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[Table] Approved Biosimilars

Attachment 3A: Selected Summary of Regulatory Biosimilar Reviews by Year

[Table] Approved Biosimilar

Drug	Approval Agency				
	EMA	FDA	HEALTH CANADA	PMDA	MFDS
Erythropoietin	■ Abseamed (2007) ■ Binocrit (2007) ■ Epoetin alfa hexal (2007) ■ Retacrit (2007) ■ Silapo (2007)			■ Epoetin alfa BS (2010)	
Filgrastim	■ Tevasgrastim (2008) ■ Ratiograstim (2008) ■ Biograstim (2008) ■ Zarzio (2009) ■ Filgrastim hexal (2009) ■ Nivestim (2010) ■ Accofil (2014) ■ Grastofil (2014)	■ Zarxio (2015)		■ FilgrastimBS (Fuji, 2012) ■ FilgrastimBS (Teva, 2013) ■ FilgrastimBS (Sandoz, 2014)	
Somatropin	■ Omnitrope (2006)		■ Omnitrope (2009)	■ Somatropin BS (2009)	■ SciTropin A (2014)
Insulin	■ Abasaglar (2014)			■ Insulin glargine BS (2015)	
Infliximab	■ Remsima (2013) ■ Inflectra (2014)		■ Inflectra (2014) ■ Remsima (2014)	■ Infliximab BS (2014)	■ Remsima (2012)
Trastuzumab					■ Herzuma (2014)
Etanercept					■ Davigtrel (2014)

ERYTHROPOIETIN ① Clinical Pharmacokinetic / Pharmacodynamic Studies			
Approved Year (Agency)	**2007 (EMA)**	**2007 (EMA)**	**2010 (PMDA)**
Products Name	**Abseamed, Binocrit, Epoetin alfa Hexal**	**Retacrit, Silapo**	**Epoetin Alfa BS Injection [JCR]**
Reference Products	**Eprex/Erypo**		**ESPO, Epoetin alfa**
Study Type	**5 PK, PD studies (1 pilot study, 2 pivotal studies)**	**2 PK studies**	**3 PK studies**
Primary + Secondary Objective	Equivalence in PK + PD	Equivalence in PK + Safety	Equivalence in PK + Safety
Study Subjects	Healthy adult male	Healthy adults	Healthy male HD patients with renal anemia Healthy
Study Design	Randomised, 2-centre, open**, parallel-group** - Multiple IV 100 IU/kg TIW Randomized, monocentric, open, **parallel-group** - Multiple SC 100 IU/kg TIW	**2-period cross-over** - Single-dose IV bolus injection **3-period cross-over** - Single-dose SC bolus injection	Exploratory, placebo-controlled, single-center, **parallel-group** **- S**ingle-dose IV injection **2-period cross-over** - Single-dose IV injection **2-period cross-over** - Single-dose SC injection
Primary Endpoint	***[PK]*** AUCτ of EPO	***[PK]*** $AUC_{0\text{-}tlast}$	***[PK]*** $AUC_{0\text{-}\infty}$ (IV), $AUC_{0\text{-}\infty,}$ & Cmax (SC)
	[PD] Absolute Hgb response (AUEC)	***[PD]*** Reticulocyte count	***[PD]*** N/A
Equivalence Margin	**post hoc acceptance range of 80-125%**	**post hoc acceptance range of 80-125% for AUC & 70-143% for Cmax**	
NOTE	- Two of the PK/PD studies irrelevant to comparability exercise - No pre-defined equivalence margin	- No specific PD studies conducted with SB309. The PD of erythropoietin is known and described in the literatures. - No pre-defined equivalence margin	- No specific clinical PD study conducted with JR-013

Abbreviation: AUC, area under the concentration-time curve; AUEC, area under the effect curve; Cmax, maximum serum concentration; EPO, erythropoietin; HD, hemodialysis; IV, intravenous; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

ERYTHROPOIETIN ② Clinical Efficacy / Safety Studies			
Approved Year (Agency)	**2007 (EMA)**	**2007 (EMA)**	**2010 (PMDA)**
Products Name	**Abseamed, Binocrit, Epoetin alfa Hexal**	**Retacrit, Silapo**	**Epoetin Alfa BS Injection [JCR]**
Reference Products	**Eprex/Erypo**		**ESPO, Epoetin alfa**
Study Type	**1 pivotal comparative study,** **1 supportive non-comparative study**	**2 pivotal comparative study,** **2 supportive, uncontrolled safety study** ****1 additional comparative SC study (2009) for Retacrit® only**	**1 phase 2/3 comparative IV study,** **1 long-term non-comparative IV study**
Primary, Secondary Objective	Therapeutic equivalence in efficacy + safety	Therapeutic equivalence in efficacy + safety	Therapeutic equivalence in efficacy + safety
Study Subjects	Renal anemia on HD	Renal anemia on HD	Renal anemia on HD
Study Design	Randomised, double blind, multicenter, **parallel-group** **-** IV	[Correction phase IV study] Randomized, double-blind, multi-center, verum-controlled, **parallel-group** **-** Multiple-dose IV [Maintenance phase IV study] Randomized, double-blind, multi-national, verum-controlled, **cross-over** **-** Multiple-dose IV **[Additional maintenance phase SC study] Randomized, double-blind, multi-national, multiple-dose SC, **parallel-group**	Randomized, double-blind, multi-center, **parallel-group** - Multiple-dose IV
Primary Endpoint	***[Efficacy]*** Mean absolute change in Hgb levels between the screening/baseline period and the evaluation period ***[Safety]*** Incidence of adverse events, serious adverse event, treatment-emergent adverse events, death, physical exam, clinical lab tests	***[Efficacy]*** [Correction phase IV study] - Mean Hgb levels during the last four -weeks of treatment - Mean weekly dosage of EPO per kg body weight during the last four weeks of treatment [Maintenance phase IV study] - Intra-individual change (test-reference) in mean weekly dosage per kg body weight of each product during the double-blind treatment period - Intra-individual change (test-reference) in mean Hgb level during double-blind treatment with each study drug **[Maintenance phase SC study] - Mean Hgb levels during the last four -weeks of treatment	***[Efficacy]*** Absolute change in Hgb levels between the screening/baseline period and the evaluation period ***[Safety]*** Not applicable

		- Mean weekly dosage of EPO per kg body weight during the last 4 weeks of treatment ***[Safety]*** Occurrence of anti-EPO antibodies, incidence of Hgb levels above 13 g/dl, ratings of tolerability, evaluation of adverse events	
Statistics	Equivalence	Equivalence	Equivalence
Equivalence Margin	- Equivalence margin of ± 0.5 g/dl in Hgb (mean baseline Hgb = < 11.5 and > 11/5 g/dl)	[Correction phase IV study] - 95% CI of the difference between both treatment groups of the primary endpoints - Equivalence margin of ± 1 g/dl in Hgb and ± 45 IU/kg/week (*corrected from 14 IU/kg/week) for mean weekly EPO dosage [Maintenance phase IV study] - 2-sided 95% CI of the intra-individual change (test-reference) - Equivalence margin of ± 0.6 g/dl in Hgb and ± 14 IU/kg/week for mean weekly EPO dosage [Maintenance phase SC study] - 95% CI of the difference between both treatment groups of the primary endpoints - Equivalence margin of ± 0.5 g/dl in Hgb and ± 45 IU/kg/week for EPO dosage	- 95% CI - Equivalence margin of ± 0.5 g/dl in Hgb
NOTE	- Pre-defined acceptance ranges for equivalence margin	- Pre-defined acceptance ranges for equivalence margin	- Pre-defined acceptance ranges for equivalence margin

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; EPO, erythropoietin; Hgb, hemoglobin; HD, hemodialysis; IU, international unit; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

FILGRASTIM ① Clinical Pharmacokinetic / Pharmacodynamic Studies*							
Approved Year (Agency)	**2008 (EMA)**	**2009 (EMA)**	**2010 (EMA)**	**2012 (PMDA)**	**2013 (PMDA)**	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Biograstim, Ratiograstim, Tevagrastim**	**Zarzio, Filgrastim Hexal**	**Nivestim**	**Filgrastim BS (Fuji), (Mochida)**	**Filgrastim BS (Teva), (Nippon Kayaku)**	**Accofil, Grastofil**	**Filgrastim BS (Sandoz)**
Reference Products	**Neupogen**			**Gran**		**Neupogen**	**Gran**
Study Type	**2 PK/PD Studies**	**4 PK/PD Studies**	**2 PK/PD Studies**	**1PK/PD, 2PK, 1PD**	**3 PK, 2 PD studies**	**4 PK/PD Studies**	**2 PK/PD, 2PD Studies**
Primary + Secondary Objective	Equivalence in PD + PK	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD or PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD or PK + Safety
Study Subject	Healthy Male/ Healthy Adults	Healthy Adults	Healthy Adults	Healthy Male	Healthy Male	Healthy Adults	Healthy Male
Study Design	Randomized, single-center, single-blind, 2-period, **2-arm crossover** - Single SC 5, 10 μg/kg - Single IV 5, 10 μg/kg	Randomized, double-blind, **2-way crossover** - Single SC 1 μg/kg - Multiple SC 2.5, 5 μg/kg/d - Multiple SC 10 μg/kg/d - Single IV 5 μg/kg	Randomized, single-center, open-label, active-controlled, **2-way crossover** - Single IV & SC 10 μg/kg Randomized, single-center, double-blind, active-controlled, **2-way crossover** - Multiple SC 5 or 10 μg/kg	Randomized, open-label, active-controlled, 2-period, **2-arm crossover** (PK/PD) - Single SC 400 μg/m^2 Randomized, double-blind, active-controlled, 2-period, **2-arm crossover** (PK) - Single IV 200 μg/m^2 (PD) - Multiple SC 400 μg/m^2/d	Randomized, single-blind, 2-period, **2-arm crossover** (PK) - Single IV 300 μg - Single SC 150 μg - Single SC 300 μg (PD) - Single SC 300 μg - Multiple SC 300 μg /d	Randomized, double-blind, active controlled, **2-way cross-over** - Single SC 75, 150 μg - Single IV 5 μg/kg Randomized, double-blind, active and placebo-controlled **parallel group** - Single SC 5 μg/kg Randomized, single-center double-blind, active-controlled, **3-arm crossover** - Multiple SC 300 μg	Randomized, double blind, 2-period-**2-way crossover** (PK/PD) - Single-dose SC 5 μg/kg, - Single-dose IV 2.5 μg/kg (PD) - Multiple doses SC 5 μg/kg/d, BID, for 3 days
Primary Endpoint	***[PK]*** AUCt of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt and Cmax of filgrastim
	[PD] AUCt and Cmax of ANC	***[PD]*** AUC of ANC	***[PD]*** AUC of ANC at Day 5	***[PD]*** Cmax and tmax of ANC & CD34+cell	***[PD]*** AUCt and Cmax of ANC & CD34+cell	***[PD]*** AUCt and Cmax of ANC	***[PD]*** AUECt and Emax of ANC & CD34+ cell
Equivalence Margin	90% CI for the test/reference GMR of the primary PK/PD endpoint needs to be within [**80-125%]**						
NOTE		- For PD primary endpoints: 95% CIs for test/reference GMR are within *predefined equivalence intervals,* 2.5 μg/kg/d (87.3 - 114.6%) & 5 and 10 μg/kg/d (86.5 - 115.6%)		- Cmax of ANC &CD34+: **95%** CI for the T/R ratio of PD endpoint needs to be within 80-125% - tmax of ANC &CD34+: **95%** CI for the T/R ratio of PD endpoint needs to be within ±0.2	- AUCt and Cmax of ANC &$CD34^+$: **95%** CI for the T/R ratio of PD endpoint needs to be within 80-125%	- The Phase I 3-arm study: Apo-Filgrastim(test), EU-approved Neupogen and US-licensed Neupogen	- PD endpoint: **95%** CI for the T/R ratio needs to be within 80-125%

Abbreviation: ANC, absolute neutrophil count; AUC, area under the concentration-time curve; AUCt, area under the concentration-time curve over the dosing interval; AUEC, area under the effect curve; CI, confidence interval; Cmax, maximum serum concentration; GMR, geometric mean ratio IV, intravenous infusion; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; T/R, test/reference

* **A Summary of FDA approved biosimilar "Zarxio" is on page 8**

FILGRASTIM ② Clinical Efficacy / Safety Studies*							
Approved Year (Agency)	**2008 (EMA)**	**2009 (EMA)**	**2010 (EMA)**	**2012 (PMDA)**	**2013 (PMDA)**	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Biograstim, Ratiograstim, Tevagrastim**	**Zarzio, Filgrastim Hexal**	**Nivestim**	**Filgrastim BS (Fuji), (Mochida)**	**Filgrastim BS (Teva),(Nippon Kayaku)**	**Accofil, Grastofil**	**Filgrastim BS (Sandoz)**
Reference Products	**Neupogen**			**Gran**		**Neupogen**	**Gran**
Study Type	**1 pivotal, 2 supportive comparative studies**	**1 supportive non-comparative study**	**1 pivotal study**	**1 non-comparative study**	*The applicant did not conduct any efficacy clinical trials.* *Just submitted overseas clinical study data as reference for safety evaluation*	**1 non-comparative study**	*The applicant did not conduct any efficacy clinical trials in Japan.* *Just submitted overseas clinical study data as reference for safety evaluation*
Primary + Secondary Objective	Equivalence in efficacy + Safety + PK subgroup	Safety, tolerability and immunogenicity + Efficacy	Equivalence in efficacy + Safety, tolerability and immunogenicity	Safety + Efficacy		Safety + Efficacy	
Study Subject	Chemotherapy-naïve breast cancer patients (stage 2, 3, 4 according to AJCC classification) receiving **docetaxel & doxorubicin** CTX			Chemotherapy-naïve breast cancer patients receiving **epirubicin & 5-FU & cyclophosphamide** for pre- or postoperative CTX		Chemotherapy-naïve breast cancer receiving **docetaxel & doxorubicin & cyclophosphamide** CTX	
Study Design	Randomized, multinational, multicenter, **placebo- and active-controlled**	Randomized, multicenter open-label, single-arm	Randomized, multicenter, double-blind, **active-controlled**	***Non***-randomized, multicenter, open-label		Randomized, multicenter open-label	
Primary Endpoint	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in CTX cycle 1. ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	***[Efficacy]*** DSN in CTX cycles 1 to 4 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in CTX cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	***[Efficacy]*** DSN (ANC <1x10^9 /L) in days in CTX cycle 2 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results		***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in CTX cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results	
Statistics	Equivalence	Not applicable	Equivalence	Not applicable		Not applicable	
Equivalence Margin	2-sided 95% CI for least square mean difference in DSN (Test−Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	Not applicable	2-sided 95% CI for least square mean difference in DSN (Test−Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	Not applicable		Not applicable	

NOTE	- Full double-masking was not possible - **In pivotal study,** DSN is confirmed by assay sensitivity in comparing test drug vs placebo - **2 other supportive studies** in patients with lung cancer and NHL focused on safety	- PK/PD results are considered sufficiently comparable to support biosimilarity effect since ANC curves are superimposeable whatever the route and the dose - This trial was non comparative and therefore of limited usefulness for comparability assessment		- Patients: stage I, II or III [General Rules for Clinical and Pathological Recording of Breast Cancer September 2008 (16^{th} ed.)] - Efficacy evaluation standard: 1-sided 97.5% CI of the DN in CTX cycle 2 not exceeds a threshold value of 3.0 days	- Safety study data of Tevagrastim® (Teva Pharmaceutical, Israel) submitted as reference for safety evaluation	- Efficacy data was not considered to provide significant support to the pivotal PD data from the phase 1 studies - This trial was non comparative and therefore of limited usefulness for comparability assessment	- Safety study data of EP06-301(clinical efficacy and safety study of Zarzio®) submitted as reference for safety evaluation

Abbreviation: AJCC, American Joint Committee on Cancer; ANC, absolute neutrophil count; CI, confidence interval; CTX, chemotherapy; DSN, duration of severe neutropenia; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; 5-FU, fluorouracil

* **A Summary of FDA approved biosimilar "Zarxio" is on page 8**

FILGRASTIM		
	① Clinical Pharmacokinetic / Pharmacodynamic Studies	② Clinical Efficacy / Safety Studies
Approved Year (Agency)	**2015 (FDA)**	
Products Name	**Zarxio**	
Reference Products	**Neupogen (US and EU)**	
Study Type	**5 PK/PD studies (1 US, 4 EU)**	**1 comparative pivotal,** **2 supportive non-compartive studies** (1 in patients with CTX, 1 in patients with PBPC mobilization therapy as post-authorization safety study)
Primary + Secondary Objective	Equivalence in PK/PD + Safety, tolerability and immunogenicity	Non-inferiority in clinical effectiveness + Safety, tolerability, immunogenicity + PK sub-study
Study Subject	Healthy Adults	Chemotherapy-naïve breast cancer receiving **docetaxel & doxorubicin & cyclophosphamide** CTX
Study Design	Randomized, double-blind, 2-way crossover - Single SC 1 μg/kg (EU-source Neupogen) - Multiple SC 2.5, 5 μg/kg/d (EU-source Neupogen) - Multiple SC 10 μg/kg/d (EU-source Neupogen) - Single IV 5 μg/kg (EU-source Neupogen) - Single SC 10 μg/kg (US-source Neupogen)	Randomized, multicenter, double-blind
Primary Endpoint	*[PK]* Cmax, AUClast *[PD]* Emax, AUEClast of ANC response	*[Effectiveness]* DSN (ANC $<1x10^9$ /L) in days in CTX cycle 1 *[Safety]* Incidence of adverse events, vital signs, formation of G-CSF antibodies, lab results
Statistics	Equivalence	Assess **non-inferiority** at a one-sided significance level of 2.5% in the mean duration of severe neutropenia (DSN, ANC $<0.5x10^9$ /L) during Cycle 1
Equivalence Margin	PK: 90% CI for the T/R arithmetic mean ratio of PD endpoint needs to be within 80-125% of the reference product PD: 95% CI for the T/R arithmetic mean ratio of PD endpoint needs to be within 80-125% of the reference product (Pre-discussed with FDA)	Lower bound of the confidence interval is above the non-inferiority margin of -1 day
NOTE	- Additionally, 1PK sub study [EP06-302] conducted during efficacy and safety trial in breast cancer patients	1 Comparative pivotal study and 1 post-authorization safety study were for the US file. *** FDA re-analyzed clinical data results as equivalence assessment: Mean DSN on Cycle 1 with two-sided 90% CI supports equivalence conclusion**

Abbreviation: ANC, absolute neutrophil count; AUC, area under the concentration-time curve; AUCt, area under the concentration-time curve over the dosing interval; AUEC, area under the effect curve; CI, confidence interval; Cmax, maximum serum concentration; GMR, geometric mean ratio IV, intravenous infusion; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; T/R, test/reference; ANC, absolute neutrophil count; CI, confidence interval; CTX, chemotherapy; DSN, duration of severe neutropenia; PBPC, Peripheral blood progenitor cell

SOMATROPIN ① Clinical Pharmacokinetic / Pharmacodynamic Studies				
Approved Year (Agency)	**2006 (EMA)**	**2009 (Health Canada)**	**2009 (PMDA)**	**2014 (MFDS)**
Products Name	**Omnitrope**		**Somatropin BS (Sandoz)**	**SciTropin A**
Reference Products	**Genotropin**			
Study Type	**3 PK/PD studies**	**4 PK/PD studies**	**6 PK/PD studies (1 pivotal, 5 supportive)**	**5 PK/PD studies**
Primary + Secondary objectives	Equivalence in PK/PD	Bioequivalence in PK/PD	Bioequivalence in PK/PD	Equivalence in PK/PD
Subjects Description	Healthy Adults			
Study Design	Randomized, double-blind, placebo-controlled, **2-way crossover study** Active-controlled, randomized, double-blind, **2-way crossover studies** - Somatropin Sandoz powder vs. Genotropin - Somatropin Sandoz powder vs. Somatropin Sandoz liquid	Active-controlled, **2-arm crossover trials** - Omnitrope powder vs. Genotropin - Omnitrope powder vs. Omnitrope solution Active-controlled, **3-arm crossover trials** - Omnitrope powder vs. Omnitrope solution (5 mg/1.5 mL) vs. Genotropin - Omnitrope powder vs. Omnitrope solution (10 mg/1.5 mL) vs. Genotropin	Randomized, double-blind, placebo-controlled, **2-way crossover study** Active-controlled, Randomized, double-blind, **2-way crossover studies** - SomatropinBS powder vs. Genotropin - SomatropinBS powder vs. liquid Active-controlled, Randomized, double-blind, **3-way crossover studies** SomatropinBS powder vs. SomatropinBS liquid vs. Genotropin - 2 Foreign studies - 1 Domestic study (single dose SC 0.07 mg/kg)	Randomized, double-blind, placebo-controlled, **2-way crossover study** Active-controlled, Randomized, double-blind, **2-way crossover studies** - Scitropin powder vs. Genotropin - Scitropin powder vs. Scitropin liquid Active-controlled, Randomized, double-blind, **3-way crossover studies** - Scitropin powder vs. Scitropin liquid (3.3 mg/mL) vs Genotropin - Scitropin powder vs. Scitropin liquid (6.7 mg/mL) vs Genotropin
	All administered at a single SC 5 mg		All administered at a single SC 5 mg except 1 domestic study	All administered at a single SC 5 mg
Primary Endpoints	***[PK]*** AUC and Cmax	***[PK]*** N/A	***[PK]*** AUC and Cmax	***[PK]*** AUC_{inf} and Cmax
	[PD] IGF-1, IGFBP-3, NEFA	***[PD]*** IGF-1, IGFBP-3, NEFA	***[PD]*** IGF-1, IGFBP-3, NEFA	***[PD]*** IGF-1, IGFBP-3, NEFA
Equivalence Margin	[PK] The acceptance range for the 90% CI was defined as 0.80-1.25 for AUC and Cmax. [PD] Not possible	N/A	90% CI of AUC and Cmax needs to be within 80-125%	90% CI of AUC and Cmax needs to be within 80-125%

NOTE	- Pharmacodynamic equivalence margin was not possible due to the following reasons. 1) endogenous GH was suppressed only part of the study duration 2) the variance of the measured parameters was high 3) pre-defined or generally accepted equivalence margin are missing	- Omnitrope powder (5.8 mg/mL)	-The margin was determined to be reasonable considering the followings. 1) Generally, 20% of difference in bioavailability shows no clinical meanings. 2) Guidelines on bioequivalence issued by Japan, the U.S., and Europe propose 0.80-1.25 as the margin of bioequivalence. 3) Somatropin is not a drug of narrow therapeutic range.	

Abbreviation: AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein 3; N/A, not available; NEFA, nonesterified fatty acid; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

SOMATROPIN ② Clinical Efficacy / Safety Studies				
Approved Year (Agency)	**2006 (EMA)**	**2009 (Health Canada)**	**2009 (PMDA)**	**2014 (MFDS)**
Products Name	**Omnitrope**		**Somatropin BS (Sandoz)**	**SciTropin A**
Reference Products	**Genotropin**			
Study Type	**2 pivotal efficacy comparative studies, 1 follow-up comparative efficacy study, 1 pivotal safety non-comparative study**	**3 comparative studies, 2 non-comparative studies**		**2 pivotal studies, 1 comparative study, 2 non-comparative studies**
Primary Objective + secondary objectives	Similarity in efficacy + Long-term safety + Immunogenicity	Efficacy + Long-term safety + Immunogenicity		Similarity in efficacy + Safety + Immunogenicity
Subjects Description	Children with growth hormone deficiency			
Study Design	Open-label, randomised, active-controlled, multicenter comparative studies - (Pivotal studies) Somatropin Sandoz powder vs. Genotropin - (Follow-up trial) Somatropin Sandoz powder → switched to Somatropin Sandoz liquid at week 15 vs. Somatropin Sandoz liquid Ongoing open, multicenter, non-comparative, non-controlled study - (Pivotal safety study) Omnitrope lyophilized formulation	Open-label, randomized, three sequential, parallel studies - Omnitrope powder continued beyond 9 months → switched to Omnitrope solution after 15 months Single-arm studies - Omnitrope solution - Omnitrope	*The applicant did not conduct any efficacy clinical trials in Japan.* *Just submitted overseas clinical study data as reference for safety evaluation*	Open-label, randomized, active-controlled comparative studies - (Pivotal studies) Scitropin powder vs. Genotropin - (Supportive study) Scitropin powder vs. Scitropin liquid Multicenter, non-comparative studies - Scitropin powder - Scitropin liquid
	All administered at a dose of SC 0.03 mg/kg/day (0.1 IU/kg/day)			
Primary Endpoints	***[Efficacy]*** - Height, HSDS at month 9 - HV, HVSDS between month 0 and 9 ***[Safety]*** Adverse events, anti-human GH antibody, anti-host cells proteins antibody	***[Efficacy]*** HV, HVSDS, height standardized for age and sex standard deviation score, serum levels of IGF-1 and IGFBP-3 ***[Safety]*** Adverse events/adverse drug reactions, anti- host cell peptides antibodies		***[Efficacy]*** HV, HVSDS, GSDS, height at month 6 and 9 ***[Safety]*** Anti-drug antibody, Neutralizing antibody
Statistics	Similarity	N/A		Similarity
Equivalence Margin	N/A	N/A		N/A

NOTE	**- One phase 3 comparative study consisting of three sub-studies**: **Arm 1**: Somatroin Sandoz Powder → Somatropin Sandoz Powder → Somatropin Sandoz solution **Arm 2**: Genotropin → Somatropin Sandoz Powder → Somatropin Sandoz solution	- Omnitrope powder (5.8 mg/mL) - Omnitrope solution (5 mg/1.5 mL) - **Arm A in three parallel studies**: Omnitrope powder → Omnitrope powder → Omnitrope solution - **Arm B in three parallel studies**: Genotropin → Omnitrope solution → Omnitrope solution		

Abbreviation: GH, growth hormone; GSDS, growth standard deviation score; HSDS, height standard deviation score; HV, height velocity; HVSDS, height velocity standard deviation score; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein 3; ISR, injection site reaction; IU, international unit; N/A, not available; SC, subcutaneous

Attachment 3A: Selected Summary of Regulatory Biosimilar Reviews by Year

INFLIXIMAB ① Clinical Pharmacokinetic / Pharmacodynamic Studies						
Approved Year (Agency)	**2012 (MFDS)**	**2013 (EMA)**	**2014 (EMA)**	**2014 (Health Canada)**	**2014 (Health Canada)**	**2014 (PMDA)**
Products Name	**Remsima**	**Remsima**	**Inflectra**	**Remsima**	**Inflectra**	**Infliximab BS (Celltrion, Nippon Kayaku)**
Reference Products	**Remicade**					
Study Type	**1 PK study**	**1 pivotal, 2 supportive PK studies**		**1 pivotal PK study**		**1 Japanese pivotal, 3 abroad supportive PK studies**
Primary + Secondary objective	Equivalence in PK					
Study Subject	Patients with AS	AS patients with active disease (supportive studies: RA patients with active disease and inadequate response to MTX while receiving MTX)				patients with active RA while receiving MTX (2 supportive abroad studies: patients with active RA while receiving MTX, 1 supportive study: Patients with active AS)
Study Design	N/A	Prospective Phase 1, randomized, double-blind, multicenter, parallel-group - Multiple single-dose IV infusion		Randomized, double-blind, multicenter, parallel-group		Randomized, double-blind, parallel-group, comparative - Multiple dose IV infusion
Primary Endpoint	***[PK]*** AUCτ, Cmax,ss between Weeks 22 and 30			***[PK]*** AUCτ, Cmax,ss		***[PK]*** Japanese study: AUCτ at Week 6-14 and Cmax at Week 6
	[PD] N/A	***[PD]*** (Supportive study: Markers of disease activity: CRP, rheumatoid factor, ESR, anti-CCP concentration at Week 14 and 30)		***[PD]*** N/A		***[PD]*** N/A
Equivalence Margin	N/A	Equivalence; 2-sided equivalence margin of 80-125% for AUCτ and Cmax,ss in all-randomized population		N/A		Japanese study: Equivalence; 2-sided equivalence margin of 80-125% for AUCτ and Cmax,ss
NOTE				When the primary endpoints were assessed not mentioned in the assessment report		Primary endpoints and equivalence margin of pivotal PK study not mentioned in the assessment report

Abbreviation: anti-CCP, antibodies against cyclic citrullinated peptide; AS, ankylosing spondylitis; AUCτ, area under the concentration-time curve over the dosing interval; Cmax.ss, maximum serum concentration at steady state; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; MTX, methotrexate; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis

INFLIXIMAB ② Clinical Efficacy / Safety Studies						
Approved Year (Agency)	**2012 (MFDS)**	**2013 (EMA)**	**2014 (EMA)**	**2014 (Health Canada)**	**2014 (Health Canada)**	**2014 (PMDA)**
Products Name	**Remsima**	**Remsima**	**Inflectra**	**Remsima**	**Inflectra**	**Infliximab BS (Celltrion, Nippon Kayaku)**
Reference Products	**Remicade**					
Study Type	**1 comparative study**	**1 pivotal, 1 supportive comparative studies**				**1 pivotal abroad comparative study**
Primary + Secondary objective	Equivalence in efficacy and safety					
Study Subjects	Patients with RA	RA patients with active disease and inadequate response to MTX while receiving MTX (supportive study: patients with active AS)				
Study Design	N/A	Prospective Phase 3, randomised, double-blind, multicentre, parallel-group - Multiple single-dose IV infusion		Randomized, double-blind, multicentre, parallel-group		Phase 3, randomised, double-blind, parallel-group, comparative
Primary Endpoint	***[Efficacy]*** % patients achieving ACR20 at week 30 ***[Safety]*** - Adverse events (infections, malignant tumor and lymphoproliferative diseases, heart failure, Infusion-related reactions, infusion-related reactions after reinfusion, delayed reactions/reaction after reinfusion, liver and biliary system, antinuclear antibodies) - Anti-infliximab antibodies	***[Efficacy]*** % patients achieving ACR20 response at week 30 (supportive study: proportion of patients achieving clinical response according to the ASAS 20 and ASAS40 criteria at Week 14 and 30) ***[Safety]*** - Adverse events, death, hypersensitivity via vital signs, electrocardiogram, physical examination, clinical laboratory tests, concomitant medications, signs and symptoms of tuberculosis, pregnancy, infections, infusion-related reactions, safety issues of special interest for infliximab - Anti-drug antibodies, neutralising anti-drug antibodies		***[Efficacy]*** Proportion of ACR20 responders at Week 30 (supportive study: proportions of patients achieving an ASAS 20 response (an improvement of ≥20%) at Week 30) ***[Safety]*** Adverse events, serious adverse event, treatment-emergent adverse events		***[Efficacy]*** % patients achieving ACR20 response at week 30 (supportive study: % patients achieving ACR20/ACR50/ACR70 response at Week 14, 30, and 54) ***[Safety]*** - Adverse events, serious adverse event, death, active tuberculosis - Anti-drug antibodies, neutralizing anti-drug antibodies at Week 14, 30, and 54
Statistics	Equivalence					
Equivalence Margin	N/A	95% CI for the difference in ACR20 contained within the equivalence margin of -15% to 15% in per-protocol population				
NOTE	Equivalence margin not mentioned in the assessment report					

Abbreviation: ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, assessment of spondyloarthritis International Society; IV, intravenous; MTX, methotrexate; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis

INSULIN GLARGINE ① Clinical Pharmacokinetic / Pharmacodynamic Studies

Attachment 3A: Selected Summary of Regulatory Biosimilar Reviews by Year

Approved Year (Agency)	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Abrasia**	**Insulin glargine BS (Lilly)**
Reference Products	**Lantus**	
Study Type	**6 PK/PD studies** (3 pivotal studies, 3 supportive studies)	**1 PK/PD study**
Primary + Secondary Objective	Equivalence in PD + PK	Equivalence in PD + PK
Study Subjects	Healthy adult male and female	Foreign healthy volunteers
Study Design	[Pivotal studies] Randomized, double-blind, single dose, crossover, 24-hour euglycemic glucose clamp studies in single centers - 2-treatment (LY2963016 and EU-approved Lantus) - 2-treatment (EU-approved Lantus and US-approved Lantus) - 2-treatment (LY2963016 and US-approved Lantus) [Supportive studies] Randomized, double-blind, single dose, crossover, 24-hour euglycemic glucose clamp studies in single centers - 4-treatment (at two additional dose levels) - Duration of action studies in patients	Randomized, double-blind, single dose, crossover, 24-hour euglycemic glucose clamp study - 2-treatment
Primary Endpoint	***[PK]*** AUC_{0-24h}, $AUC_{0-\infty}$, Cmax	***[PK]*** AUC_{0-24h}, Cmax
	[PD] Gtot, Rmax	***[PD]*** Gtot, Rmax
Statistics	Equivalence	
Equivalence Margin	90% CIs within the pre-specified interval 0.80 to 1.25	[PK] 90% CIs within the pre-specified interval 0.80 to 1.25 [PD] 95% CIs within the pre-specified interval 0.80 to 1.25
NOTE		

Abbreviation: AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; Gtot, total amount of glucose infused ; N/A, not available; PD, pharmacodynamics; PK, pharmacokinetics; Rmax, maximum glucose infusion rate; T1DM, type 1 diabetes mellitus

INSULIN GLARGINE ② Clinical Efficacy / Safety Studies		
Approved Year (Agency)	**2014 (EMA)**	**2014 (PMDA)**
Products Name	**Abrasia**	**Insulin glargine BS (Lilly)**
Reference Products	**Lantus**	
Study Type	**2 comparative studies**	**2 comparative studies** (1 study for evaluation, 1 supportive study)
Primary, Secondary Objective	Non-inferiority in efficacy + safety	Non-inferiority in efficacy + safety
Study Subjects	T1DM T2DM	[Evaluation study] Foreign and Japanese T1DM patients [Supportive study] Foreign T2DM patients
Study Design	Phase 3, prospective, randomized, multicenter, 2-arm, active-control, parallel studies - Open label - Double-blind	[Evaluation study] Phase 3, randomized, parallel study - Open label [Supportive study] Phase 3, randomized, parallel study - Double label
Primary Endpoint	***[Efficacy]*** Change in HbA1c (%) at 24 weeks % of patients achieving HbA1c target <7.0% or ≤6.5%at 24 weeks ***[Safety]*** AEs, study discontinuations, hypoglycaemic episodes, injection site reactions, serious AEs, deaths, treatment-related AEs	***[Efficacy]*** Change in HbA1c (%) at 24 weeks ***[Safety]*** AEs, study discontinuations, hypoglycaemic episodes, injection site reactions, serious AEs, deaths
Statistics	Non-inferiority	
Equivalence Margin	0.05 two-sided 0.3% non-inferiority margin with 90% power (the same sample size needed to show 0.4% non-inferiority margin with > 99% power)	95% CIs for 0.4% non-inferiority margin
NOTE		

Abbreviations: AEs, adverse events; CI, confidence interval; HbA1c, glycated hemoglobin; N/A, not available; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus