KYOWA KIRIN

FUJIFILM

ヒュミラバイオシミラー（FKB327）のグローバル開発

協和キリン富士フイルムバイオロジクス株式会社
鳥居義史
2018年12月14日

KYOWA KIRIN FUJIFILM

内容

1. 先発品（Humira）の基本情報
2. 製剤開発戦略
3. 臨床開発戦略
4. シミラリティー評価
5. バイオシミラー開発上の留意点・課題

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先発品基本情報1

商品名(一般名)	ヒュミラ（アダリムマブ）		
分子種	ヒト型抗TNF-αモノクローナル抗体 (IgG)		
投与経路	皮下投与		
剤型	欧州	米国	日本
80mg/0.8mL PFS・AI	○	△ （AI発売）	○
40mg/0.8mL PFS・AI	△ （高濃度へ切替え）	○	×
40mg/0.4mL PFS・AI	○	△ （AI発売）	○
20mg/0.4mL PFS	×	○	△ （19年3月で経過措置期間終了）
20mg/0.2mL PFS	△ （英・独　既に発売）	○	○
10mg/0.2mL PFS	×	○	×
10mg/0.1mL PFS	×	○	×
40mg/0.8mL キット製剤 （バイアル＋シリンジ）	○	×	×

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先発品基本情報2

適応症	欧州	米国	日本
関節リウマチ（RA）	**40mg隔週（毎週可）**	**40mg隔週（毎週可）**	**40mg隔週（80mg可）**
強直性脊椎炎（AS）	**40mg隔週**	**40mg隔週（毎週可）**	**40mg隔週（80mg可）**
関節症性乾癬（PsA）	40mg隔週	40mg隔週（毎週可）	80→40mg隔週（80mg可）
尋常性乾癬（Ps）：成人	**80→40mg隔週**	**80→40mg隔週**	**80→40mg隔週（80mg可）**
尋常性乾癬（Ps）：小児	BW<30kg; 20mg隔週 BW≧30kg; 40mg隔週	NA	NA
膿疱性乾癬	NA	NA	80→40mg隔週（80mg可）
クローン病（CD）：成人	80→40mg隔週 （160→80mg隔週可）	160→80→40mg隔週	160→80→40mg隔週 （80mg可）
クローン病（CD）：小児	BW<40kg; 40→20mg隔週 BW≧40kg; 80→40mg隔週	BW<40kg; 80→40→20mg隔週 BW≧40kg; 160→80→40mg隔週	NA
潰瘍性大腸炎（UC）	**160→80→40mg隔週**	**160→80→40mg隔週**	**160→80→40mg隔週**

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先発品基本情報3

適応症	欧州	米国	日本
ベーチェット病	NA	NA	160→80→40mg 隔週
若年性特発性関節炎（JIA）	10-30kg:20mg隔週 ≧30kg:40mg隔週	10-15kg:10mg隔週 15-30kg:20mg隔週 ≧30kg:40mg隔週	15-30kg:20mg隔週 ≧30kg:40mg隔週
汗腺膿瘍（HS）：成人	160→80→40mg	160→80→40mg	NA
汗腺膿瘍（HS）：青少年	80→40mg隔週（毎週可）	<60kg: 80mg→40mg隔週 ≧60kg: 160mg→80mg→40mg	NA
ぶどう膜炎（UV）：成人	**80→40mg隔週**	**80→40mg隔週**	**80→40mg隔週**
ぶどう膜炎（UV）：小児	<30kg:20mg隔週 (40→20mg隔週可) ≧30kg:40mg隔週 (80→40mg隔週可)	NA	NA

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内容

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FKB327製剤開発戦略

有効性・安全性に影響しない範囲内で、先発薬との差別化を図る。

1. ラインナップ
   - 先発品と同じプレフィルドシリンジ（PFS），オートインジェクター（AI），バイアルの3剤形を開発
2. 処方
   - 痛みとの関連性が報告されているクエン酸を含まない処方を開発
3. 容器・デバイス
   - 針を27Gから、より細い29Gへ変更
   - シリンジ素材をガラス製からプラスティック製に変更
   - PFSにセーフティデバイスを付加
   - AIをより操作が容易な機構・デザインに変更

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FKB327/Humiraの処方

FKB327	Humira (50mg/ml)
Monosodium Glutamate Sorbitol Methionine Polysorbate 80 Hydrochloric Acid	Sodium Chloride Monobasic Sodium Phosphate Dihydrate Dibasic Sodium Phosphate Dihydrate Sodium Citrate Citric Acid Monohydrate Mannitol Polysorbate 80 Sodium Hydrate
	Humira (100mg/ml)
	Mannitol Polysorbate 80

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FKB327/Humiraの剤形（PFS/AI）

FKB327

plastic syringe
with safety device

Humira

glass syringe

FKB327

2 steps AI

Humira

3 steps AI

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(NICE guidance)

FKB327臨床開発戦略

1. 適応症
   - 主要国間で共通の用法用量
   - 先発薬の臨床試験結果の可用性
   - Extraporationの可能性
     - Amgen: RA & Ps
     - Sandoz: Ps
     - Boehringer Ingelheim, Samsung: RA
   - 想定被験者数、試験期間

2. 主要評価項目
   - 規制当局の異なる要求を調整

3. その他
   - 先発薬との盲検性の担保
   - 先発品のソース
   - 臨床使用状況、保険償還状況等を考慮した治験実施国の選定

(NICE guidance)

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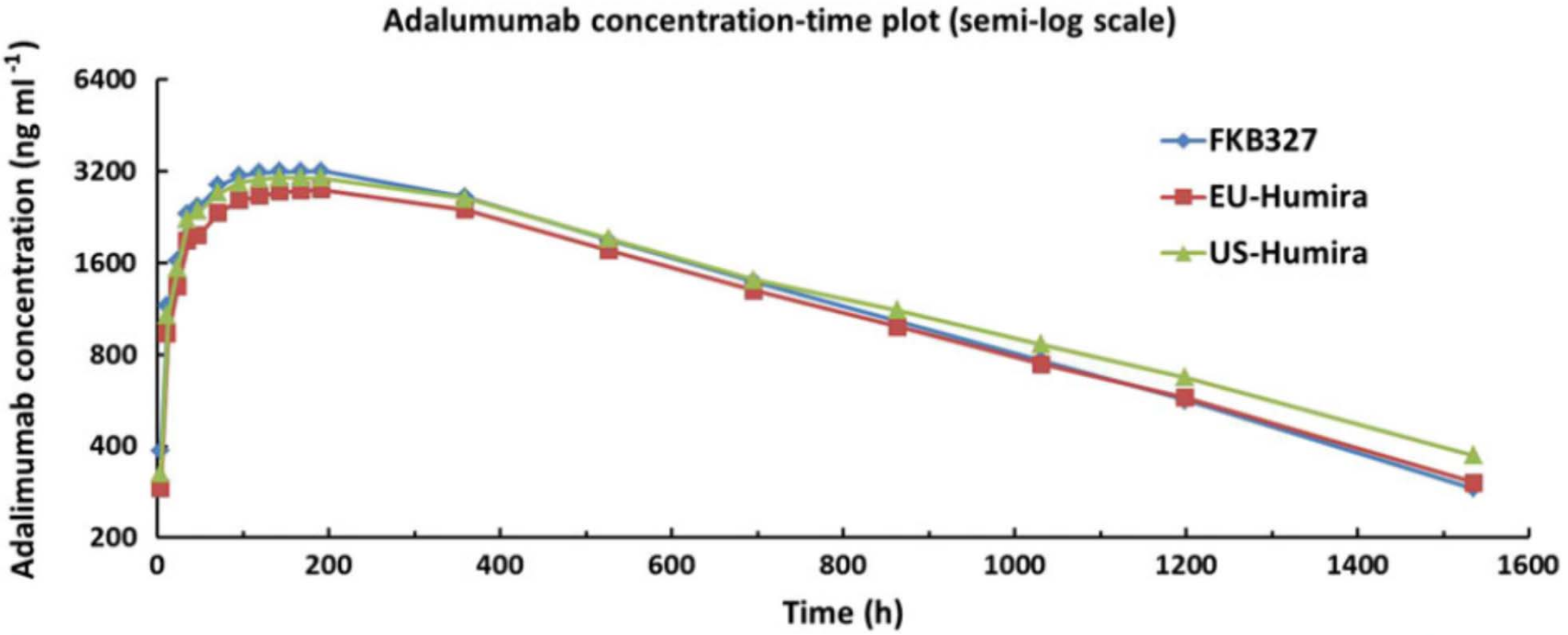
FKB327_ pivotal PK study



Pharmacokinetic parameter		Ratio of geometric least squares means (90% CI)		
		FKB327/ EU-Humira	FKB327/ US-Humira	EU-Humira/ US-Humira
Primary	$AUC_{0-\infty}$ (h*ng ml^{-1})	1.06 (0.94, 1.18)[a]	0.98 (0.88, 1.10)[a]	0.93 (0.83, 1.04)[a]
	AUC_{0-t} (h*ng ml^{-1})	1.08 (0.97, 1.20)[a]	1.01 (0.91, 1.12)[a]	0.93 (0.84, 1.03)[a]
	C_{max} (ng ml^{-1})	1.13 (1.03, 1.23)[a]	1.07 (0.98, 1.17)[a]	0.95 (0.87, 1.04)[a]
Secondary	AUC_{0-360h} (h*ng ml^{-1})	1.12 (1.02, 1.23)[a]	1.04 (0.95, 1.14)[a]	0.93 (0.85, 1.02)[a]
	t½ (h)	0.95 (0.83, 1.10)[a]	0.90 (0.78, 1.03)	0.94 (0.82, 1.08)[a]

$AUC_{0-\infty}$, area under concentration–time curve extrapolated to infinity; AUC_{0-t}, area under concentration–time curve up to last nonzero value; C_{max}, peak plasma concentration; AUC_{0-360h}, area under concentration–time curve up to 360 h; $t_{½}$, elimination half-life.
Note: for C_{max}, age, weight and sex were included in the model; for both $AUC_{0-\infty}$ and AUC_{0-t}, age and weight were included in the model. For the secondary parameters, the covariates were forced to be age and weight as for the primary AUC parameters.
[a]90% CI within predefined limits (0.80, 1.25) concluding equivalence

(Br J Clin Pharmacol 2017 Jul; 83(7): 1405-1415)

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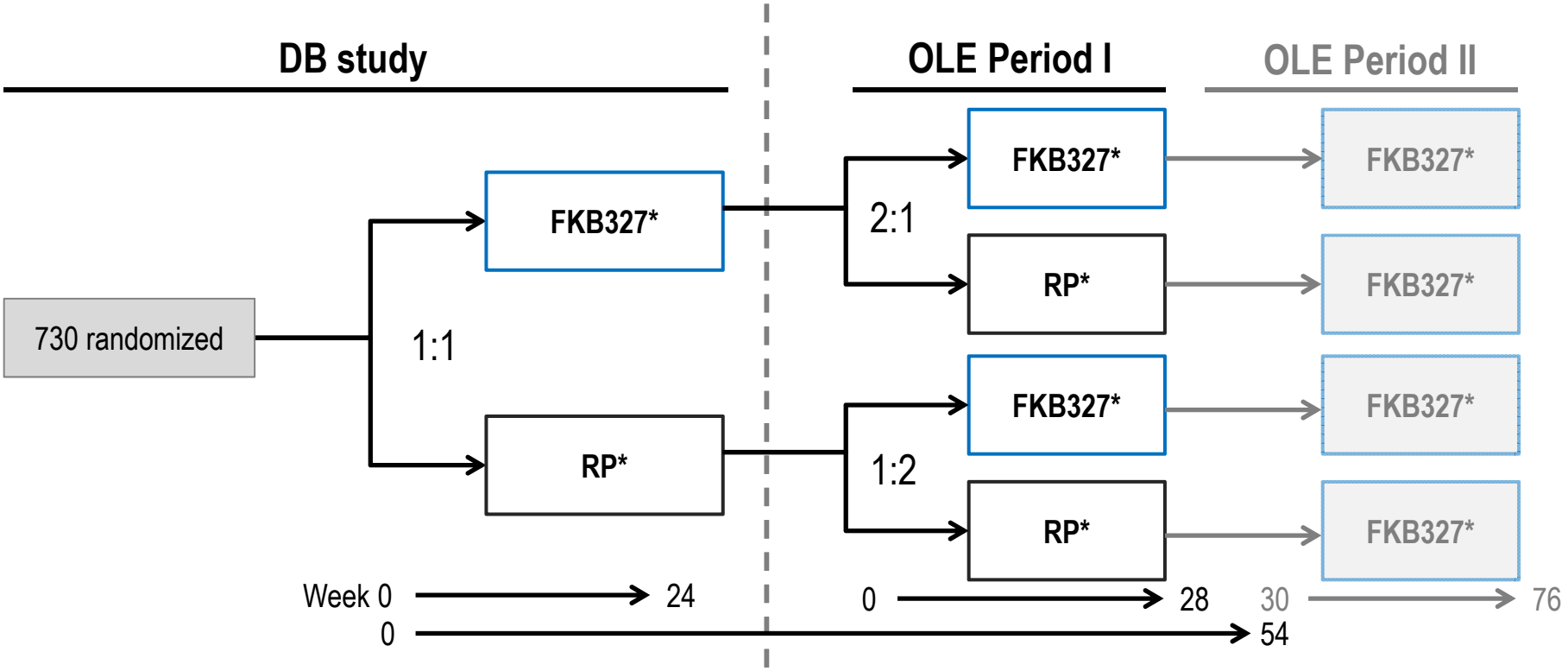
FKB327_ Phase 3 study_ Designs



*40 mg subcutaneously every other week with MTX.

DB, double-blind; MTX, methotrexate; OLE, open-label extension; RP, reference product.

(ACR / ARHP Annual Meeting, San Diego, CA, USA, 17 November 2017)

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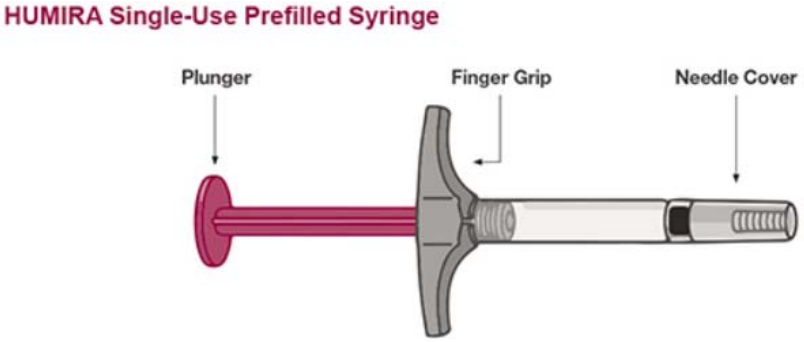
臨床試験での盲検性確保

1. 概観が同一な対照薬と治験薬
2. マスキング
3. Unblinded teamによる投与

Blinding Solutions

More than just Labels
Blinding products



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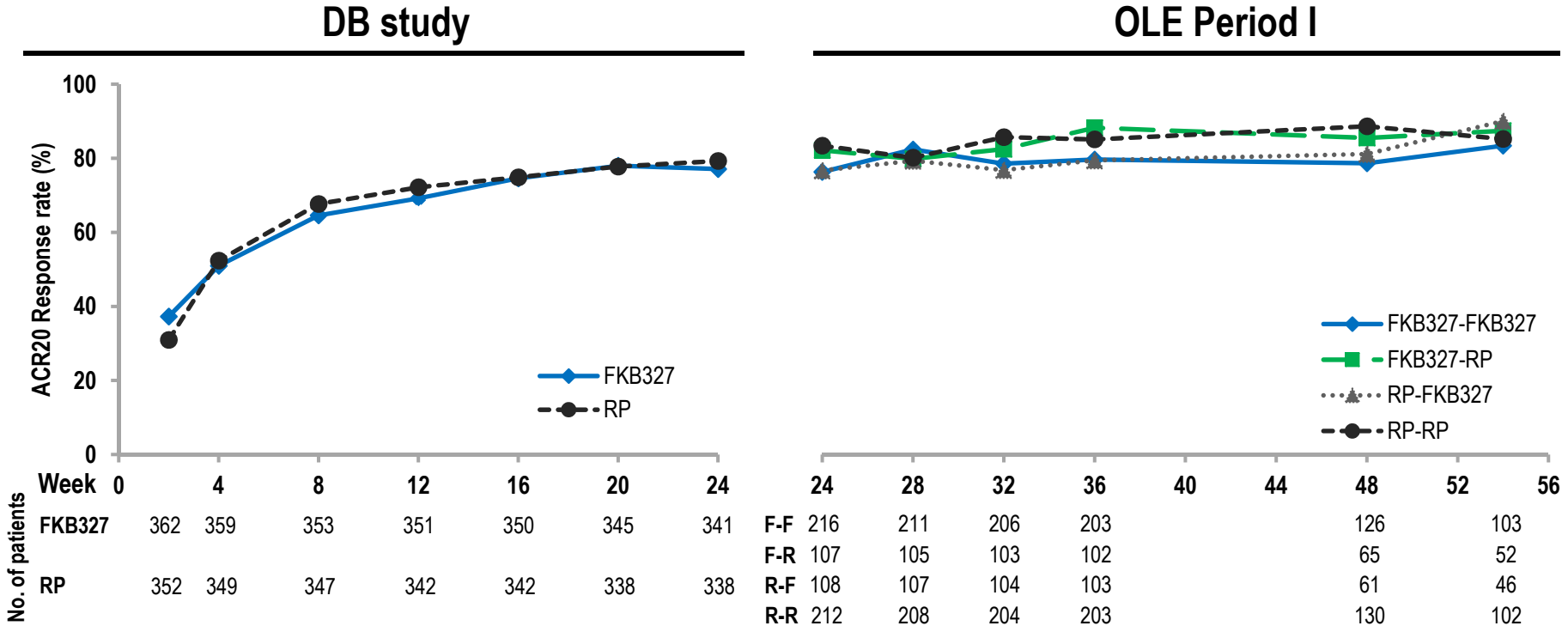
FKB327_ Phase 3 study_ Efficacy



ACR20 at Week 24 (Full Analysis Set)	FKB327 (n=363)	RP (n=358)
Patients achieving an ACR20 response, n (%)	263 (72.5)	266 (74.3)
Difference (FKB327 minus RP)	–1.8	
90% CI	–7.3, 3.6	

Data are from the Full Analysis Set (as observed) of the DB study and OLE individual analyses respectively.
ACR, American College of Rheumatology; DB, double-blind; OLE, open-label extension; RP, reference product.

(ACR / ARHP Annual Meeting, San Diego, CA, USA, 17 November 2017)

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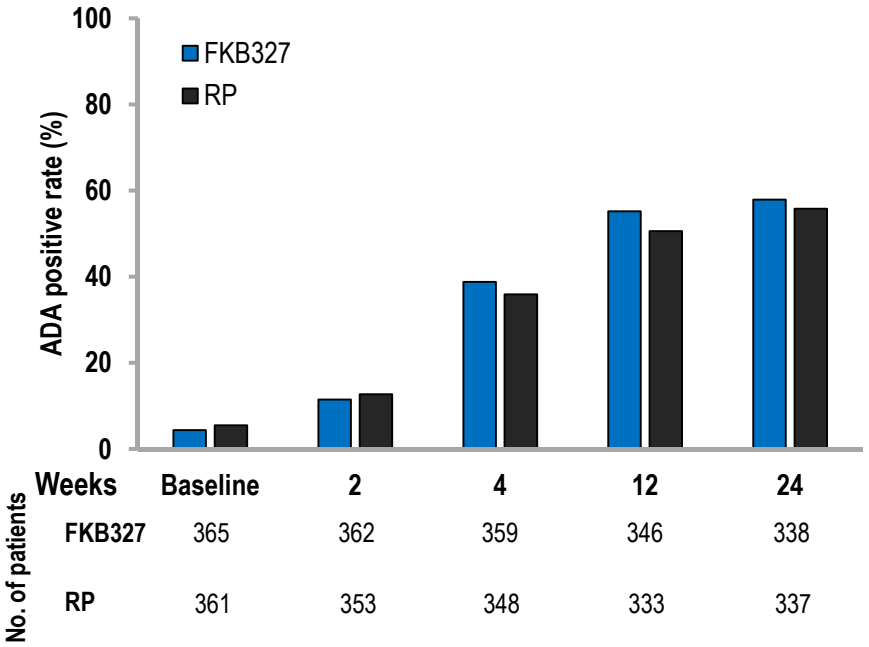
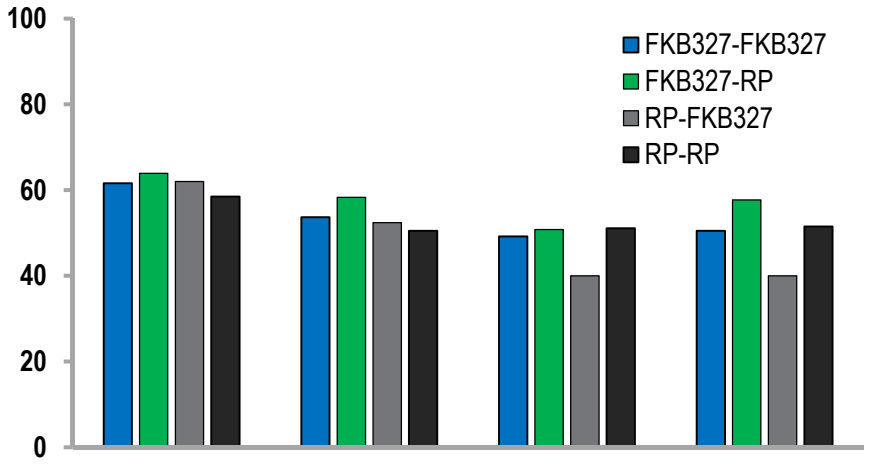
FKB327_ Phase 3 study_ Immunogenicity

DB study



No. of patients	Weeks	Baseline	2	4	12	24
	FKB327	365	362	359	346	338
	RP	361	353	348	333	337

OLE Period I



	24	36	48	54
F-F	216	201	126	103
F-R	108	102	63	52
R-F	108	103	60	45
R-R	212	202	131	103

Data are at the last sampling time point, from the DB study and OLE individual analyses respectively.
ADA, anti-drug antibody; DB, double-blind; OLE, open-label extension; RP, reference product.

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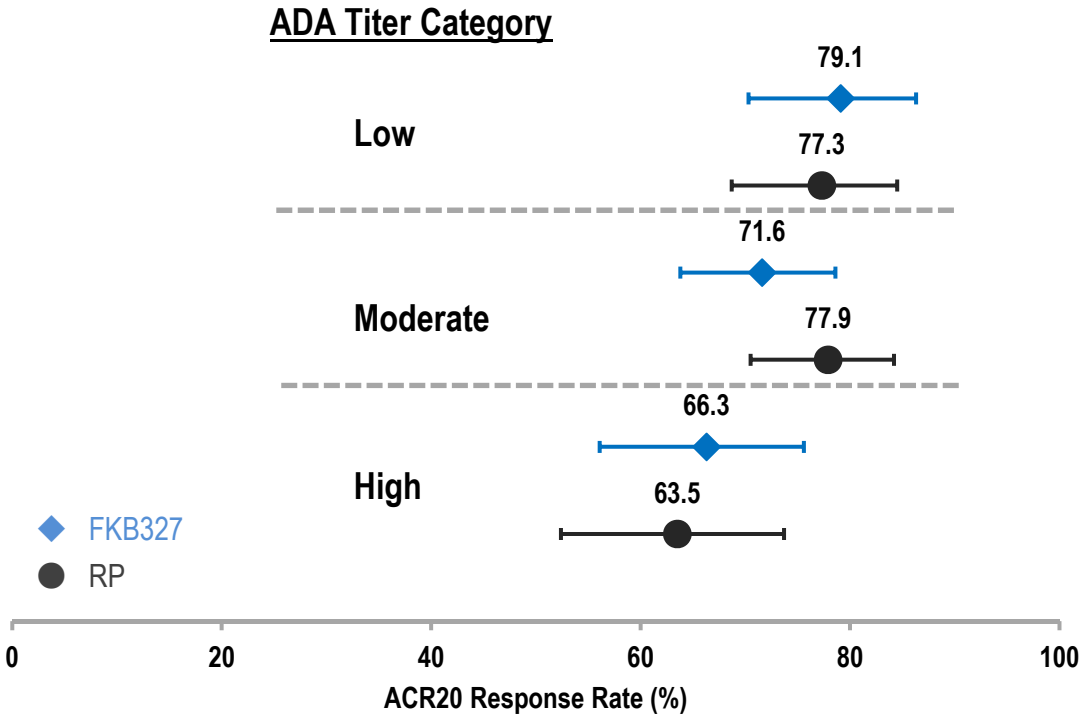
FKB327_ Phase 3 study_ Immunogenicity



ADA titer category

Based on Maximum ADA titer result during treatment:

- **Low:** Less than or equal to the lower quartile
- **Moderate:** Between the lower and upper quartile (neither included)
- **High:** Greater than or equal to the upper quartile

Data are from the Full Analysis Set (non-responder imputation) of the DB study.
ACR, American College of Rheumatology; ADA, anti-drug antibody; DB, double-blind; RP, reference product.

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FKB327_ Phase 3 study_ Safety

Integrated analysis: Summary of the incidence of TEAEs

	FKB327 (N=577) 371.87 patient-years		RP (N=470) 309.88 patient-years	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Deaths	2 (0.3)	NC	1 (0.2)	NC
Patients with ≥1 TEAE	308 (53.4)	2.55 (2.39–2.72)	298 (63.4)	2.70 (2.52–2.89)
Patients with ≥1 severe TEAE	17 (2.9)	NC	12 (2.6)	NC
Patients with ≥1 treatment-related TEAE	125 (21.7)	0.70 (0.62–0.79)	125 (26.6)	0.75 (0.66–0.85)
Patients who prematurely discontinued due to a TEAE	28 (4.9)	0.10 (0.08–0.14)	20 (4.3)	0.07 (0.04–0.10)
TESAEs (number of events)	40	NC	34	NC
Patients with ≥1 TESAE	29 (5.0)	0.11 (0.08–0.15)	31 (6.6)	0.11 (0.08–0.15)

Data are from an integrated analysis of the Safety Analysis Sets from the DB and OLE studies. n, number of patients experiencing event.
CI, confidence interval; DB, double-blind; IR, incidence rate (events per patient-year); NC, not calculated; OLE, open-label extension; RP, reference product; TEAE, treatment-emergent adverse event; TESAE, treatment emergent serious adverse event.

(ACR / ARHP Annual Meeting, San Diego, CA, USA, 17 November 2017)

KYOWA KIRIN FUJIFILM

FKB327_ Phase 3 study_ Safety

Integrated analysis: Incidence of TEAEs occurring in ≥3% patients

System organ class preferred term	FKB327 (N=577) 371.87 patient-years			RP (N=470) 309.88 patient-years		
	n (%)	Events	IR (95% CI)	n (%)	Events	IR (95% CI)
Gastrointestinal disorders	50 (8.7)	68	0.18 (0.14–0.23)	52 (11.1)	65	0.21 (0.16–0.27)
Diarrhoea	12 (2.1)	14	0.04 (0.02–0.06)	18 (3.8)	22	0.07 (0.05–0.11)
Infections and infestations	151 (26.2)	256	0.69 (0.61–0.78)	160 (34.0)	245	0.79 (0.70–0.90)
Bronchitis	18 (3.1)	18	0.05 (0.03–0.08)	26 (5.5)	28	0.09 (0.06–0.13)
Nasopharyngitis	38 (6.6)	47	0.13 (0.09–0.17)	43 (9.1)	51	0.16 (0.13–0.22)
Pharyngitis	14 (2.4)	16	0.04 (0.03–0.07)	14 (3.0)	15	0.05 (0.03–0.08)
Upper respiratory tract infection	18 (3.1)	21	0.06 (0.04–0.09)	28 (6.0)	30	0.10 (0.07–0.14)
Urinary tract infection	25 (4.3)	33	0.09 (0.06–0.12)	16 (3.4)	23	0.07 (0.05–0.11)
Metabolism and nutrition disorders	43 (7.5)	51	0.14 (0.10–0.18)	32 (6.8)	43	0.14 (0.10–0.19)
Hypercholesterolaemia	20 (3.5)	22	0.06 (0.04–0.09)	15 (3.2)	17	0.05 (0.03–0.09)
Musculoskeletal and connective tissue disorders	70 (12.1)	111	0.30 (0.25–0.36)	61 (13.0)	89	0.29 (0.23–0.35)
Rheumatoid arthritis	28 (4.9)	40	0.11 (0.08–0.15)	22 (4.7)	28	0.09 (0.06–0.13)
Vascular disorders	25 (4.3)	27	0.07 (0.05–0.11)	24 (5.1)	29	0.09 (0.07–0.13)
Hypertension	13 (2.3)	14	0.04 (0.02–0.06)	18 (3.8)	19	0.06 (0.04–0.10)

Data are from an integrated analysis of the Safety Analysis Sets from the DB and OLE studies. N, number of patients in Safety Analysis Set; n, total number of patients with observation
CI, confidence interval; DB, double-blind; IR, incidence rate (events per patient-year); OLE, open-label extension; RP, reference product; TEAE, treatment-emergent adverse event.

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(NICE guidance)

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Biosimilarity assessment

1. Physicochemical method
   - Primary structure
   - High order structure
   - Glycosylation
   - Size heterogeneity
   - Amino acid modifications
   - Process related impurities
   - Visible and sub-visible particles
   - Strength

2. Binding assays

3. in-vitro bioassays

(EPAR, EMA)

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Physicochemical method			
Primary structure	Amino acid sequence	N-terminal amino acid sequencing	Consistent with Humira
		Peptide mapping (LC/MS)	Consistent with Humira
		C-terminal amino acid	Consistent with Humira
	Disulfide bond	Reduced/Non-reduced peptide mapping (LC/MS)	Consistent with Humira
	N-glycosylation site	N-glycosydase F-digested/Non-digested peptide mapping	Consistent with Humira
	Molecular weight	Intact MS	Consistent with Humira
	pI	IEF	Consistent with Humira
	Extinction coefficient	AAA and UV spectroscopy	Consistent with Humira

(EPAR, EMA)

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Physicochemical method			
High order structure	Secondary structure	Far-UV CD	Visually identical to Humira
		FT-IR	Visually identical to Humira
	Tertiary structure	Near-UV CD	Visually identical to Humira
		IF	Similar maximum wavelength.
		DSC	Similar profile, with a minor difference in T_m due to the formulation buffers. Difference not clinically meaningful

(EPAR, EMA)

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Physicochemical method			
Glycosylation	Mannosylation (M5), Galactosylation, Fucosylation and Sialylation	N-linked glycan profiling	Minor quantitative differences in non-fucosylated variants and sialic acid. Differences not clinical meaningful.
	Galactose, Fucose, Mannose, GlcNac and Sialic acid contents	Monosaccharide analysis	Minor quantitative differences in galactose and sialic acid. Differences not clinical meaningful.
	Glycosylation site occupancy	CE-SDS (R)	Comparable amounts of glycosylation site occupancy
	Non-consensus glycosylation content	CE-SDS (R)	Comparable amounts of non-consensus glycosylation content

(EPAR, EMA)

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Physicochemical method			
Size heterogeneity	HMWS (aggregates), Main species (HC+LC or monomer), MMWS and LMWS (fragments)	CE-SDS (R), CE-SDS (NR)	Minor quantitative differences in MMWS and LMWS. Differences not clinically meaningful.
	HMWS (aggregates), Monomer, LMWS (fragments)	SE-HPLC	Level of HMWS are quantitatively comparable.
	HMWS (aggregates), Monomer, LMWS (fragments)	FFF	Level of HMWS are quantitatively comparable.

(EPAR, EMA)

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Physicochemical method			
Amino acid modifications	C-terminal variants (Lys variants, amidated proline)	Reduced Peptide mapping (LC/MS)	Quantitative differences in C-terminal variants. Difference not clinically meaningful.
	N-terminal variants	Reduced Peptide mapping (LC/MS)	Comparable amounts of N-terminal variants
	Deamination/ Isomerization	Reduced Peptide mapping (LC/MS)	Comparable amounts of deamidated/isomerized variants
	Glycation	BAC	Comparable amounts of glycated variants
	Oxidation	Reduced Peptide mapping (LC/MS)	Comparable amounts of oxidized variants
	Sulfhydryl content	Ellman's assay	Comparable amounts of sulfhydryl content
	Trisulfide	Non-reduced Peptide mapping (LC/MS)	Quantitative differences in the trisulfide variants. Difference not clinically meaningful.
	Thioether	CE-SDS (R)	Comparable amounts of thioether
	Cysteinylation	CE-SDS (NR)	Comparable amounts of cysteinylated variants

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Physicochemical method			
Process related impurities	Residual DNA	Threshold assay	Comparable amounts of residual DNA
	HCP	ELISA	Lower HCP content in Hulio
Visible and sub-visible particles	Visible particles	Visual inspection	Practically free from particles
	Sub-visible particles	Light obscuration	Lower amounts of sub-visible particles in Hulio
		MFI	Common features to Humira
Strength	Protein concentration	UV absorbance at 280 nm	Comparable concentration

(EPAR, EMA)

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Binding assays and *in-vitro* bioassays			
Binding assays	Soluble rhTNF-α binding	ELISA assay	Comparable binding
	Soluble rhTNF-α binding	Surface Plasmon	Comparable K_D
	tm rhTNF-α binding	Flow cytometry assay	Comparable binding
	FcγRI binding	SPR assay	Comparable KD
	FcγRIIa binding	SPR assay	Comparable KD
	FcγRIIb binding	SPR assay	Comparable KD
	FcγRIIIa(V) binding	SPR assay	Comparable KD
	FcγRIIIa(F) binding	SPR assay	Comparable KD
	FcγRIIIbNA1 binding	SPR assay	Comparable KD
	FcγRIIIbNA2 binding	SPR assay	Comparable KD
	FcRn binding	SPR assay	Comparable KD
	C1q binding	ELISA assay	Comparable binding

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Biosimilarity assessment

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Binding assays and *in-vitro* bioassays			
In-vitro bioassays	Cytotoxicity neutralization	Cell-based assay	Comparable activity
	Apoptosis inhibition	Cell-based assay	Comparable activity
	ADCC	Cell-based assay	Comparable activity
	CDC	Cell-based assay	Comparable activity
	Regulatory macrophage induction in MLR assay	Cell-based assay	Comparable activity

(EPAR, EMA)

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競合品の欧州承認及び先発品企業との和解状況

AbbVieとの和解により、2018年10月16日以降に欧州マーケットへ上市可能

Product	Company	EU Approval	Settlement w/ AbbVie
AMGEVITA	Amgen	22 Mar 2017	Done
IMRALDI	Samsung Bioepis	24 Aug 2017	Done
CYLTEZO	Boehringer Ingelheim	10 Nov 2017	Not yet
HYRIMOZ	Sandoz	26 Jul 2018	Done
HULIO	FKB/Mylan	17 Sep 2018	Done
MSB11022	Fresenius Kabi	Not approved	Done
M923	Momenta	Not approved	Done

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(NICE guidance)

KYOWA KIRIN FUJIFILM

バイオシミラー開発における留意点及び課題

■ TPPの設定
1. 差別化ポイント
2. 製剤選択
3. 製造コスト削減

■ 知財__自社権利の行使より Freedom to Operate の確保
1. 用法・用量特許、製法関連特許が大きなハードル
2. 参入時期を設定し、各種試験、PPQ等のスケジュールをバックキャスティング
3. 用途（適応症）が残存している場合、適応症パターン毎に申請ブランド名
4. BSメーカー間の特許問題

■ 臨床開発
1. 各国規制当局要求への対応
2. 臨床試験を実施する適応症の選定
3. 治験実施国の選定（用法用量等の確認）
4. 実薬比較DBTでの盲検性の確保

■ その他
1. 先発品のBS対抗施策
2. 政治・地政学的リスク