 50% (95% CI) • ß error: 0.2 (power 80%) • α error: 0.05, 2-side • Drop-out rate: 20% • Primary population: all-randomized population,per protocol population
Analytical method for Primary endpoint	• Binomial exact method

*Eleven patients from fraudulent study center were excluded in all-randomized population

Results

Figure 1. Study design

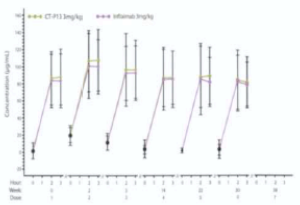
Table 2. Patient baseline characteristics

	CT-P13 (n = 302)	Infliximab (n = 304)
Age (years) median (range)	50 (18–75)	50 (21–74)
Sex, no (%)		
Male	57 (18.9)	48 (15.8)
Female	245 (81.1)	256 (84.2)
Ethnicity, no (%)		
White	220 (72.8)	222 (73.0)
Asian	34 (11.3)	37 (12.2)
Black	2 (0.7)	1 (0.3)
Other	46 (15.2)	44 (14.5)
Height (cm), median (range)	162 (144–186)	162 (142–190)
Weight (kg), median (range)	69.0 (36.5–134)	68.0 (36–136)
Body mass index (kg/m²), median (range)	26.28 (13.9–49.8)	25.40 (15.0–53.1)
Baseline serum CRP concentration, no (%)		
≤2 mg/dL	163 (54.0)	167 (54.9)
>2 mg/dL	139 (46.0)	137 (45.1)

Pharmacokinetics (PK) (pharmacokinetic population, n = 581)

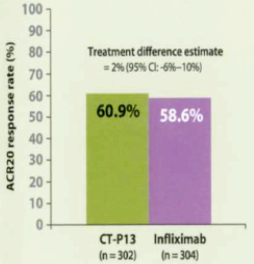
- PK endpoints were comparable between CT-P13 and infliximab treatment groups at week 30 [Figure 2]
  - C_{max} (peak serum concentration) of infliximab in CT-P13 group similar to C_{max} in infliximab group (84–112 µg/mL and 84–135 µg/mL, respectively)
  - C_{min} (minimum serum concentration) differed by <10% between treatment groups (exception = 24% after dose 2)
  - PK (antibody-negative subset) achieved similar results (IC_{50}: 90.8 vs 86.3 µg/mL; C_{min}: 0.99 vs 1.02 µg/mL, respectively)

Figure 2. Mean (±SD) serum concentration of infliximab versus time by treatment (PK population)



Efficacy: Primary endpoint (ACR20 response rate)

Figure 3. ACR20 response rates by treatment group at week 30 (all-randomized population)

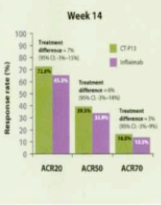


- The results of the per protocol population supported the results of the all randomized population [Figure 4]

Efficacy: Secondary endpoints

- In the per protocol population (CT-P13, n = 248; Infliximab, n= 251) results for secondary efficacy endpoints were comparable between CT-P13 and infliximab treatment groups at weeks 14 and 30 [Figure 4]

Figure 4. ACR response rates by treatment group and timepoint (per protocol population)



Pharmacodynamics (PD) (pharmacodynamic population, n = 582)

- There was no evidence of a difference between the CT-P13 and infliximab treatment groups in change from Baseline in CRP, ESR, IgA RF, or IgM RF at either week 14 or week 30

Safety

- Overall, CT-P13 was well tolerated and the safety profile of CT-P13 was comparable to that of infliximab in this phase 3 trial [Table 3]
- The majority of treatment -emergent adverse events (TEAEs) were mild or moderate in severity
- The rate of infusion reactions noted in both groups was lower than the 20% incidence listed in infliximab product information[4]
- Incidences of active tuberculosis (TB) in the two treatment groups were similar to those noted in two large, phase 3 trials of infliximab in RA: the ATTRACT and ASPIRE trials (1.2% and 0.8% active TB, respectively)[5,6]
  - Rate of positive conversion in IGRA test was similar between groups
- Immunogenicity testing [Table 4] demonstrated a similar profile for CT-P13 compared with infliximab

Table 3. Key safety findings

	CT-P13 (n = 361)	Infliximab (n = 301)
TEAEs, total no (%)	487	490
Patients with ≥1 TEAE, no (%)	181 (60.1)	183 (60.8)
Related to treatment	106 (35.2)	108 (35.9)
Unrelated to treatment	132 (43.9)	130 (43.2)
Infusion reactions – incidence, no (%)	15 (5.0)	17 (5.6)
Positive for antidrug antibody, no (%)	12 (80)	14 (82)
Active tuberculosis – incidence, no (%)	3 (1.0)	1 (0.3)
Positive conversion in IGRA test* – no (%)	30 (21.6)	28 (20.3)

*Interferon-γ release assay was performed at week 14, 30, 54 at SCEs visit during study period is only for countries with an increased TB prevalence and incidence: Philippines, Indonesia, Russia, Romania, Ukraine, Peru,Korea, Lithuania, Bulgaria and Columbia. Numbers of patients tested by IGRA were CT-P13 (n = 178) infliximab (n = 138)

Table 4. Immunogenicity testing summary

Visit	Result, no (%)	CT-P13 (n = 361)	Infliximab (n = 301)
Screening*	Positive	9 (3.0%)	6 (2.0%)
	Negative	284 (94.4%)	291 (96.7%)
Week 14	Positive	68 (22.6%)	70 (23.3%)
	Negative	204 (67.8%)	201 (66.8%)
Week 30	Positive	121 (40.2%)	120 (39.9%)
	Negative	129 (42.9%)	133 (44.2%)

*Blood samples of 8 patients in the CT-P13 group and 4 in the infliximab group were not obtained for immunogenicity at screening visit

Conclusions

- CT-P13 has demonstrated equivalent efficacy to infliximab in this phase 3 trial:
  - The efficacy of CT-P13 was equivalent to that of infliximab up to week 30 as determined by clinical response according to the ACR20 criteria (primary efficacy endpoint)
  - Results for the primary efficacy endpoint were supported by the per protocol analysis and results of secondary clinical efficacy endpoints (ACR50 and ACR70 response rates)
- CT-P13 was well tolerated and the safety profile of CT-P13 was comparable to that of infliximab
- Results for pharmacokinetic and pharmacodynamic endpoints were also comparable between CT-P13 and infliximab treatment groups at weeks 14 and 30

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