



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

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1. BIOWAVER REQUEST FOR DIFFERENT STRENGTHS

1.1. Qualitative and Quantitative Composition of the Test Product

Table 1: Qualitative and Quantitative Composition of the Test Product BDP/FFD pMDI 100/6 mcg/actuation

Ingredient	Function	Strength (label claim)			
		Quantity per container (mg)	Quantity per actuation (ex-valve) (mcg)	%w/w	Ref to Standard
Beclometasone dipropionate	Active Ingredient	15.996	100	0.172	Ph. Eur.
Formoterol fumarate dihydrate	Active Ingredient	0.93	6	0.01	Ph. Eur.
Ethanol, anhydrous	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
Water	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
Maleic acid	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
HFA-134a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
TOTAL	[REDACTED]	[REDACTED]	[REDACTED]	100	-

From Section 3.2.P.1



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

Table 2: Qualitative and Quantitative Composition of the Test Product BDP/FFD pMDI 200/6 mcg/actuation

Ingredient	Function	Strength (label claim)			
		Quantity per container (mg)	Quantity per actuation (ex-valve) (mcg)	%w/w	Ref to Standard
Beclometasone dipropionate	Active Ingredient	31.98	200	0.271	Ph. Eur.
Formoterol fumarate dihydrate	Active Ingredient	0.94	6	0.008	Ph. Eur.
Ethanol, anhydrous	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
Water	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
Maleic acid	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
HFA-134a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Ph. Eur.
TOTAL	[REDACTED]	[REDACTED]	[REDACTED]	100	-

From Section 3.2.P.1



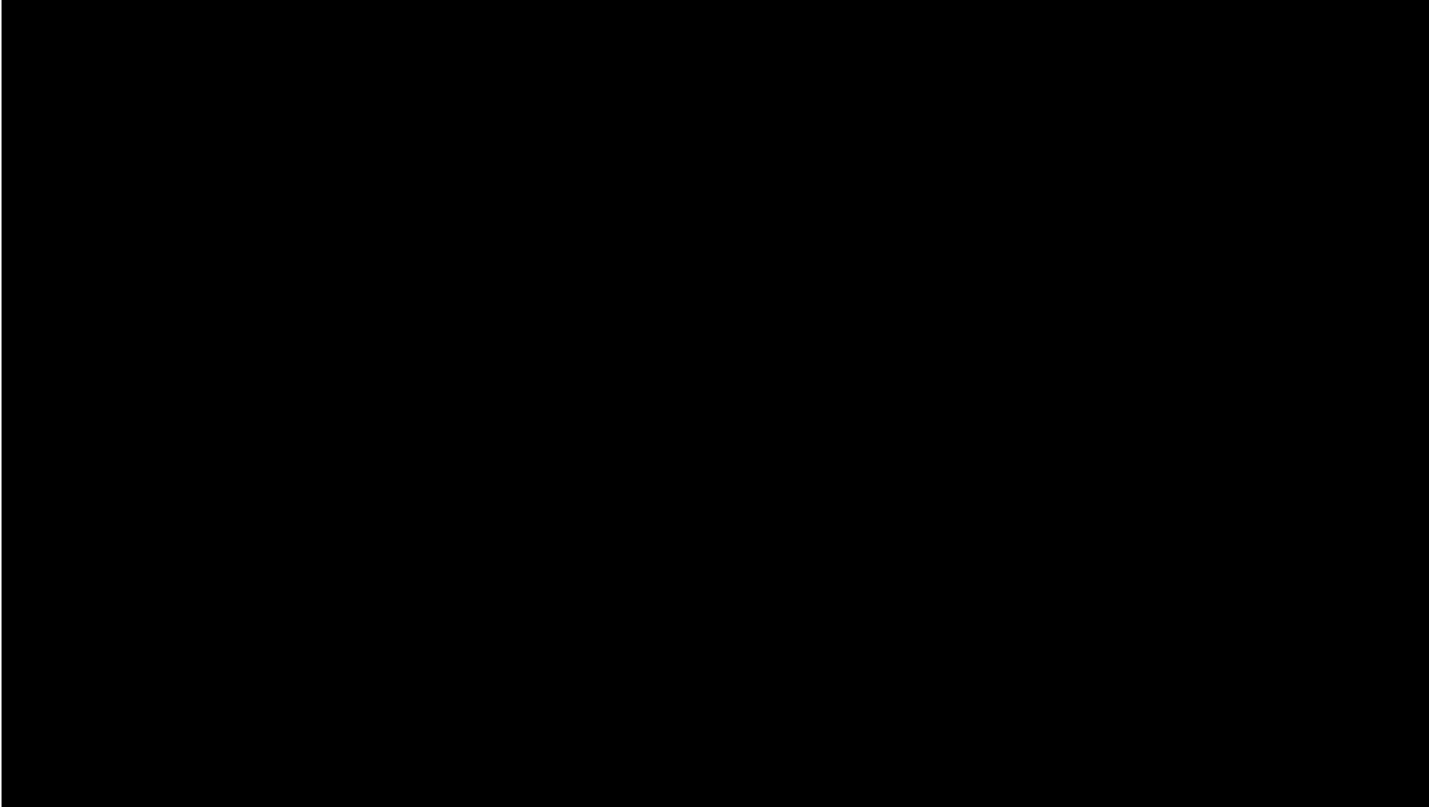
Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

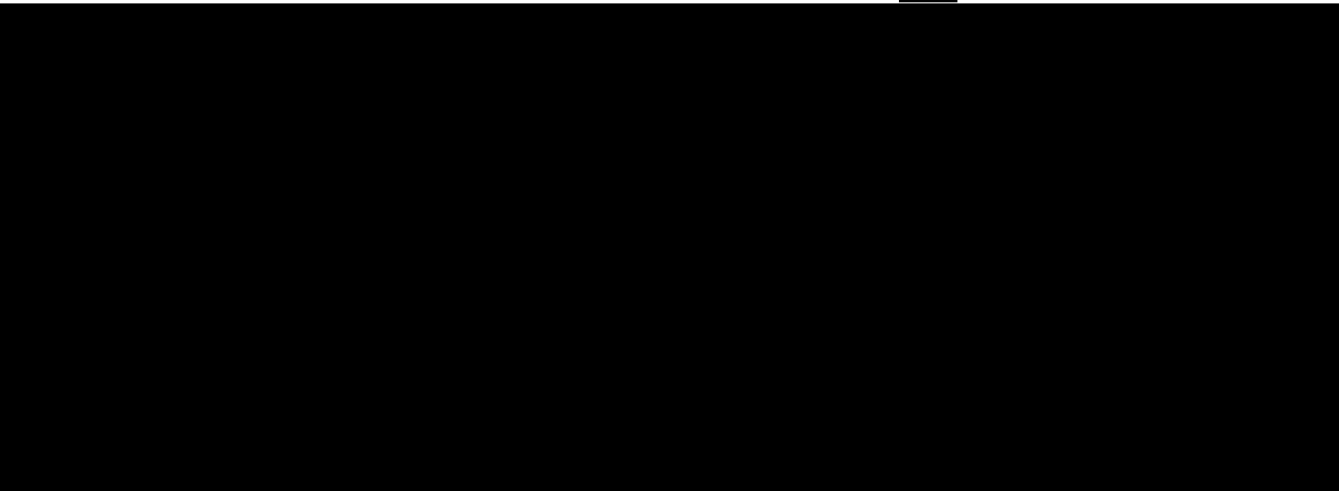
1.2. In Vitro Data for Biowaiver Request

1.2.1. Delivered Dose Uniformity and Aerodynamic Particle Size Distribution



1.2.1.2. Delivered Dose Uniformity

The evaluation of *in-vitro* equivalence between Reference Product (RP) and the Test Product (TP) for Delivered Dose Uniformity (DDU) was conducted for the [REDACTED] strength (100/6) product.





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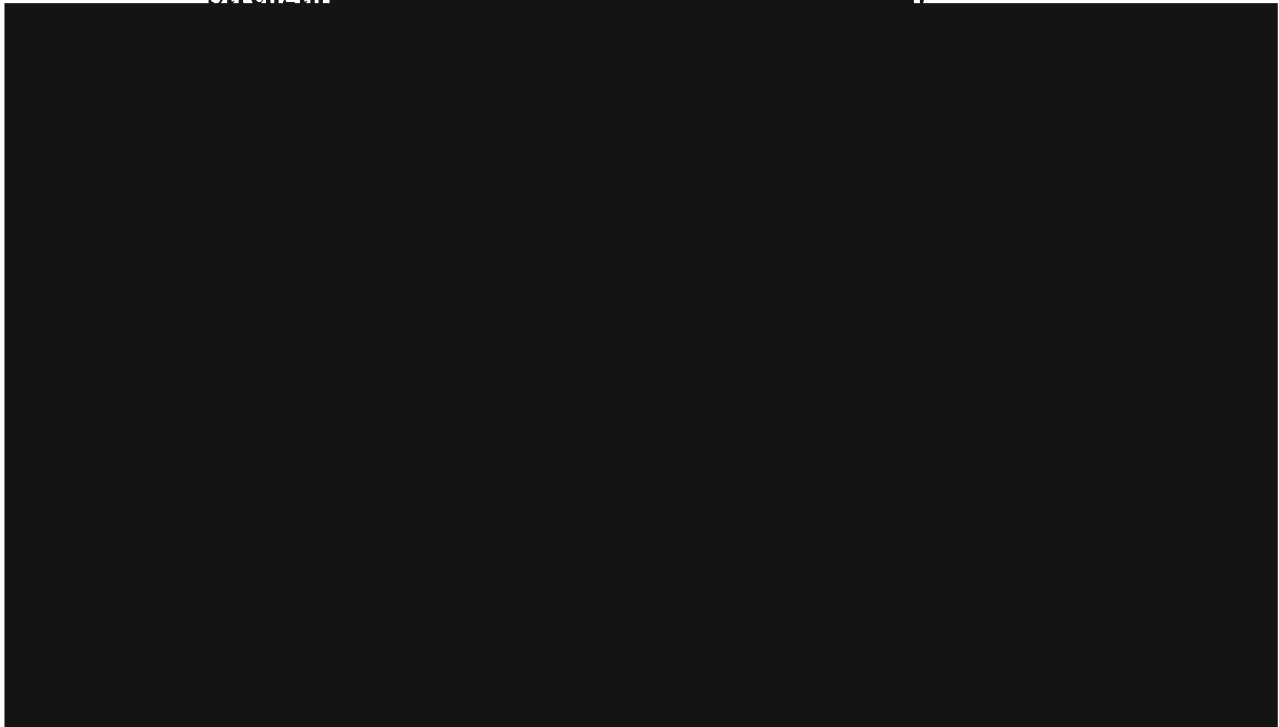
Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
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both API were comparable for all three lots at each strength with most having overlapping ranges. The TP/RP ratios for each API and strength are also calculated in [Table 6](#).

The TP/RP ratios for mean delivered dose for both API (BDP, FFD) met the pre-defined acceptance criteria of 85-115% for both BDP and FFD.

Table 4: Delivered Dose Uniformity for BPD from TP and RP of the 100/6 mcg Strength





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Product beclometasone dipropionate/formoterol fumarate dihydrate
Name: pressurised inhalation solution; 100/6 mcg [REDACTED]

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Table 5: Delivered Dose Uniformity for FFD from TP and RP of the 100/6 mcg Strength [REDACTED]

[REDACTED]

Table 6: Overall Mean Delivered Dose Results (mcg) for TP and RP of the 100/6 mcg Strength [REDACTED]

[REDACTED]



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pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

Figure 1: Boxplot Comparison of Overall Delivered Dose Results (mcg) between TP and RP of the 100/6 mcg Strength [REDACTED]



1.2.1.3. Aerodynamic Particle Size Distribution (APSD) by Next Generation Impactor

The evaluation of *in-vitro* equivalence between Reference Product (RP) and the Test Product (TP) for Aerodynamic Particle Size Distribution (APSD) was conducted for the [REDACTED] strength (100/6µg) products.



1.2.1.3.1.1. Fine Particle Mass and Mass Median Aerodynamic Diameter

The results of the analysis for the 100/6 mcg Test Product and Reference Product are presented [REDACTED]



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

Table 7: Means and Ranges of FPM [REDACTED] (mcg/actuation) for 100/6 mcg TP and RP [REDACTED]



Table 8: Means and Ranges of MMAD (μm) for 100/6 mcg TP and RP [REDACTED]



1.2.1.3.1.2. NGI Individual Stages

NGI individual stage deposition profiles of BDP and FFD for the 100/6 mcg Test Product are presented in [Table 9](#) with profiles plotted and presented in [Figure 2](#). The 100/6 mcg Reference Product are presented in [Table 10](#) with profiles of BDP and FFD plotted and presented in [Figure 3](#). The overall product profiles of BDP and FFD between Test Product and Reference Product are overlaid in [Figure 4](#).





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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

[REDACTED]

Table 9: Mean NGI Individual Stage Depositions for 100/6 mcg TP

[REDACTED]



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Product beclometasone dipropionate/formoterol fumarate dihydrate
Name: pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

Table 10: Mean NGI Individual Stage Depositions for 100/6 mcg RP

[REDACTED]



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

Figure 2: Graphical Representations of NGI Individual Stage Depositions for BDP and FFD from the 100/6 mcg TP [REDACTED]



Figure 3: Graphical Representations of NGI Individual Stage Depositions for BDP and FFD from the 100/6 mcg RP [REDACTED]





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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

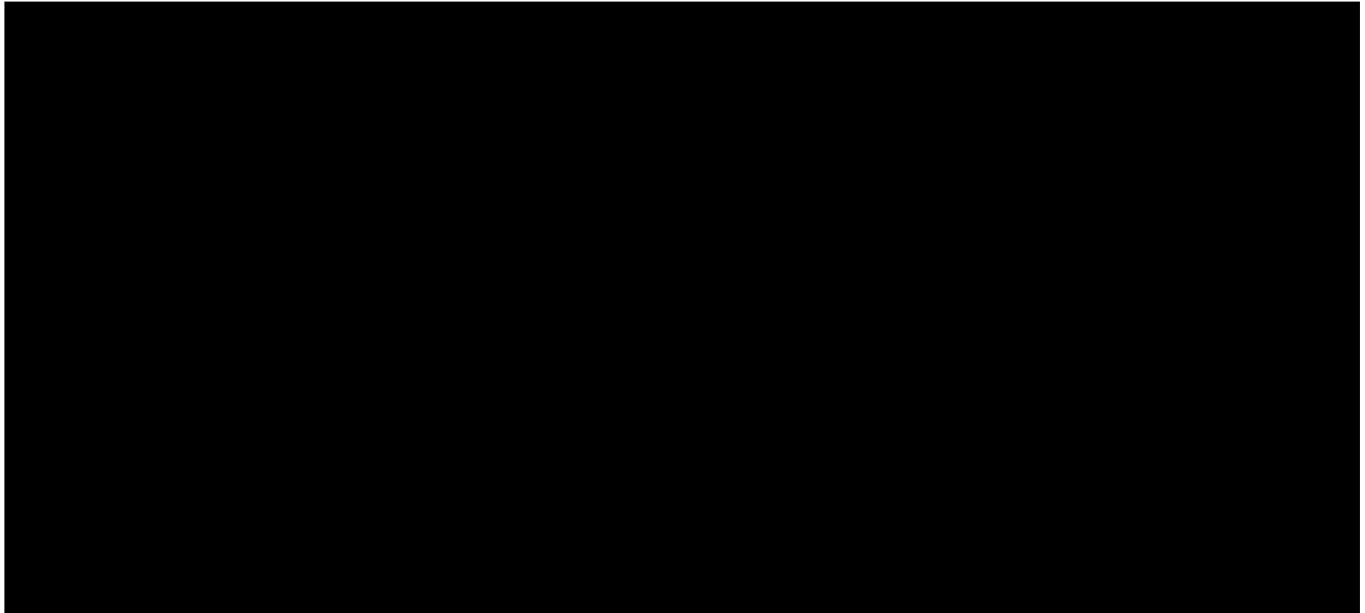
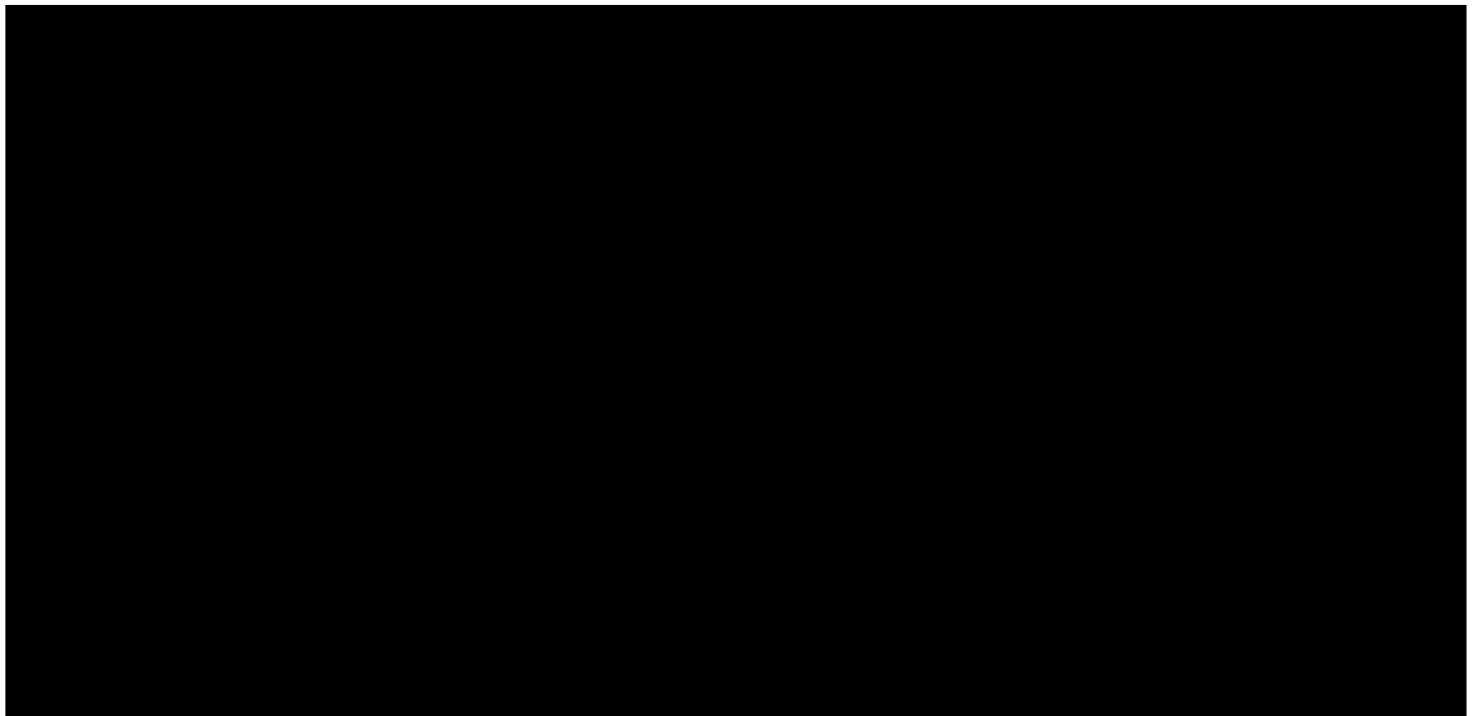


Figure 4: Comparison of NGI Individual Stage Deposition Curves for BDP and FFD for 100/6 mcg of TP and RP [REDACTED]



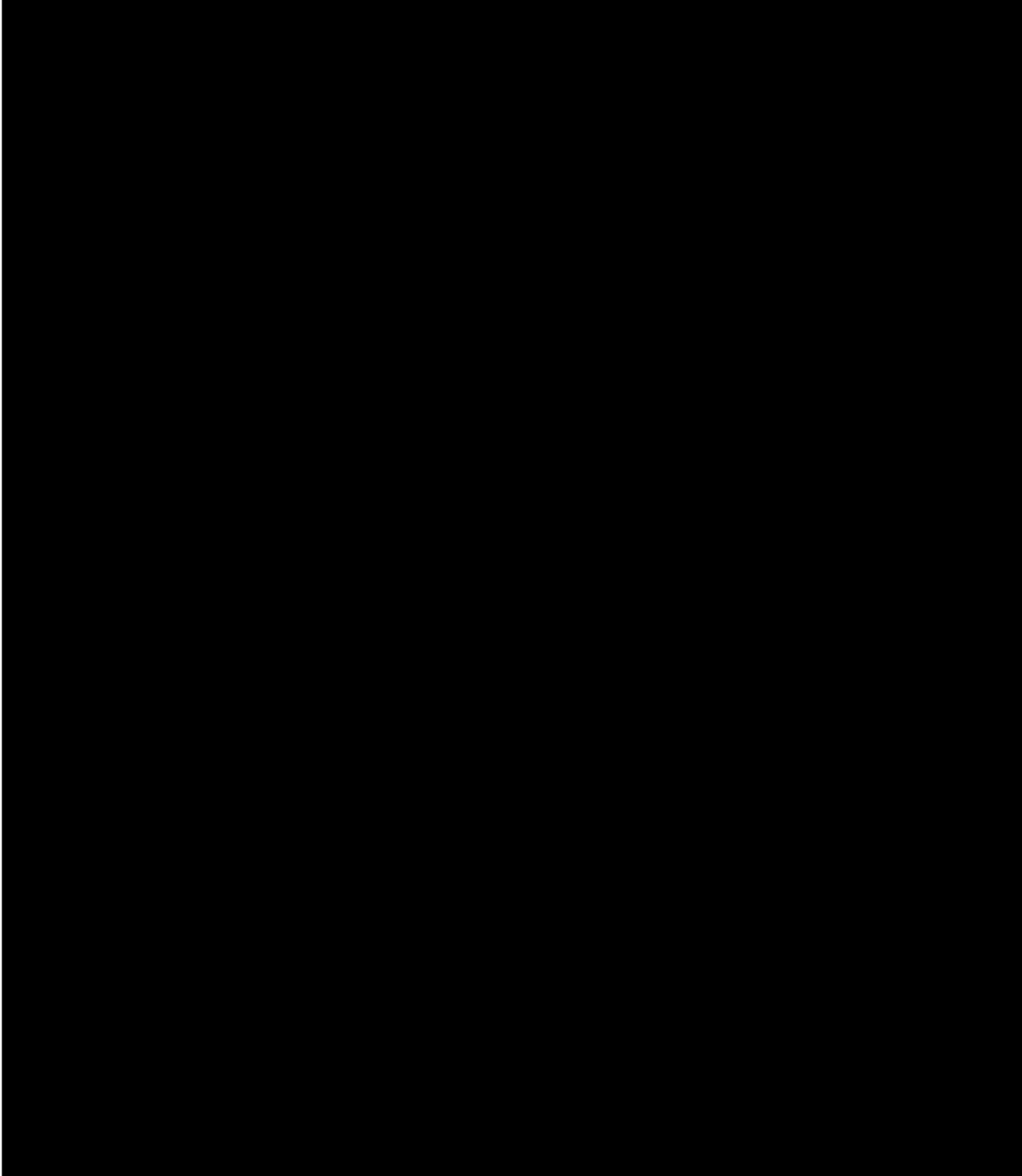


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Product beclometasone dipropionate/formoterol fumarate dihydrate
Name: pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

1.2.1.3.1.3. NGI Stage Grouping





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Product beclometasone dipropionate/formoterol fumarate dihydrate
Name: pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

[REDACTED]

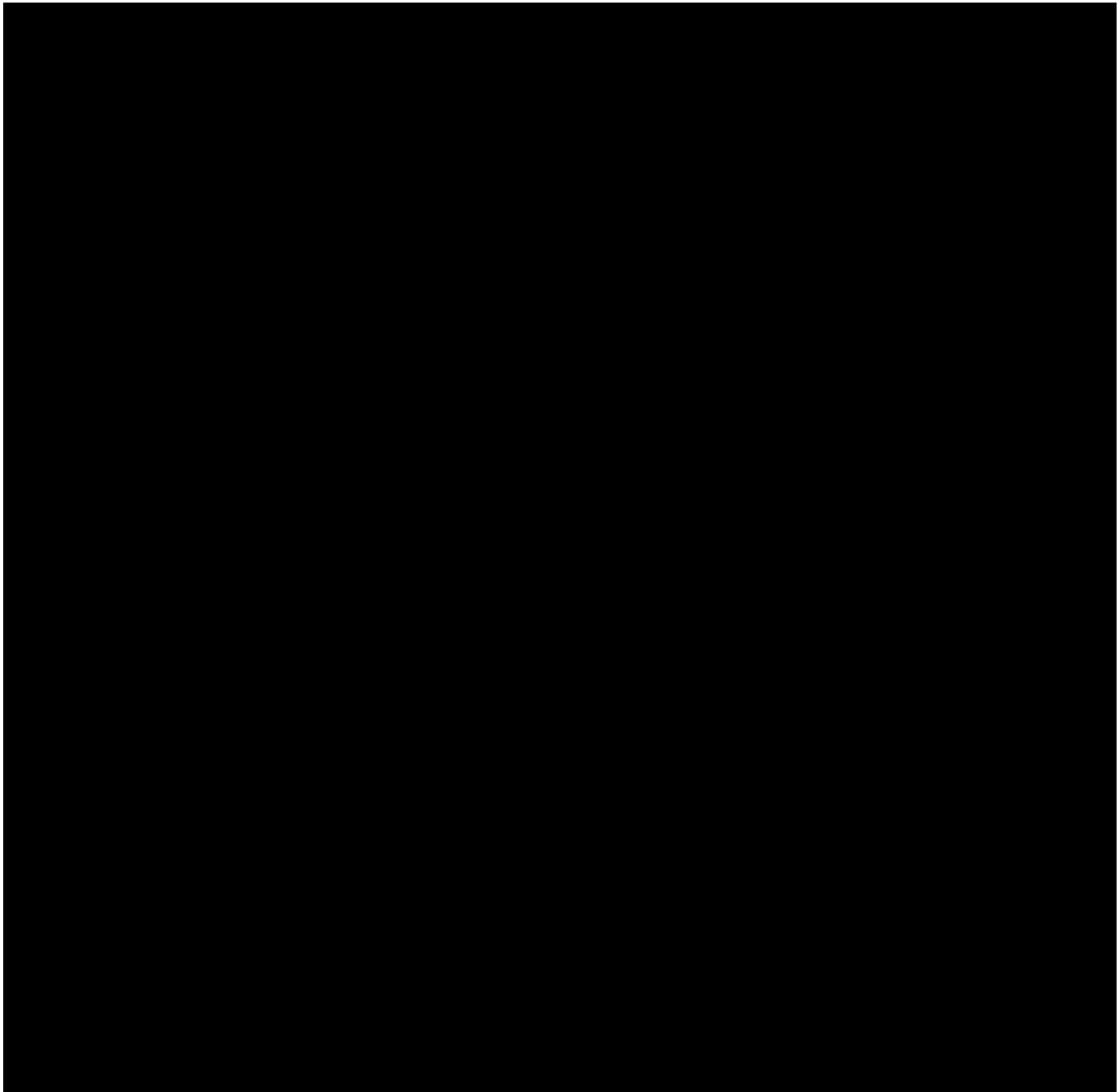


Lupin Healthcare (UK) Limited

Product beclometasone dipropionate/formoterol fumarate dihydrate

Name: pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

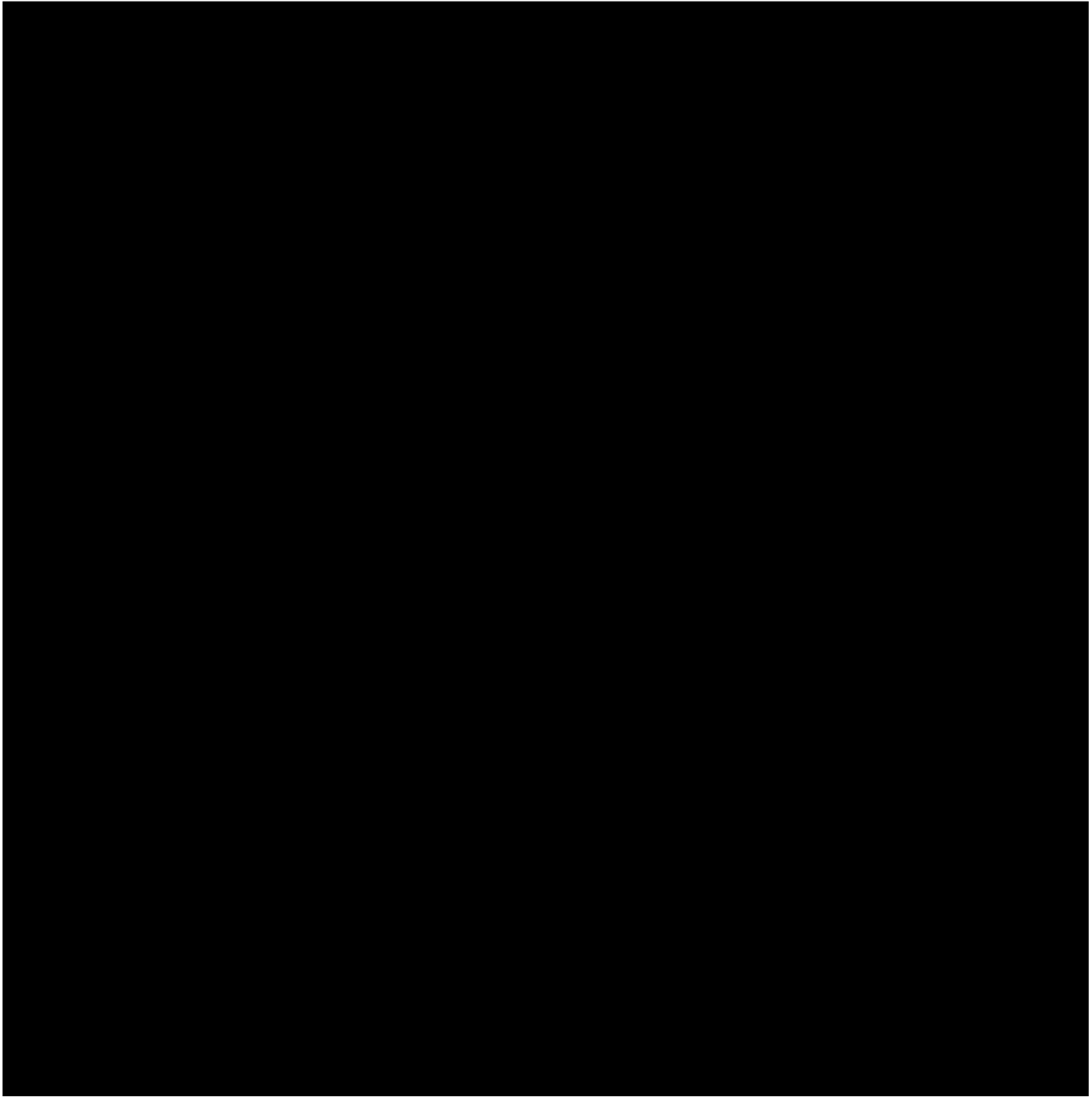




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Product beclometasone dipropionate/formoterol fumarate dihydrate
Name: pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary





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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

Table 16: Summary of TP/RP Ratios for BDP and FFD for the 100/6 mcg Strength

[REDACTED]

Table 17: Summary Statistics of NGI Group Depositions for BDP from the TP and RP of the 100/6 mcg Strength

[REDACTED]



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Product beclometasone dipropionate/formoterol fumarate dihydrate

Name: pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary



Table 18: Summary Statistics of NGI Group Depositions for FFP from the TP and RP

A large black rectangular redaction box covering the entire content of Table 18, which would otherwise contain summary statistics of NGI Group Depositions for FFP from the TP and RP.



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pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7.1 Clinical Summary

Table 19: All Statistical Comparisons of NGI Group Depositions for BDP between the TP and RP of the 100/6 mcg Strength

[REDACTED]

Table 20: All Statistical Comparisons of NGI Group Depositions for FFD between the TP and RP of the 100/6 mcg Strengths

[REDACTED]



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7. Clinical Summary

1.2.1.4. Conclusion

The TP/RP ratios for mean delivered dose for both API (BDP, FFD) met the pre-defined acceptance criteria of [REDACTED] for both BDP and FFD.

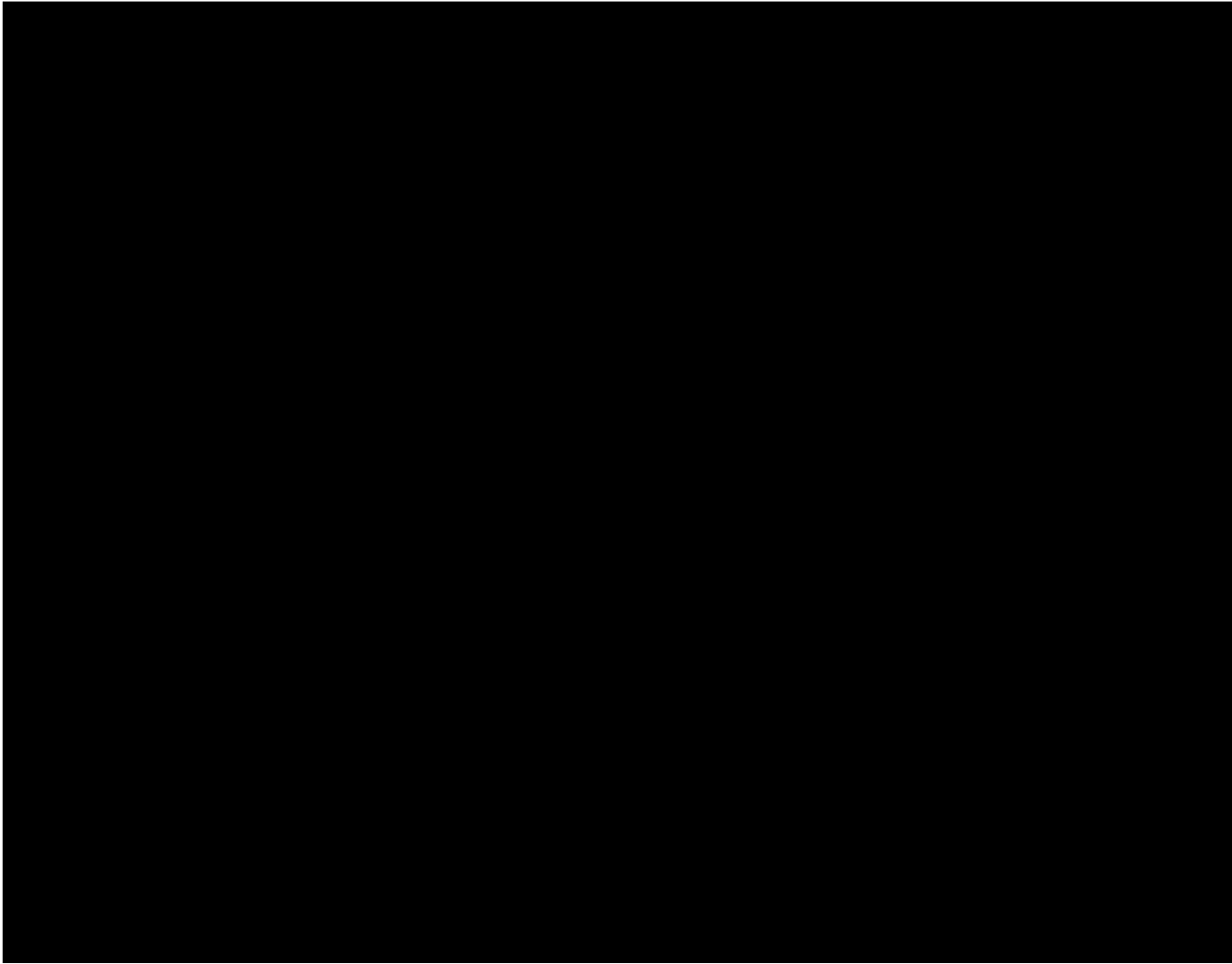
The TP/RP ratios for each NGI stage group met the predefined acceptance criteria of [REDACTED] for BDP and the acceptance criteria of [REDACTED] for FFD.

In addition, the 90% confidence intervals for the geometric mean TP/RP ratios of [REDACTED] are contained within the range of 80- 125% (Range: [REDACTED]).

Therefore, the Test Product and Reference Product of 100/6 mcg strength are considered equivalent.

1.2.2. Dose Linearity

Dose linearity has been demonstrated using the same data used to demonstrate APSD IVBE.





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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7. Clinical Summary

1.2.3. Spray Pattern and Plume Geometry

1.2.3.1. Batch Details for Reference Product Fostair® and BDP/FFD 100/6 Product

Table 22: Batch Details for the Reference Product Fostair® and BDP/FFD 100/6 Product

BDP/FFD Product Strength	Product Code	Batch Number	Expiration Date
BDP/FFD 100/6 mcg	[REDACTED]	[REDACTED]	N/A
			N/A
			N/A

[REDACTED]

Fostair® 100/6 mcg	N/A	06/30/2020
		04/30/2020
		05/31/2020

[REDACTED]

1.2.3.2. Spray Pattern

Spray pattern analysis was carried out at [REDACTED] from the actuator mouthpiece for each of the products. [REDACTED]

[REDACTED]



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7. Clinical Summary

Table 23: Spray Pattern Results for 100/6 mcg TP and RP at [REDACTED] Distance ([REDACTED])

[REDACTED]

Table 24: Spray Pattern Results for 100/6 mcg TP and RP at [REDACTED] Distance ([REDACTED])

[REDACTED]

[REDACTED]



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7. Clinical Summary

Figure 5: Spray Pattern [REDACTED]

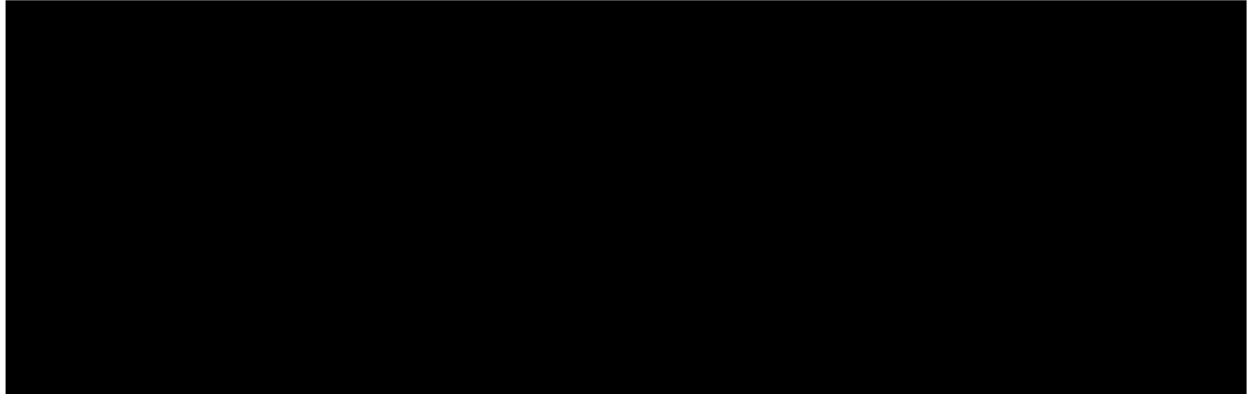


Figure 6: Spray Pattern [REDACTED]



[REDACTED]



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7. Clinical Summary

Figure 7: Spray Pattern [REDACTED]

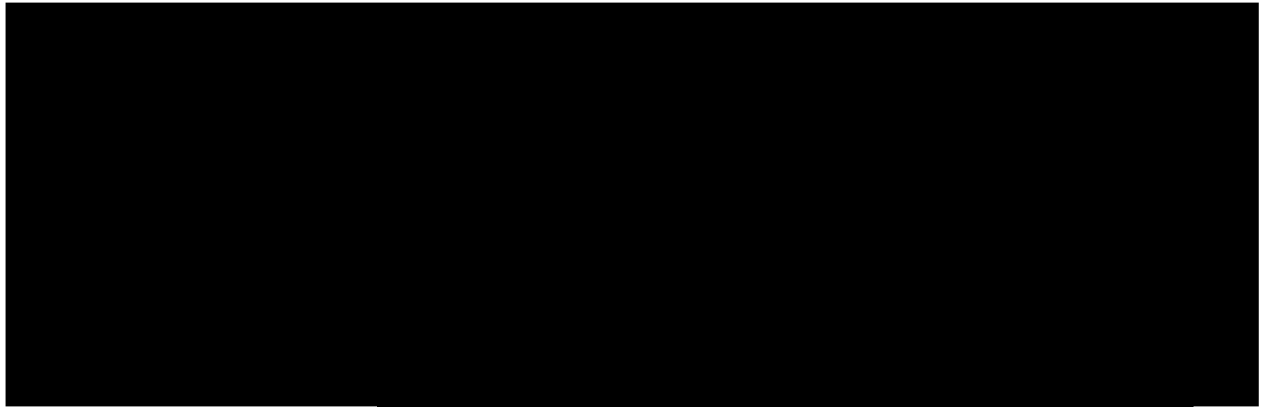
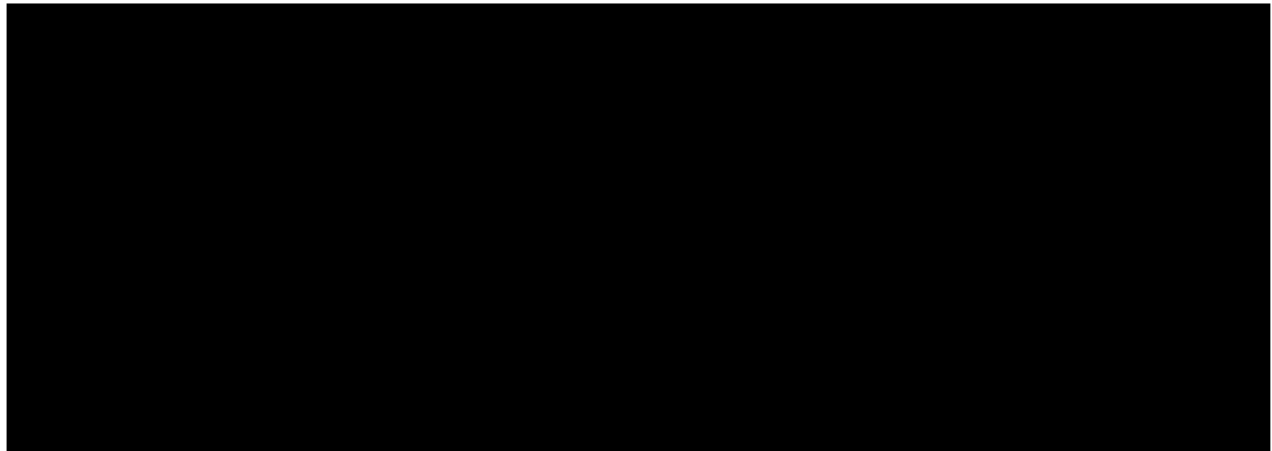


Figure 8: Spray Pattern [REDACTED]



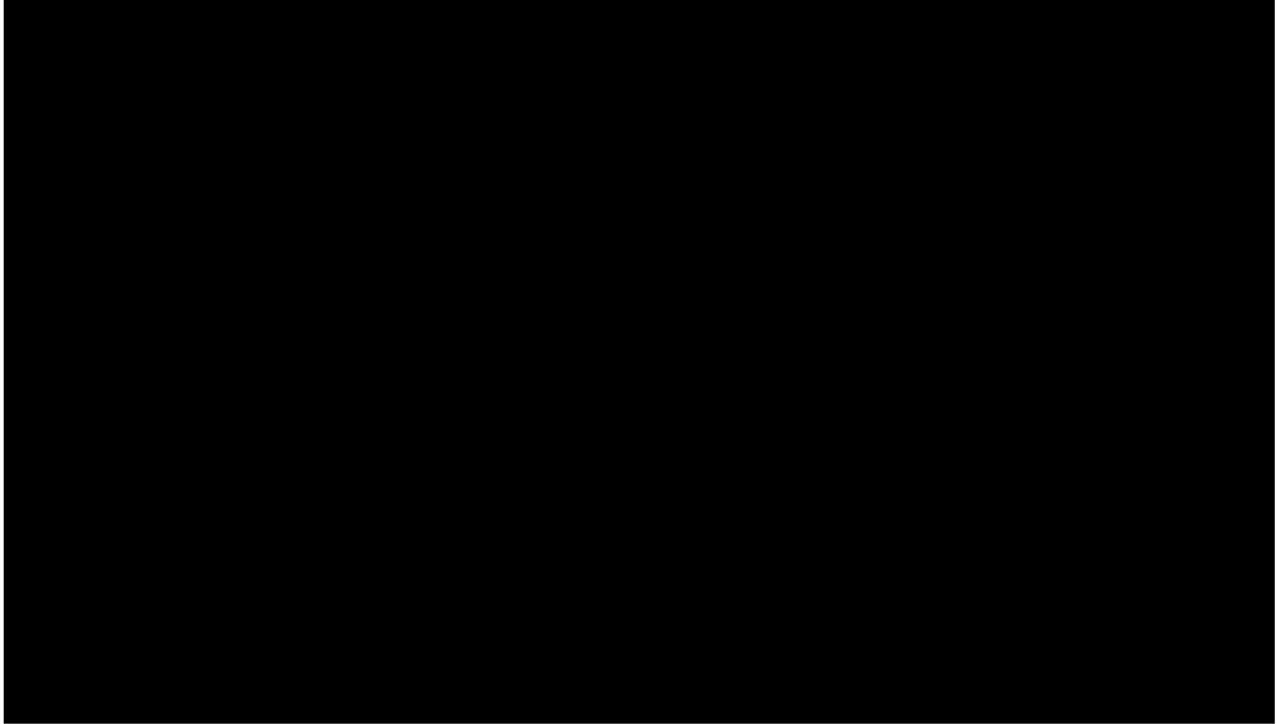


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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

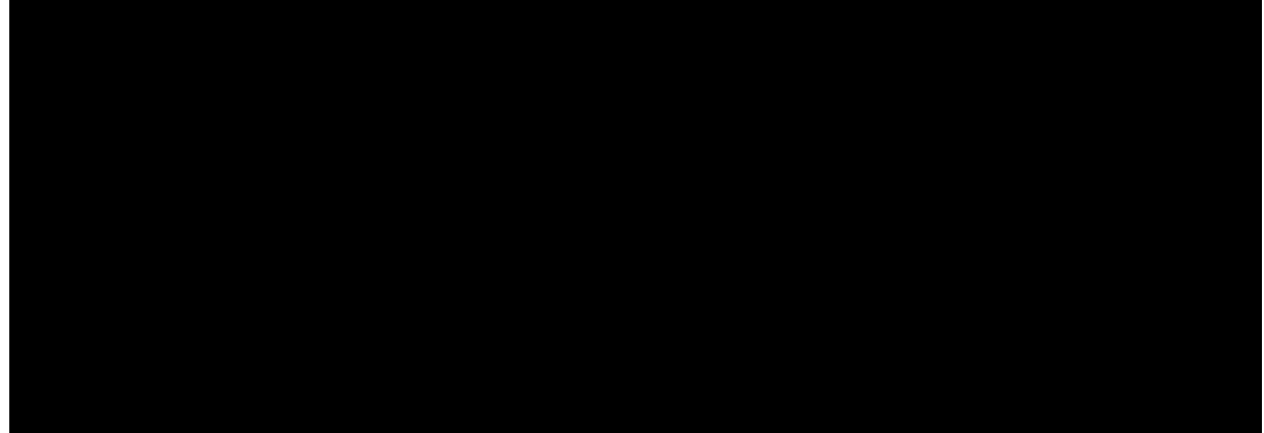
2.7. Clinical Summary

Figure 9: Spray Pattern – Representative Spray Patterns of TP and RP products



1.2.3.3. Plume Geometry

Plume geometry analysis was carried out at [REDACTED] from the actuator mouthpiece for each of the products. [REDACTED]





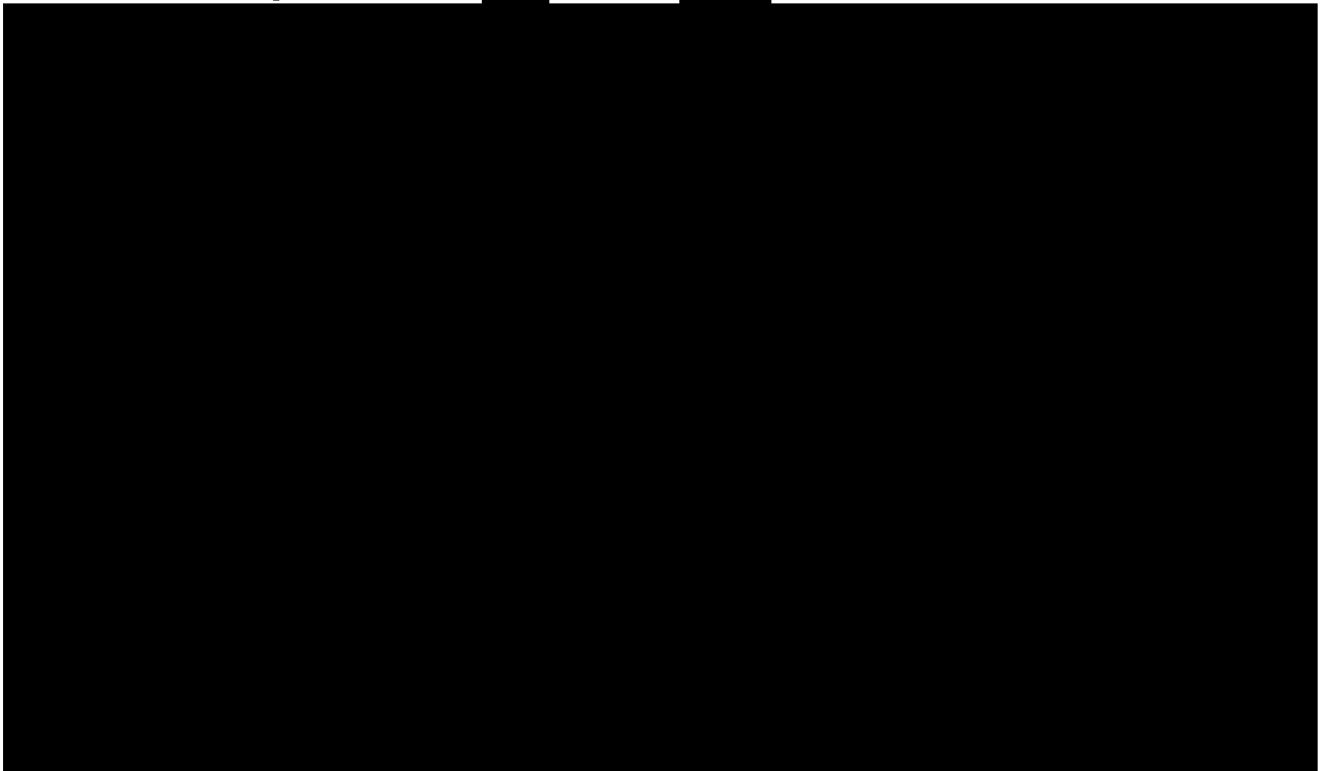
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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [redacted]

2.7. Clinical Summary

Table 25: Plume Geometry Results for 100/6 mcg TP and RP at [redacted] Distance [redacted]

Figure 10: Plume Geometry [redacted] for 100/6 mcg TP and RP at [redacted] Distance [redacted]



[redacted]

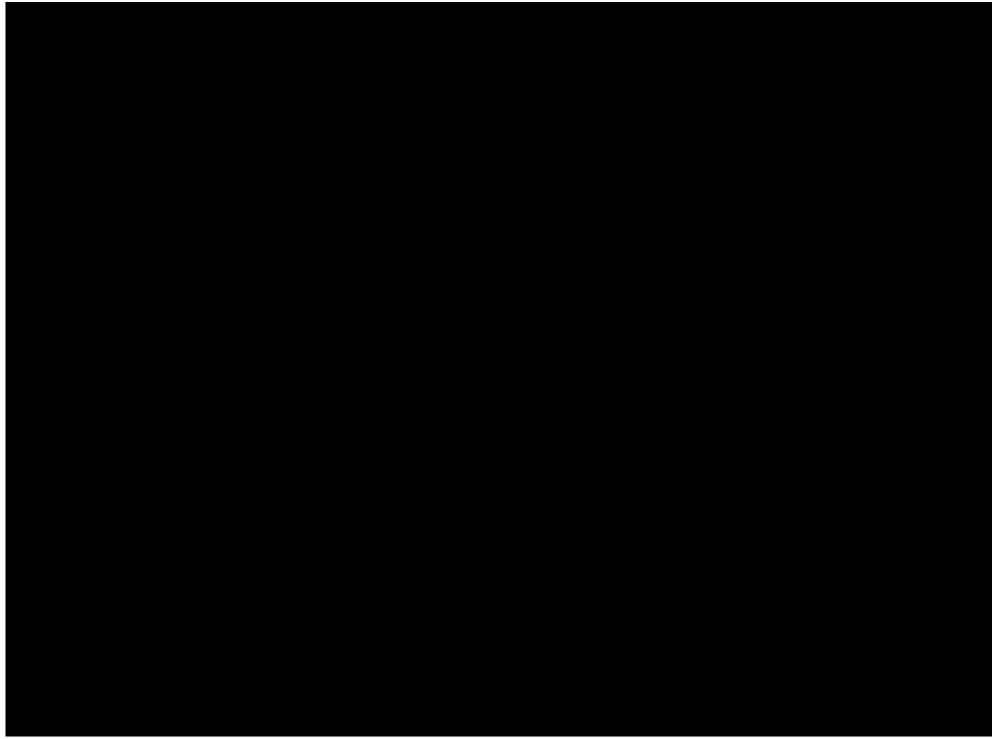


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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7. Clinical Summary

Figure 11:



1.2.3.4. Conclusion

The spray pattern [REDACTED] and plume geometry [REDACTED] results show overlapping ranges and comparable means [REDACTED] between the Test Product and Reference Product.

Therefore, the Test Product and Reference Product of 100/6 mcg strength are considered equivalent.

1.2.4. Overall Conclusion

On the basis of in-vitro equivalence results from delivered dose uniformity, aerodynamic particle size distribution, dose linearity, spray pattern and plume geometry of which equivalency has been demonstrated between the Test Product and Reference Product, both products are considered equivalent.



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2.7. Clinical Summary

2. BIOEQUIVALENCE TRIAL INFORMATION

Table 2.1 Test and Reference product information

Product Characteristics	Test Product	Reference Product
Name	Beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg per actuation pressurised inhalation solution	FOSTAIR 200/6 micrograms per actuation pressurised inhalation solution
Strength	200/6 mcg	200/6 mcg
Dosage form	Oral pressurised inhalation solution	Oral pressurised inhalation solution
Manufacturer		
Batch number		
Batch size		
Measured Content (s) ^a (% of label claim)		
Commercial Batch Size		
Expiry date (Retest date)	08 February 2020	August 2020
Location of Certificate of Analysis		
	(Section 3.2.P.5.4)	(Section 3.2.P.5.4)
Member State Where the reference product is purchased from:		United Kingdom
This product was used in the following trials:	BDPFF-AS-101	BDPFF-AS-101

^a List for each active substance for fixed combinations



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg [REDACTED]

2.7. Clinical Summary

Table 2.2 Study Site of BDPFF-AS-101 (LBC-19-052)

	Name	Address	EU Authority Inspection	
			Year	Authority
Clinical Study Site	Lupin Bioresearch Center	[REDACTED]	19 – 23 Sep 2011	AFSSAPS - France
			05 - 09 Sep 2016	UK-MHRA
Bioanalytical Study Site	Lupin Bioresearch Center		19 – 23 Sep 2011	AFSSAPS - France
			05 - 09 Sep 2016	UK-MHRA
			11-14 Nov 2019	European Medicines Agency GCP Inspection
PK and Statistical Analysis	Lupin Bioresearch Center		19 – 23 Sep 2011	AFSSAPS - France
		05 - 09 Sep 2016	UK-MHRA	
		11-14 Nov 2019	European Medicines Agency GCP Inspection	
Sponsor of the Study	Lupin Atlantis Holdings SA	Landis+Gyr Strasse 1 6300 Zug Switzerland		



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2.7. Clinical Summary

Table 2.3 Study description of BDPFF-AS-101

Report Location:	BDPFF-AS-101-CSR (Section 5.3.1.2)	
Study Periods		
Clinical:	30 April 2019 – 27 September 2019	
Bioanalytical:	Beclometasone Dipropionate and Beclometasone 17-monopropionate: 01 August 2019 – 04 October 2019 Formoterol: 02 August 2019 – 27 September 2019	
Design		
Dose:	200/6 mcg	
Single/Multiple dose:	Single-dose	
Number of periods:	4	
Two-stage design:	No	
Fasting/Fed:	Fasting	
Number of subjects		
- dosed:	112	
-completed the study:	102	
-included in the final statistical analysis of AUC:	104	
-included in the final statistical analysis of C _{max} :	104	



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3. RESULTS

Table 3.1a Pharmacokinetic data for Beclomethasone 17-monopropionate in BDPFF-AS-101

Pharmacokinetic parameter	Arithmetic Means (\pm SD)	
	Test Product	Reference Product
AUC _(0-t)	2518.3756 (\pm 1068.0521)	2486.6713 (\pm 961.2931)
AUC _(0-∞)	2793.6792 (\pm 1053.3647)	2749.1034 (\pm 953.1493)
C _{max}	602.9960 (\pm 307.4615)	579.7414 (\pm 266.5610)
t _{max} ^a	0.255 (0.060, 4.008)	0.254 (0.060, 8.003)

^a Median (Min, Max)

Table 3.1b Pharmacokinetic data for Formoterol in BDPFF-AS-101, Without Charcoal

Pharmacokinetic parameter	Arithmetic Means (\pm SD) ^a	
	Test Product	Reference Product
AUC _(0-t)	48.2820 (\pm 18.8251)	46.7734 (\pm 17.9951)
AUC _(0-∞)	56.4531 (\pm 20.1010)	54.4086 (\pm 18.2098)
C _{max}	18.3924 (\pm 8.7472)	17.4271 (\pm 8.3431)
t _{max} ^a	0.103 (0.062, 0.756)	0.104 (0.061, 1.008)

^a Median (Min, Max)

Table 3.1c Pharmacokinetic data for Formoterol Fumarate in BDPFF-AS-101, With Charcoal

Pharmacokinetic parameter	Arithmetic Means (\pm SD)	
	Test Product	Reference Product
AUC _(0-t)	28.0978 (\pm 16.2823)	25.0775 (\pm 14.3769)
AUC _(0-∞)	41.6203 (\pm 16.8839)	38.0143 (\pm 14.2674)
C _{max}	16.7410 (\pm 7.6773)	15.2828 (\pm 7.4185)
t _{max} ^a	0.103 (0.031, 0.251)	0.1130 (0.060, 0.185)

^a Median (Min, Max)



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Table 3.1d Pharmacokinetic data for Beclometasone Dipropionate in BDPFF-AS-101

Pharmacokinetic parameter	Arithmetic Means (\pm SD)	
	Test Product	Reference Product
AUC _(0-t)	282.3162 (\pm 191.5901)	282.9575 (\pm 188.8517)
AUC _(0-∞)	289.9633 (\pm 196.8895)	301.0003 (\pm 204.3515)
C _{max}	3011.6444 (\pm 2419.0212)	3010.5315 (\pm 2279.2760)
t _{max} ^a	0.034 (0.030, 0.103)	0.034 (0.031, 0.102)

^a Median (Min, Max)

Table 3.2a Additional pharmacokinetic data for Beclomethasone-17-monopropionate in BDPFF-AS-101

Plasma Concentration curves where	Related information
AUC _(0-t) /AUC _(0-∞) <0.8	003, 3, R 007, 1, T 048, 3, T 090, 2, T 111, 4, T
C _{max} is the first point	None
Pre-dose sample > 5% C _{max}	None

T=Test formulation

R=Reference formulation

Table 3.2b Additional pharmacokinetic data for Formoterol in BDPFF-AS-101, Without Charcoal

Plasma Concentration curves where	Related information
AUC _(0-t) /AUC _(0-∞) <0.8	002, 1, R 003, 3, R 013, 2, T 018, 4, T 026, 2, T 026, 4, R 027, 1, R 027, 3, T 034, 3, R 036, 4, R 038, 2, T 040, 1, R 042, 1, R 048, 3, T 049, 4, T



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Plasma Concentration curves where	Related information
	055, 3, T 056, 1, T 067, 3, R 071, 1, R 071, 3, T 072, 4, R 073, 1, R 073, 3, T 079, 3, R 081, 4, T 082, 2, T 087, 1, T 088, 1, R 092, 1, R 093, 1, T 094, 3, T 111, 4, T
C _{max} is the first point	001, 2, T*
Pre-dose sample > 5% C _{max}	None

*=First planned timepoint at 0.03 hours missing (not done due to cannula blocked), first non-missing timepoint at 0.06 hours is C_{max}.

T=Test formulation

R=Reference formulation

Table 3.2c Additional pharmacokinetic data for Formoterol Fumarate in BDPFF-AS-101, With Charcoal

Plasma Concentration curves where	Related information
AUC _(0-t) /AUC _(0-∞) <0.8	002, 4, R 003, 1, T 003, 2, R 004, 3, R 004, 4, T 005, 4, R 006, 1, R 008, 1, T 008, 2, R 009, 1, T 009, 2, R 011, 1, R 011, 3, T 012, 3, R 012, 4, T 013, 1, R 013, 3, T 014, 2, T 017, 1, R 019, 2, T 019, 4, R



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Plasma Concentration curves where	Related information
	021, 2, T
	024, 2, R
	025, 1, T
	025, 2, R
	026, 1, R
	026, 3, T
	027, 4, R
	028, 4, T
	029, 2, T
	029, 4, R
	031, 4, T
	032, 1, T
	032, 2, R
	036, 1, R
	036, 3, T
	038, 2, T
	040, 2, T
	042, 2, T
	043, 1, R
	045, 3, T
	046, 1, T
	046, 2, R
	047, 3, R
	048, 2, T
	048, 4, R
	049, 1, T
	049, 2, R
	052, 1, R
	052, 3, T
	055, 2, T
	055, 4, R
	056, 4, T
	057, 1, R
	057, 3, T
	058, 1, T
	058, 2, R
	060, 3, R
	060, 4, T
	063, 3, R
	063, 4, T
	065, 1, R
	066, 2, T
	066, 4, R
	067, 1, T
	067, 2, R
	069, 2, R
	070, 3, R
	071, 4, R
	072, 1, R
	073, 2, T



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Plasma Concentration curves where	Related information
	074, 1, R 074, 3, T 075, 1, T 076, 4, T 077, 3, R 081, 1, T 081, 2, R 082, 1, R 082, 3, T 083, 2, T 085, 1, R 085, 3, T 087, 3, R 087, 4, T 088, 4, R 089, 3, R 089, 4, T 091, 1, T 092, 4, R 093, 3, R 094, 2, T 095, 2, R 096, 1, R 096, 3, T 097, 1, R 097, 3, T 098, 1, T 100, 4 T 101, 1, T 102, 4, T 104, 2, T 104, 4, R 107, 3, R 107, 4, T 109, 1, R 109, 3, T 111, 1, T 111, 2, R
C _{max} is the first point	031, 3, R 039, 1, T
Pre-dose sample > 5% C _{max}	None

T=Test formulation

R=Reference formulation



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Table 3.2d Additional pharmacokinetic data for Beclometasone Dipropionate in BDPFF-AS-101

Plasma Concentration curves where	Related information
$AUC_{(0-t)}/AUC_{(0-\infty)} < 0.8$	047, 1, T 055, 1, R 056, 1, T 058, 3, R 107, 1, T
C_{max} is the first point	001, 2, T* 001, 4, R 002, 3, T 003, 3, R 003, 4, T 004, 1, T 004, 2, R 005, 1, R 005, 3, T 006, 2, T 006, 4, R 007, 1, T 007, 2, R 009, 3, R 009, 4, T 010, 1, R 010, 3, T 011, 2, T 011, 4, R 012, 1, T 012, 2, R 013, 2, T 013, 4, R 014, 1, R 014, 3, T 015, 3, R 015, 4, T 016, 1, T 016, 2, R 017, 2, T 017, 4, R 018, 3, R 019, 1, R 019, 3, T 020, 1, T 022, 2, T 022, 4, R 023, 1, T 023, 2, R 024, 3, R 024, 4, T 025, 3, R



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Plasma Concentration curves where	Related information
	026, 2, T
	026, 4, R
	028, 1, T
	028, 2, R
	030, 2, T
	030, 4, R
	031, 1, T
	031, 2, R
	032, 3, R
	033, 3, T
	034, 3, R
	034, 4, T
	036, 2, T
	036, 4, R
	038, 2, T
	038, 4, R
	039, 3, R
	039, 4, T
	040, 1, R
	040, 3, T
	042, 3, T
	043, 4, R
	044, 1, T
	044, 2, R
	045, 4, R
	047, 1, T
	048, 1, R
	048, 3, T
	049, 3, R
	049, 4, T
	050, 1, T
	050, 2, R
	051, 1, R
	051, 3, T
	052, 2, T
	052, 4, R
	055, 3, T
	056, 1, T
	057, 2, T
	057, 4, R
	058, 3, R
	058, 4, T
	059, 1, R
	059, 3, T
	060, 1, T
	060, 2, R
	062, 2, T
	062, 4, R
	063, 1, T
	063, 2, R



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Plasma Concentration curves where	Related information
	064, 3, R
	064, 4, T
	065, 2, T
	065, 4, R
	066, 1, R
	066, 3, T
	067, 3, R
	067, 4, T
	068, 1, T
	068, 2, R
	069, 4, T
	070, 1, T
	070, 2, R
	071, 1, R
	071, 3, T
	072, 4, R
	073, 1, R
	073, 3, T
	075, 3, R
	077, 2, R
	078, 1, R
	078, 3, T
	079, 3, R
	080, 2, T
	080, 4, R
	081, 3, R
	081, 4, T
	082, 2, T
	082, 4, R
	083, 3, T
	085, 2, T
	085, 4, R
	086, 3, R
	087, 1, T
	087, 2, R
	088, 3, T
	089, 2, R
	090, 2, T
	090, 4, R
	091, 3, R
	091, 4, T
	093, 2, R
	095, 4, T
	096, 2, T
	096, 4, R
	097, 2, T
	097, 4, R
	099, 1, R
	099, 3, T
	100, 1, T



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Plasma Concentration curves where	Related information
	100, 2, R 101, 3, R 101, 4, T 102, 2, R 104, 1, R 104, 3, T 105, 1, R 105, 3, T 106, 4, T 107, 1, T 107, 2, R 108, 2, T 108, 4, R 109, 2, T 109, 4, R 110, 2, R 111, 3, R 111, 4, T 112, 1, R 112, 3, T
Pre-dose sample > 5% C _{max}	None

*=First planned timepoint at 0.03 hours missing (not done due to cannula blocked), first non-missing timepoint at 0.06 hours is C_{max}.

T=Test formulation

R=Reference formulation



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Table 3.3a Bioequivalence evaluation of Beclometasone-17-monopropionate in BDPFF-AS-101

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV% ^a
AUC _(0-t)	100.13	95.10-105.42	21.66
C _{max}	102.44	96.47-108.79	25.38

^a Estimated from the Residual Mean Squares.

Table 3.3b Bioequivalence evaluation of Formoterol Without Charcoal in BDPFF-AS-101

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV% ^a
AUC _(0-t)	102.73	94.21-112.03	37.03
C _{max}	105.14	98.67-112.03	26.75

^a Estimated from the Residual Mean Squares.

Table 3.3c Bioequivalence evaluation of Formoterol With Charcoal in BDPFF-AS-101

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV% ^a
AUC _(0-t)	111.59	102.12-121.93	37.03
C _{max}	110.43	103.48-117.85	26.75

^a Estimated from the Residual Mean Squares.

Table 3.3d Bioequivalence evaluation of Beclometasone Dipropionate in BDPFF-AS-101

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV% ^a
AUC _(0-t)	97.22	90.97-103.91	28.19
C _{max}	97.61	89.81-106.09	35.68

^a Estimated from the Residual Mean Squares.



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

4. BIOANALYTICS

4.1a Bioanalytical method validation for Beclometasone 17-Propionate

Analytical Validation Report Location (s)	Refer to Module : 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.5.1 method validation report Volume (s) : Not applicable Page 1 to 282
This analytical method was used in the following studies:	BDPFF-AS-101
Short description of the method	Solid phase extraction method
Biological matrix	Human Plasma
Analyte Location of product certificate	Beclometasone 17-Propionate For Location Refer to Module : 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.5.2 CoA Volume (s) : Not applicable Page 10-14 of 30
Internal standard (IS) ^a Location of product certificate	Beclometasone 17-Propionate D5 For Location Refer to Module : 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.5.2 CoA Volume (s) : Not applicable Page 22-28 of 30
Calibration concentrations (units)	25.077 to 2501.750 pg/mL
Lower limit of quantification (units)	25.077 pg/mL
QC concentration (units)	HQC: 2000.179 pg/mL MQC: 1004.09 pg/mL LQC: 75.005 pg/mL LLOQQC: 25.089 pg/mL
Between-run accuracy	94.78-98.23%
Between-run precision	7.64-12.43%
Within-run accuracy	HQC: 91.72-110.46% MQC: 93.19-111.07% LQC: 89.88-102.62% LLOQQC: 84.58-105.18%
Within-run precision	HQC: 0.36-5.00% MQC: 0.80-4.43% LQC: 0.53-6.52% LLOQQC: 1.60-10.09%



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

<p>Matrix Factor (MF) (all QC) ^a IS normalized MF (all QC) ^a C.V.% of IS normalized MF (all QC) % of QCs with >85% and <115% n.v. ^{a, b} %matrix lots with mean <80% or>120% n.v. ^{a, b}</p>	<p><u>Beclometasone 17-Propionate</u></p> <table border="1"> <thead> <tr> <th></th> <th>Mean Matrix factor</th> <th>% CV</th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>0.844</td> <td>2.96%</td> </tr> <tr> <td>MQC</td> <td>0.818</td> <td>1.83%</td> </tr> <tr> <td>LQC</td> <td>0.798</td> <td>4.14%</td> </tr> </tbody> </table> <p><u>Beclometasone 17-Propionate D5</u></p> <table border="1"> <thead> <tr> <th></th> <th>Mean Matrix factor</th> <th>% CV</th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>0.836</td> <td>1.08%</td> </tr> <tr> <td>MQC</td> <td>0.802</td> <td>0.87%</td> </tr> <tr> <td>LQC</td> <td>0.786</td> <td>0.89%</td> </tr> </tbody> </table> <p><u>IS Normalized matrix factor for Beclometasone 17-Propionate/ Beclometasone 17-Propionate D5</u></p> <table border="1"> <thead> <tr> <th></th> <th>Mean Matrix factor</th> <th>% CV</th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>1.010</td> <td>2.48%</td> </tr> <tr> <td>MQC</td> <td>1.020</td> <td>1.47%</td> </tr> <tr> <td>LQC</td> <td>1.015</td> <td>3.94%</td> </tr> </tbody> </table>		Mean Matrix factor	% CV	HQC	0.844	2.96%	MQC	0.818	1.83%	LQC	0.798	4.14%		Mean Matrix factor	% CV	HQC	0.836	1.08%	MQC	0.802	0.87%	LQC	0.786	0.89%		Mean Matrix factor	% CV	HQC	1.010	2.48%	MQC	1.020	1.47%	LQC	1.015	3.94%
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<p>Long term stability of the stock solution and working solutions^c (Observed change %)</p>	<p><u>Beclometasone 17-Propionate</u></p> <p><u>% Stock solution stability after 152 Days and 00 Hours at -20°C:</u> (Observed change HQC: 1.15%, LQC: -2.13%)</p> <p><u>% Spiking solution stability after 152 days and 00 hours at -20°C:</u> (Observed change HQC: 1.86%, LQC: -4.48%)</p> <p><u>Beclometasone 17-Propionate D5</u></p> <p><u>% Stock solution stability after 152 days and 00 hours at -20°C:</u> (Observed change: -2.35%)</p> <p><u>% Spiking solution stability after 152 days and 00 hours at -20°C:</u> (Observed change: -2.71%)</p>																																				
<p>Short term stability in biological matrix at room temperature or at sample processing temperature (Observed change %)</p>	<p>Bench top Stability: Confirmed up to 06 hours and 48 minutes in Ice water bath (Observed change HQC: -1.20%, MQC: -0.67%, LQC: 0.37%)</p>																																				
<p>Long term stability in biological matrix (Observed change %) Location</p>	<p>Confirmed up to 169 Days at -75°C (Observed change HQC: 4.58%, MQC: 3.95%, LQC: 3.63%)</p> <p>Location: Page 42 of 282</p>																																				
<p>Autosampler storage stability (Observed change %)</p>	<p>Confirmed up to 66 hours and 32 minutes Condition: at 10.0°C ± 3.0°C</p>																																				



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

	(Observed change HQC: -0.09%, MQC: -0.06%, LQC: 1.41%)									
Post-preparative stability (Observed change %)	Post Extract Stability Confirmed up to 02 hours and 24 minutes at RT and 23 Hours and 59 minutes at 2-8°C (Observed change HQC: -0.15%, MQC: -0.04%, LQC: 0.22%)									
Freeze and thaw stability (Observed change %)	-30°C, V cycles (Observed change HQC: -0.98, MQC: 0.72, LQC: 1.70) -75°C, V cycles (Observed change HQC: -2.60, MQC: -2.04, LQC: 0.94)									
Dilution integrity	<table border="1"> <thead> <tr> <th></th> <th>1/2nd dilution</th> <th>1/4th dilution</th> </tr> </thead> <tbody> <tr> <td>Precision</td> <td>1.34%</td> <td>1.10%</td> </tr> <tr> <td>Accuracy</td> <td>89.31%</td> <td>91.57%</td> </tr> </tbody> </table>		1/2 nd dilution	1/4 th dilution	Precision	1.34%	1.10%	Accuracy	89.31%	91.57%
	1/2 nd dilution	1/4 th dilution								
Precision	1.34%	1.10%								
Accuracy	89.31%	91.57%								
Partial validation ^d Location(s)	NA									
Cross validation(s) ^d Location(s)	NA									

^a Might not be applicable for the given analytical method

^b n.v. = nominal value

^c Report short term stability results if no long term stability on stock and working solutions are available.

^d These rows are optional. Report any validation study which was completed after the initial validation study.

4.1b Bioanalytical method validation for Formoterol

Analytical Validation Report Location (s)	Refer to Module : 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.6.1 method validation report Volume (s) : Not applicable Page 1 to 322
This analytical method was used in the following studies:	BDPFF-AS-101 (LBC-19-052[FOR])
Short description of the method	Solid Phase extraction method
Biological matrix	Human Plasma
Analyte Location of product certificate	Formoterol For Location Refer to Module: 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.6.2 CoA Volume (s): Not applicable Page 2-3 of 15



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Internal standard (IS) ^a Location of product certificate	Formoterol D6 For Location Refer to Module: 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.6.2 CoA Volume (s): Not applicable Page 4-7 of 15																																				
Calibration concentrations (units)	0.409 to 80.593 pg/mL																																				
Lower limit of quantification (units)	0.409 pg/mL																																				
QC concentration (units)	HQC: 63.970 MQC: 35.183 LQC: 1.214 LLOQOC: 0.409																																				
Between-run accuracy	95.94% to 97.54%																																				
Between-run precision	5.17% to 6.65%																																				
Within-run accuracy	HQC: 91.45-106.82% MQC: 90.96-106.64% LQC: 90.40-106.63% LLOQOC: 91.69-105.70%																																				
Within-run precision	HQC: 0.81-1.78% MQC: 0.67-2.01% LQC: 1.39-6.70% LLOQOC: 2.93-6.71%																																				
Matrix Factor (MF) (all QC) ^a IS normalized MF (all QC) ^a C.V.% of IS normalized MF (all QC) % of QCs with >85% and <115% n.v. ^{a, b} %matrix lots with mean <80% or>120% n.v. ^{a, b}	<p><u>Formoterol</u></p> <table border="1"> <thead> <tr> <th></th> <th><u>Mean Matrix factor</u></th> <th><u>% CV</u></th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>0.957</td> <td>1.25%</td> </tr> <tr> <td>MQC</td> <td>0.966</td> <td>1.24%</td> </tr> <tr> <td>LQC</td> <td>0.975</td> <td>3.28%</td> </tr> </tbody> </table> <p><u>Formoterol D6</u></p> <table border="1"> <thead> <tr> <th></th> <th><u>Mean Matrix factor</u></th> <th><u>% CV</u></th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>0.889</td> <td>2.59%</td> </tr> <tr> <td>MQC</td> <td>0.912</td> <td>1.75%</td> </tr> <tr> <td>LQC</td> <td>0.912</td> <td>1.75%</td> </tr> </tbody> </table> <p><u>IS Normalized Matrix Factor for Formoterol</u></p> <table border="1"> <thead> <tr> <th></th> <th><u>Mean Matrix factor</u></th> <th><u>% CV</u></th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>1.076</td> <td>2.97%</td> </tr> <tr> <td>MQC</td> <td>1.059</td> <td>2.64%</td> </tr> <tr> <td>LQC</td> <td>1.069</td> <td>4.49%</td> </tr> </tbody> </table>		<u>Mean Matrix factor</u>	<u>% CV</u>	HQC	0.957	1.25%	MQC	0.966	1.24%	LQC	0.975	3.28%		<u>Mean Matrix factor</u>	<u>% CV</u>	HQC	0.889	2.59%	MQC	0.912	1.75%	LQC	0.912	1.75%		<u>Mean Matrix factor</u>	<u>% CV</u>	HQC	1.076	2.97%	MQC	1.059	2.64%	LQC	1.069	4.49%
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Long term stability of the stock solution and working solutions ^c (Observed change %)	<p>Formoterol</p> <p><u>% Stock solution stability after 58 days and 22 hours at 2-8°C</u></p> <p>(Observed change HQC: -0.24%, LQC: 1.16%)</p> <p>Location: Page 93 of 322</p>																																				



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

	<p><u>% Spiking solution stability after 58 days and 18 hours at 2-8°C</u></p> <p>(Observed change HQC: -0.32%, LQC: 0.34%)</p> <p>Location: Page 94 of 322</p> <p><u>Formoterol D6</u></p> <p><u>% Stock solution stability after 58 days and 22 hours at 2-8°C</u></p> <p>(Observed change: -0.16%) Location: Page 95 of 322</p> <p><u>% Spiking solution stability after 58 days and 18 hours at 2-8°C</u></p> <p>(Observed change: -0.72%)</p> <p>Location: Page 96 of 322</p>
Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	<p>Bench top Stability: Confirmed up to 07 hours and 12 minutes at room temperature (Observed change HQC: -10.40%, MQC: -7.09%, LQC: 14.33 %)</p>
Long term stability in biological matrix (Observed change %) Location	<p>Confirmed up to 180 days at -30°C (Observed change HQC: -0.47%, MQC: -0.13%, LQC: -0.37%) Location: Page 20 of 322</p> <p>Confirmed up to 180 days at -75°C (Observed change HQC: -0.07%, MQC: 0.19%, LQC: 0.01%) Location: Page 21 of 322</p> <p>Confirmed up to 180 days at -20°C (Observed change HQC: -0.32%, MQC: 0.39%, LQC: 0.48%) Location: Page 22 of 322</p>
Auto-sampler storage stability (Observed change %)	<p>Confirmed up to 91 hours and 13 minutes at 10.0°C±3.0°C (Observed change HQC: -1.39%, MQC: -2.33%, LQC: 0.41%)</p>
Post-preparative stability (Observed change %)	<p>Post Extract Stability Confirmed up 02 hours 10 minutes at room temperature and 42 hours and 11 minutes at 2-8°C</p> <p>(Observed change HQC: -0.57%, MQC: 0.67%, LQC: -0.77%)</p>



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Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Freeze and thaw stability (Observed change %)	-30°C, V cycles (Observed change HQC: -8.03%, MQC: -7.50%, LQC: 13.91%) -75°C, V cycles (Observed change HQC: -8.07%, MQC: -7.52%, LQC: 0.84%) -20°C, V cycles (Observed change HQC: -7.47%, MQC: -7.98%, LQC: 13.36%)									
Dilution integrity	<table border="1"> <thead> <tr> <th></th> <th>1/2nd dilution</th> <th>1/4th dilution</th> </tr> </thead> <tbody> <tr> <td>Precision</td> <td>1.70%</td> <td>0.67%</td> </tr> <tr> <td>Accuracy</td> <td>103.67%</td> <td>103.04%</td> </tr> </tbody> </table>		1/2 nd dilution	1/4 th dilution	Precision	1.70%	0.67%	Accuracy	103.67%	103.04%
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Partial validation ^d Location(s)	Addendum I and Addendum III									
Cross validation(s) ^d Location(s)	Addendum III									

^a Might not be applicable for the given analytical method

^b n.v. = nominal value

^c Report short term stability results if no long term stability on stock and working solutions are available.

^d These rows are optional. Report any validation study which was completed after the initial validation study.

Table 4.1c Bioanalytical method validation for Beclometasone Dipropionate

Analytical Validation Report Location (s)	Refer to Module : 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.5.1 method validation report Volume (s) : Not applicable Page 1 to 282
This analytical method was used in the following studies:	BDPFF-AS-101
Short description of the method	Solid phase extraction method
Biological matrix	Human Plasma
Analyte Location of product certificate	Beclometasone Dipropionate For Location Refer to Module : 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.5.2 CoA Volume (s) : Not applicable Pages 2-9 of 30
Internal standard (IS) ^a Location of product certificate	Beclometasone D10 Dipropionate For Location Refer to Module : 5 Section : m5-3-clinical-study-reports Subsection: m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies Appendix: 16.5.2 CoA Volume (s) : Not applicable



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

	Page 15-21 of 30																																				
Calibration concentrations (units)	5.017 to 5003.640 pg/mL																																				
Lower limit of quantification (units)	5.017 pg/mL																																				
QC concentration (units)	HQC: 3999.076 pg/mL MQC: 2001.938 pg/mL LQC: 14.414 pg/mL LLOQQC: 5.059 pg/mL																																				
Between-run accuracy	93.35-98.01%																																				
Between-run precision	5.02-19.53%																																				
Within-run accuracy	HQC: 86.90-98.41% MQC: 88.71-101.79% LQC: 88.14-106.43% LLOQQC: 86.69-118.07%																																				
Within-run precision	HQC: 0.63-3.71% MQC: 0.55-3.08% LQC: 2.64-7.73% LLOQQC: 4.69-19.26%																																				
Matrix Factor (MF) (all QC) ^a IS normalized MF (all QC) ^a C.V.% of IS normalized MF (all QC) % of QCs with >85% and <115% n.v. ^{a, b} %matrix lots with mean <80% or >120% n.v. ^{a, b}	<p><u>Beclometasone Dipropionate</u></p> <table border="1"> <thead> <tr> <th></th> <th>Mean Matrix Factor</th> <th>% CV</th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>0.918</td> <td>2.51%</td> </tr> <tr> <td>MQC</td> <td>0.885</td> <td>2.15%</td> </tr> <tr> <td>LQC</td> <td>0.836</td> <td>4.31%</td> </tr> </tbody> </table> <p><u>Beclometasone D₁₀ Dipropionate</u></p> <table border="1"> <thead> <tr> <th></th> <th>Mean Matrix Factor</th> <th>% CV</th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>0.848</td> <td>1.53%</td> </tr> <tr> <td>MQC</td> <td>0.810</td> <td>1.73%</td> </tr> <tr> <td>LQC</td> <td>0.796</td> <td>1.13%</td> </tr> </tbody> </table> <p><u>IS Normalized Matrix Factor for Beclometasone Dipropionate/ Beclometasone D₁₀ Dipropionate</u></p> <table border="1"> <thead> <tr> <th></th> <th>Mean Matrix factor</th> <th>% CV</th> </tr> </thead> <tbody> <tr> <td>HQC</td> <td>1.083</td> <td>2.95%</td> </tr> <tr> <td>MQC</td> <td>1.094</td> <td>2.19%</td> </tr> <tr> <td>LQC</td> <td>1.051</td> <td>4.09%</td> </tr> </tbody> </table>		Mean Matrix Factor	% CV	HQC	0.918	2.51%	MQC	0.885	2.15%	LQC	0.836	4.31%		Mean Matrix Factor	% CV	HQC	0.848	1.53%	MQC	0.810	1.73%	LQC	0.796	1.13%		Mean Matrix factor	% CV	HQC	1.083	2.95%	MQC	1.094	2.19%	LQC	1.051	4.09%
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Long term stability of the stock solution and working solutions ^c (Observed change %)	<p><u>Beclometasone Dipropionate</u></p> <p><u>% Stock solution stability after 152 Days and 00 Hours at -20°C:</u> (Observed change HQC: 1.19%, LQC: -1.54%)</p> <p><u>% Spiking solution stability after 152 days and 00 hours at -20°C:</u></p>																																				



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

	(Observed change HQC: 1.49%, LQC: 1.72%) <u>Beclometasone D₁₀ Dipropionate</u> <u>% Stock solution stability after 152 Days and 00 Hours at -20°C:</u> (Observed change: -2.32%) <u>% Spiking solution stability after 152 days and 00 hour at -20°C:</u> (Observed change: -2.80%)									
Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Bench top Stability: Confirmed up to 06 hours and 48 minutes in Ice water bath (Observed change HQC: -2.00%, MQC: -0.77%, LQC: -2.36%) Location: Page 133 of 205									
Long term stability in biological matrix (Observed change %) Location	Confirmed up to 169 Days at -75°C (Observed change HQC: 2.82%, MQC: 1.07%, LQC: 1.75%) Location: Page 41 of 282									
Autosampler storage stability (Observed change %)	Confirmed up to 66 hours and 32 minutes Condition: at 10.0°C ± 3.0°C (Observed change HQC: 2.75%, MQC: -2.19%, LQC: -3.83%)									
Post-preparative stability (Observed change %)	Post Extract Stability Confirmed up to 02 hours and 24 minutes at RT and 23 Hours and 59 minutes at 2-8°C (Observed change HQC: -1.61%, MQC: -0.42%, LQC: -1.81%)									
Dilution integrity	<table border="1"> <thead> <tr> <th></th> <th>1/2nd dilution</th> <th>1/4th dilution</th> </tr> </thead> <tbody> <tr> <td>Precision</td> <td>2.92%</td> <td>1.12%</td> </tr> <tr> <td>Accuracy</td> <td>86.19%</td> <td>89.24%</td> </tr> </tbody> </table>		1/2 nd dilution	1/4 th dilution	Precision	2.92%	1.12%	Accuracy	86.19%	89.24%
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Partial validation ^d Location(s)	NA									
Cross validation(s) ^d Location(s)	NA									

^a Might not be applicable for the given analytical method

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Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Table 4.2a Storage period of study samples for Beclometasone 17-Propionate

Study ID ^a and analyte	Longest storage period
BDPFF-AS-101 (LBC-19-052 (BDP)) and Beclometasone 17-Propionate	142 days at -75 ± 10°C (Clinical) and (Bioanalytical)

^a Only pivotal trials

Table 4.2b Storage period of study samples for Formoterol

Study ID ^a and analyte	Longest storage period
BDPFF-AS-101 (LBC-19-052 (BDP)) and Formoterol	135 days at -75±10°C

^a Only pivotal trials

Table 4.2c Storage period of study samples for Beclometasone Dipropionate

Study ID ^a and analyte	Longest storage period
BDPFF-AS-101 (LBC-19-052 (BDP))and Beclometasone Dipropionate	142 days at -75 ± 10°C (Clinical) and (Bioanalytical)

^a Only pivotal trials

Table 4.3a Sample analysis of Beclometasone 17-Propionate BDPFF-AS-101 (LBC-19-052 (BDP))

Analyte	Beclometasone 17-Propionate
Total numbers of collected samples	4236
Total number of samples with valid results	4236
Total number of reassayed samples ^{a, b}	23
Total number of analytical runs ^a	62
Total number of valid analytical runs ^a	60
Incurred sample reanalysis	
Number of samples	449
Percentage of sample where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays.	88.84%

^a Without incurred samples.

^b Due to other reasons than not valid run.



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution; 100/6 mcg

2.7. Clinical Summary

Table 4.3b Sample analysis of Formoterol BDPFF-AS-101 (LBC-19-052 (FOR))

Analyte	Formoterol
Total numbers of collected samples	8574
Total number of samples with valid results	8574
Total number of reassayed samples ^{a, b}	93
Total number of analytical runs ^a	113
Total number of valid analytical runs ^a	108
Incurred sample reanalysis	
Number of samples	578
Percentage of sample where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays.	93.41%

^a Without incurred samples.

^b Due to other reasons than not valid run.

Table 4.3c Sample analysis of Beclometasone Dipropionate BDPFF-AS-101 (LBC-19-052 (BDP))

Analyte	Beclometasone Dipropionate
Total numbers of collected samples	4236
Total number of samples with valid results	4236
Total number of reassayed samples ^{a, b}	234
Total number of analytical runs ^a	62
Total number of valid analytical runs ^a	59
Incurred sample reanalysis	
Number of samples	407
Percentage of sample where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays.	82.63%

^a Without incurred samples.

^b Due to other reasons than not valid run.