respire

Ablynx
A SANOFI COMPANY

Nanobodies®
Innovative therapeutics

Respire (ALX-0171-C201) Phase 2b results

Professor Steve Cunningham, University of Edinburgh, UK. Chief Investigator
on behalf of the RESPIRE study team

Conflict of Interest

RSV related

Consultancy with fees paid to the University of Edinburgh

- Ablynx (Sanofi), Janssen, Reviral, Pulmocide

Other

Consultancy with fees paid to the University of Edinburgh

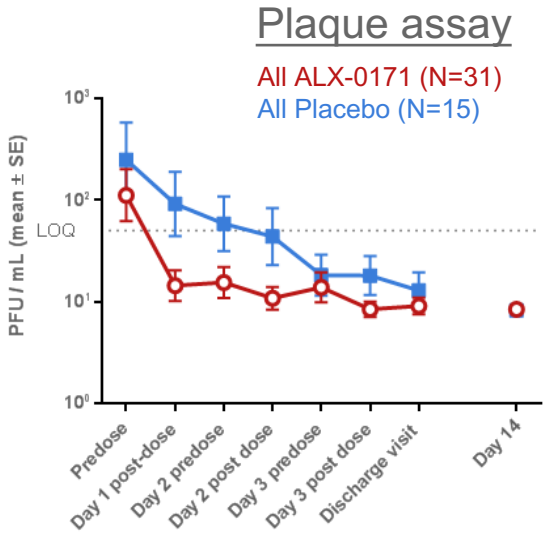
- Boehringer Ingelheim, Galapagos, Vertex, UK Cystic Fibrosis Trust

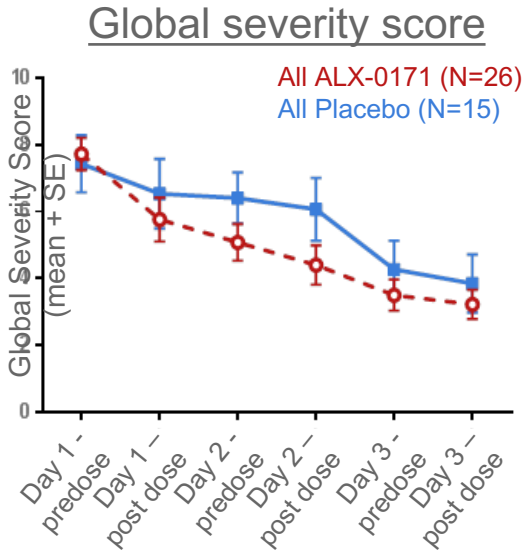
Study Funding: the study was funded by Ablynx, which was acquired by Sanofi at study completion

Lead up to Phase 2b programme

Inhaled anti-RSV Nanobody® – ALX-0171

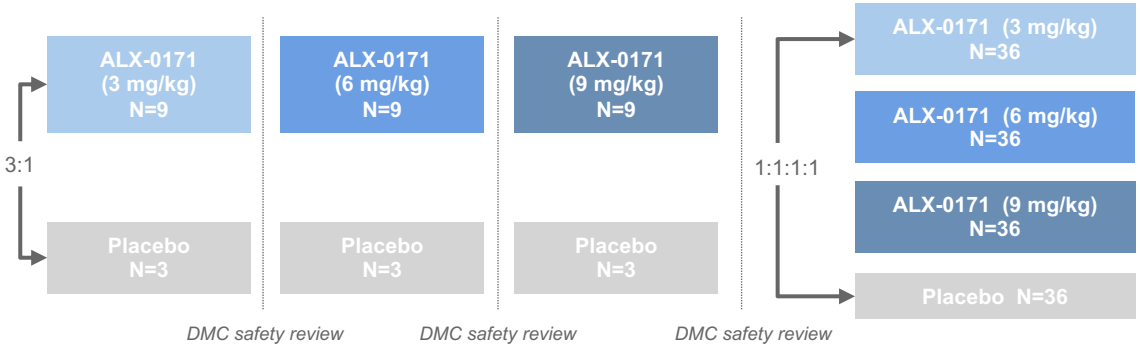
- Nanobody® (trivalent) - based on Camelid Antibodies - Nebulised
- Lamb Model – reduction in viral load and clinical disease
- Adults – safety (healthy and hypersensitive airways)
- Phase I/IIa; N= 53
  Hospitalised Infants





Phase 2b
Study Design

- Randomized, Double-Blind, Placebo-Controlled, Multicenter Dose-Ranging Study
- 180 infants hospitalized for RSV Lower Respiratory Tract Disease
- Aged 28 days to < 24m; gestational age > 33 weeks
- Delivery via vibrating mesh nebuliser (FOX-Flamingo, Vectura Group plc, UK)
- Inhaled ALX-0171 (3 doses; higher than in phase I/IIa) administered once/day, for 3 consecutive days



Primary Objectives: anti-viral effect and safety

Secondary Objectives: clinical activity, pharmacokinetics, pharmacodynamics, and immunogenicity

Eudra CT 2016-001651-49

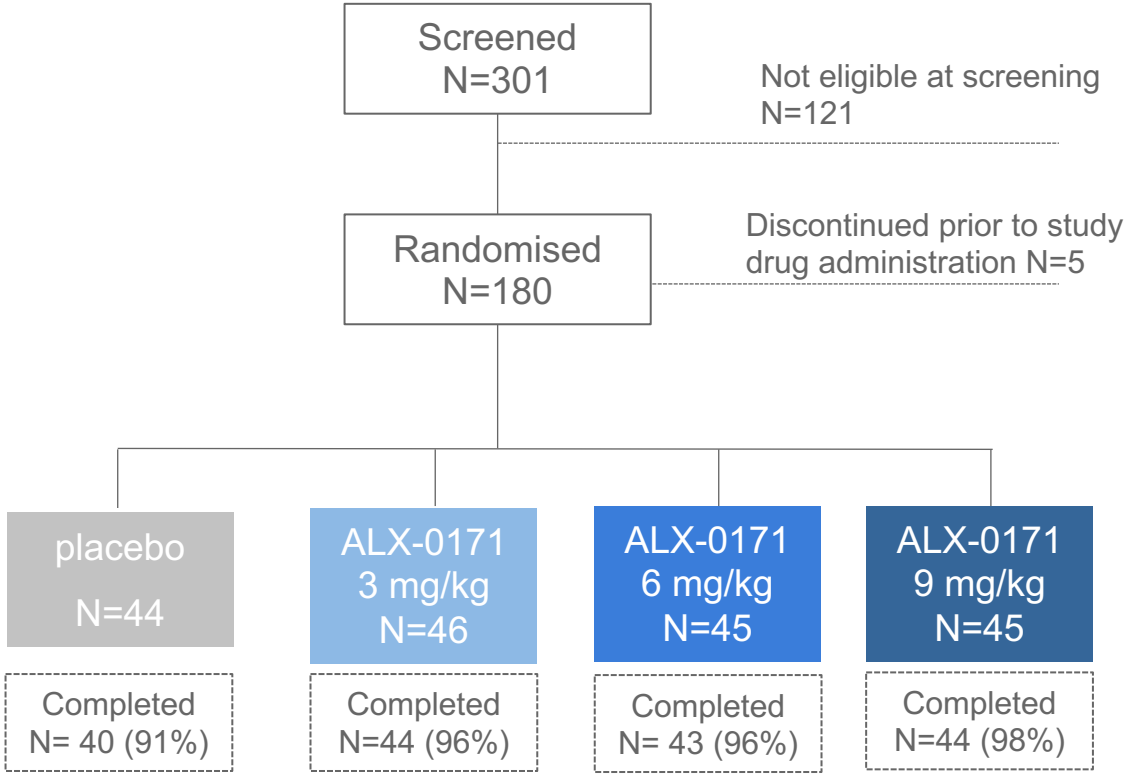
Main inclusion criteria

- **RSV positive**
  Site diagnostic test (e.g., PCR or rapid test), or using a Sponsor-provided commercial kit

- **RSV disease severity criteria:** ≥2 of
  - Inadequate oral feeding requiring support (i.e. IV line or nasogastric tube)
  - Inadequate oxygen saturation defined as:
    - Oxygen saturation ≤92% on room air or
    - Requiring oxygen supplementation to maintain oxygen saturation >90% (documented pre-supplementation value ≤ 92%)
  - Signs of respiratory distress defined as:
    - Respiratory rate ≥ 50 per minute in infants up to 12 months of age, and ≥ 40 per minute in children above 12 months or
    - Moderate or marked respiratory muscle retractions

- **Symptoms arising in last 4 days that are likely related to RSV infection**

Subject disposition



Demographics

mITT population, mean (SD) unless otherwise specified	Placebo N=42	ALX-0171 3 mg/kg N=45	ALX-0171 6 mg/kg N=43	ALX-0171 9 mg/kg N=45
Age (months)	6.96 (6.07)	6.93 (5.88)	6.66 (6.26)	7.02 (5.69)
<6 months n(%)	24 (57.1)	23 (51.1)	27 (62.8)	25 (55.6)
>=6 months and <12 months n(%)	8 (19.0)	13 (28.9)	7 (16.3)	12 (26.7)
>=12 months n(%)	10 (23.8)	9 (20.0)	9 (20.9)	8 (17.8)
Males (%)	42.9	66.7	55.8	62.2
Weight (kg)	7.07 (2.4)	7.19 (2.2)	6.99 (2.4)	7.02 (2.2)

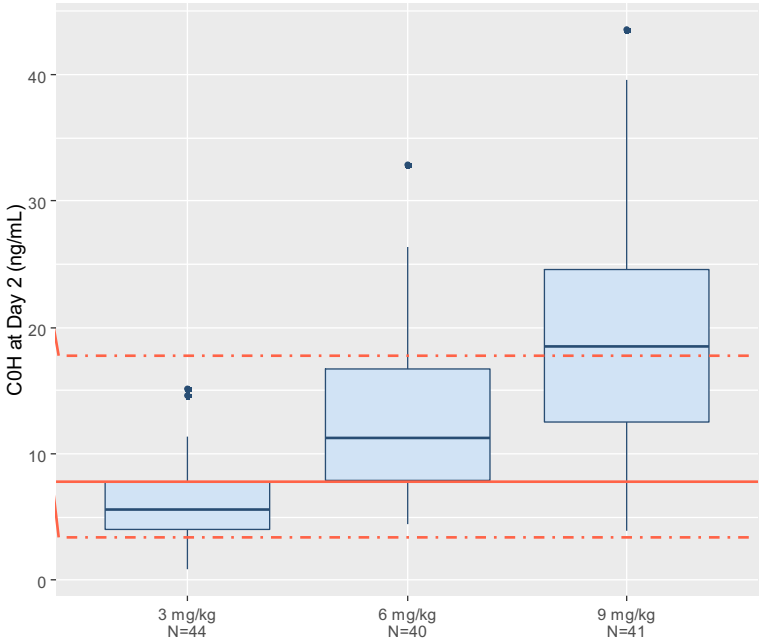
Baseline Characteristics

mITT Mean (SD), unless otherwise specified	Placebo N=42	ALX-0171 3 mg/kg N=45	ALX-0171 6 mg/kg N=43	ALX-0171 9 mg/kg N=45
Days onset symptoms to first dose	3.2 (1.2)	3.3 (1.1)	3.2 (0.9)	3.3 (1.2)
Global Severity Score	9.1 (2.4)	9.2 (2.0)	9.3 (2.1)	9.4 (2.4)
RDAI score	8.5 (3.7)	8.4 (4.1)	8.7 (3.2)	8.1 (3.8)
Number (%) on oxygen	21 (50.0)	26 (57.8)	25 (58.1)	27 (60.0)
Number (%) on feeding support	25 (59.5)	20 (44.4)	22 (51.28)	28 (62.2)
Number (%) with Severe RSV disease*	15 (35.7)	6 (13.3)	12 (27.9)	17 (37.8)

*Severe RSV = Both oxygen and feeding support

Pharmacokinetics

Trough concentration before dose at Day2



- Individual predicted C_{0h}
- Red lines: median (full) and 5^{th} & 95^{th} percentile (dash) predicted C_{0h} for which target lung exposure is reached in 95% of population simulated through PBPK
- 6 and 9 mg/kg both achieve sufficient exposure

Middle line: median; lower and upper hinges: 25th and 75th percentiles; lower and upper whiskers extend to the smallest or largest value no further than 1.5*IQR from the hinge; full dots: outliers above whiskers

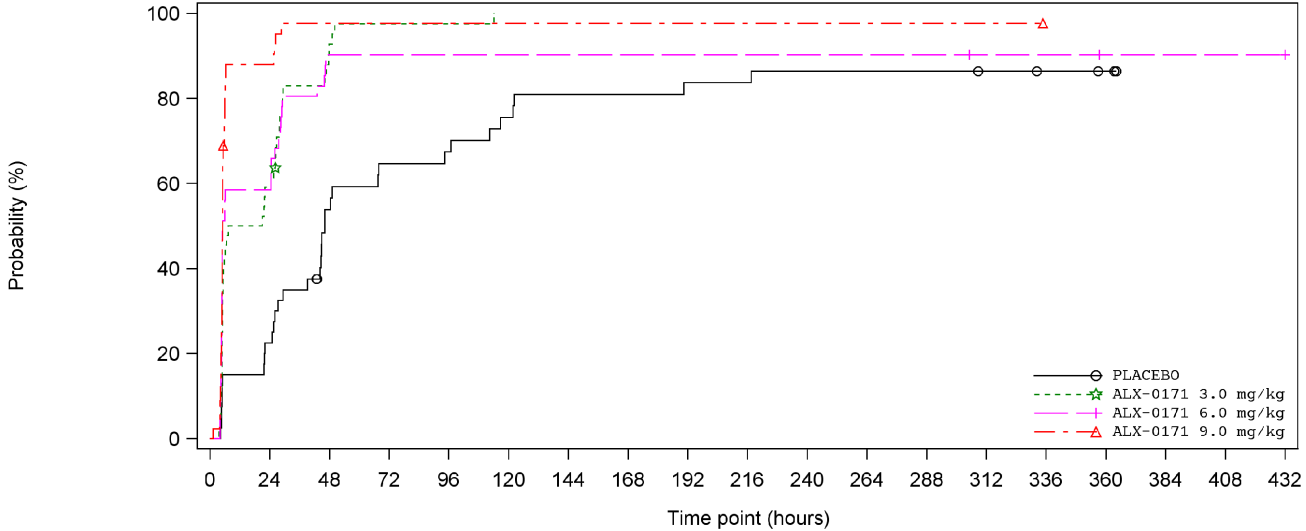
Primary endpoint

Time-to-BQL Infectious RSV (plaque assay)

15:53 Thursday, October 4, 2018
Page 1 of 1

ALX0171-C201 - FINAL ANALYSIS
FIGURE 14.2.1.1: PRIMARY ENDPOINT: TIME TO BELOW QUANTIFICATION LIMIT IN RSV VIRAL LOAD (PLAQUE ASSAY) - mITT POPULATION

POPULATION: mITT POPULATION



NUMBER OF SUBJECTS AT RISK

PLACEBO	40	31	17	13	12	9	7	7	6	6	5	5	5	4	3	2	0		
ALX-0171 3.0 mg/kg	44	18	3	1	1	0													
ALX-0171 6.0 mg/kg	41	17	4	4	4	4	4	4	4	4	4	4	4	3	3	1	1	1	1
ALX-0171 9.0 mg/kg	45	5	1	1	1	1	1	1	1	1	1	1	1	1	0				

REFERENCE: LISTING 16.2.3.1

Primary endpoint

Time-to-BQL of infectious RSV (Plaque Assay)

mITT population	Placebo N=42	ALX-0171 3 mg/kg N=45	ALX-0171 6 mg/kg N=43	ALX-0171 9 mg/kg N=45
Median Time-to-BQL in hours	46.1	14.2	5.1	5.1
CI 95%	(29.33; 94.42)	(5.17 ; 26.28)	(4.78 ; 24.72)	(4.97 ; 5.17)
P-value (versus placebo) – Log rank test		<0.001	0.001	<0.001

Consistent statistically significant effect in RSV-infected population and per protocol population

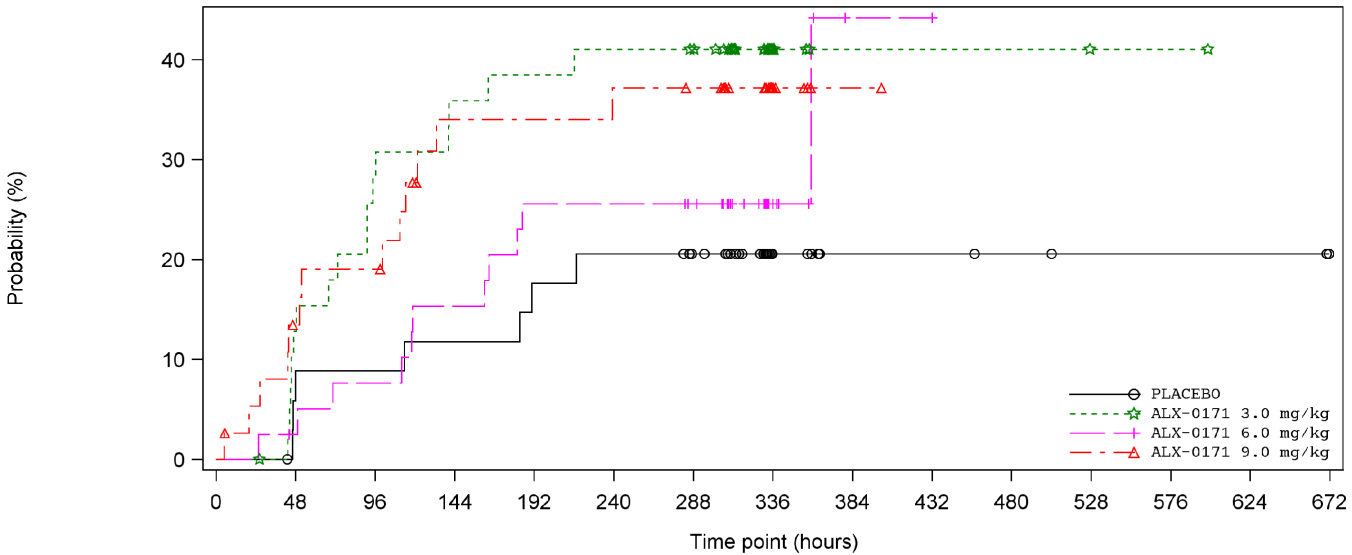
Secondary endpoints

Time-to-Undetectable viral load by qPCR

15:53 Thursday, October 4, 2018
Page 1 of 1

ALX0171-C201 - FINAL ANALYSIS
FIGURE 14.2.1.9: VIRAL LOAD: TIME TO UNDETECTABLE IN RSV VIRAL LOAD (RT-qPCR ASSAY) - RSV INFECTED POPULATION

POPULATION: RSV INFECTED



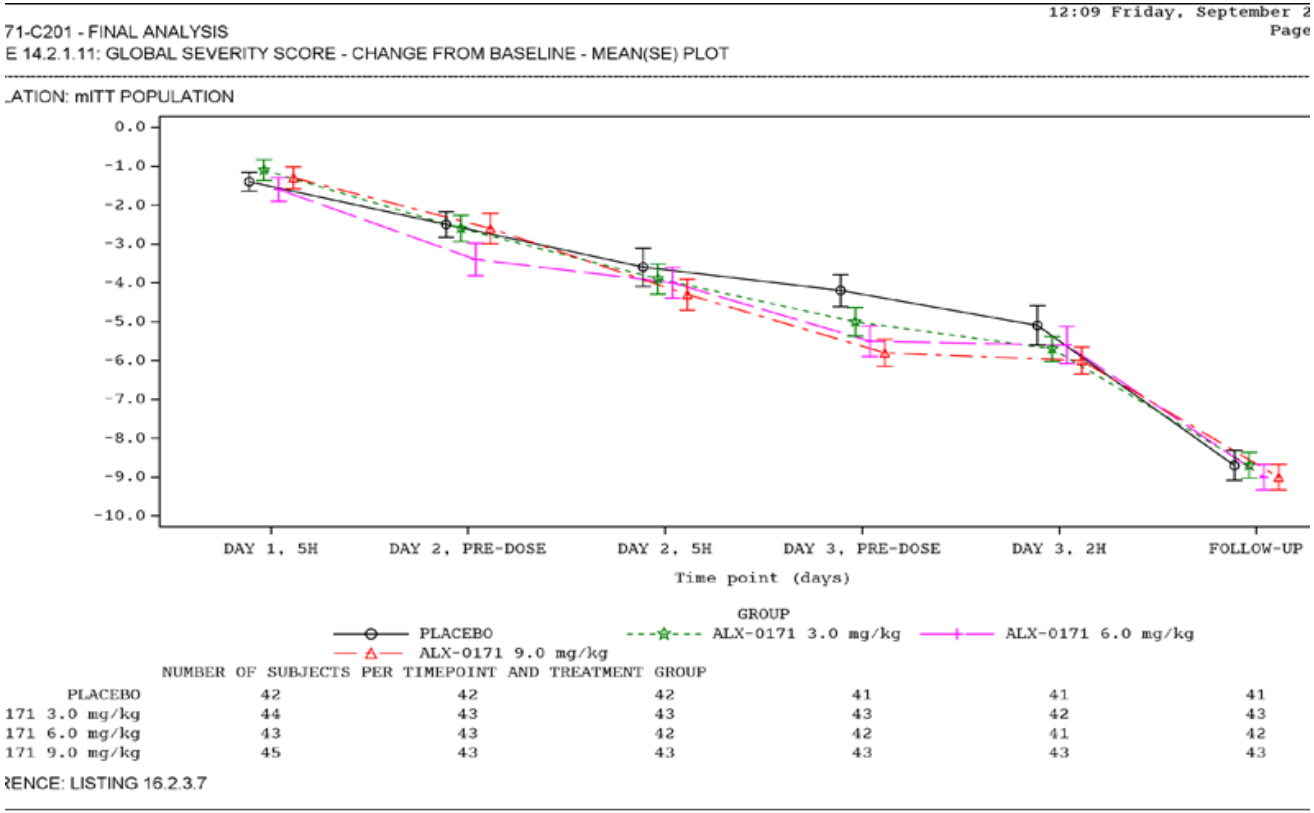
NUMBER OF SUBJECTS AT RISK

PLACEBO	35	35	31	31	31	30	30	30	28	28	27	27	24	20	8	6	4	4	4	4	3	2	2	2	2	2	2	0
ALX-0171 3.0 mg/kg	40	40	34	32	28	27	25	24	24	24	23	23	22	16	6	2	2	2	2	2	2	2	1	1	1	0		
ALX-0171 6.0 mg/kg	40	40	38	36	36	33	33	31	29	29	29	29	27	20	8	3	1	1	1									
ALX-0171 9.0 mg/kg	38	35	31	29	29	24	21	21	21	21	20	20	19	14	6	1	1	0										

REFERENCE: LISTING 16.2.3.6

Global Severity Score

Change from baseline



Global Severity Score

Day 2 5h post-dose

mITT Change from baseline to Day 2, 5h post dose		Placebo N=42	ALX-0171 3 mg/kg N=45	ALX-0171 6 mg/kg N=43	ALX-0171 9 mg/kg N=45
Mean (SE)		-3.64 (0.42)	-3.85 (0.41)	-4.13 (0.41)	-4.28 (0.41)
Difference vs Placebo	Mean (SE)		-0.22 (0.58)	-0.49 (0.59)	-0.65 (0.58)
	P-value		0.713	0.404	0.271

Post hoc

Global Severity Score, Day 3 pre-dose

mITT Change from baseline to Day 2, 5h post dose		Placebo N=42	ALX-0171 3 mg/kg N=45	ALX-0171 6 mg/kg N=43	ALX-0171 9 mg/kg N=45
Mean (SE)		-4.17 (0.39)	-5.05 (0.38)	-5.41 (0.38)	-5.77 (0.38)
Difference vs Placebo	Mean (SE)		-0.88 (0.54)	-1.24 (0.54)	-1.60 (0.54)
	P-value		0.105	0.023	0.003

Clinical Outcomes

Median (95%CI) mITT population	Placebo N = 42	ALX-0171 3 mg/kg N = 45	ALX-0171 6 mg/kg N = 43	ALX-0171 9 mg/kg N = 45
Time to clinical Response (hours)	**47.9** (29.17; 64.08)	**44.1** (28.33; 51.20)	**27.9** (21.08; 43.68)	**46.3** (38.00; 50.38)
Time to adequate feeding	**43.7** (22.50; 47.58) (n=28)	**44.0** (25.92; 52.00) (n=34)	**17.6** (6.50; 25.85) (n=32)	**23.8** (17.17; 38.00) (n=32)
Time to adequate oxygenation	**53.4** (28.70; 71.78) (n=33)	**38.5** (24.75; 61.93) (n=34)	**29.5** (20.75; 47.43) (n=34)	**46.5** (42.15; 48.25) (n=37)
Time from first dose to discharge (days)	**4.09** (2.87; 4.89)	**3.75** (2.92; 4.03)	**3.96** (2.97; 4.91)	**3.77** (2.98; 4.22)

n = number assessed

Immunogenicity

Anti-drug antibodies in serum

- Two serum samples per infant were available for ADA analysis (1 pre- and 1 post-dose)
- Similar rates of TE binding ADA were observed in placebo (25.6%) as well as ALX-0171 treated groups (34.1%)
- A higher incidence of TE neutralizing ADA (NAb) was detected in ALX-0171 treated compared to placebo subjects
- No dose dependency observed in ALX-0171-treated groups for ADA or NAb

	ALX-0171 N=135 (%)	Placebo N=39 (%)
Pre-existing antibody	77 (57.0)	18 (46.2)
Treatment emergent ADA	46 (34.1)	10 (25.6)
Neutralizing ADA	41 (30.4)	2 (5.1)

TE ADA: treatment emergent anti drug antibodies, NAb: neutralizing antibodies towards the drug

Safety

Adverse Events

Subjects (N (%)) with treatment-emergent adverse events (TEAE)	Placebo N = 40	ALX-0171 Total N = 135	ALX-0171 3 mg/kg N = 45	ALX-0171 6 mg/kg N = 44	ALX-0171 9 mg/kg N = 46
Any TEAE	19 (47.5)	63 (46.7)	25 (55.6)	22 (50.0)	16 (34.8)
-treatment related	0	0	0	0	0
-leading to study treatment discontinuation*	0	3 (2.2)	2 (4.4)	1 (2.3)	0
-classified as severe by the investigator	1 (2.5)	4 (3.0)	2 (4.4)	1 (2.3)	1 (2.2)
Any SAE	5 (12.5)	10 (7.4)	4 (8.9)	3 (6.8)	3 (6.5)
-treatment related	0	0	0	0	0

* bronchiolitis, RSV infection (worsening), respiratory failure (due to RSV worsening)

Conclusions – ALX-0171 Phase 2b

- **Effective in reducing infectious RSV viral load – primary efficacy endpoint met**
  - RSV viral load measured by plaque assay demonstrated shorter Time-to-BQL at each dose versus placebo.
  - RT-qPCR Time-to-undetectable viral load was shorter in ALX-0171 vs Placebo, with no dose dependency
    - RT-qPCR effect was less robust but consistent with the plaque assay
- **Serum target exposure achieved** for 6.0 mg/kg and 9.0 mg/kg
- **No significant clinical benefit observed**
  - Global Severity Score - not statistically different from placebo (predefined Day 2, 5h post dose).
  - Quick and highly variable between subject clinical response in all treatment groups, including placebo
- **Neutralising antibodies towards ALX-0171 detected on Day 14**
  - Neutralizing Abs detected in 30.4% of the ALX-0171 treated group as measured in serum on Day 14
- **Safety profile**
  - Overall safety and occurrence of SAEs similar between ALX-0171 and placebo
    Most SAEs were respiratory/infectious as expected in this patient population.

Thank You

To all the children, parents and study teams that made this work possible

steve.cunningham@ed.ac.uk

RSV severity subgroup

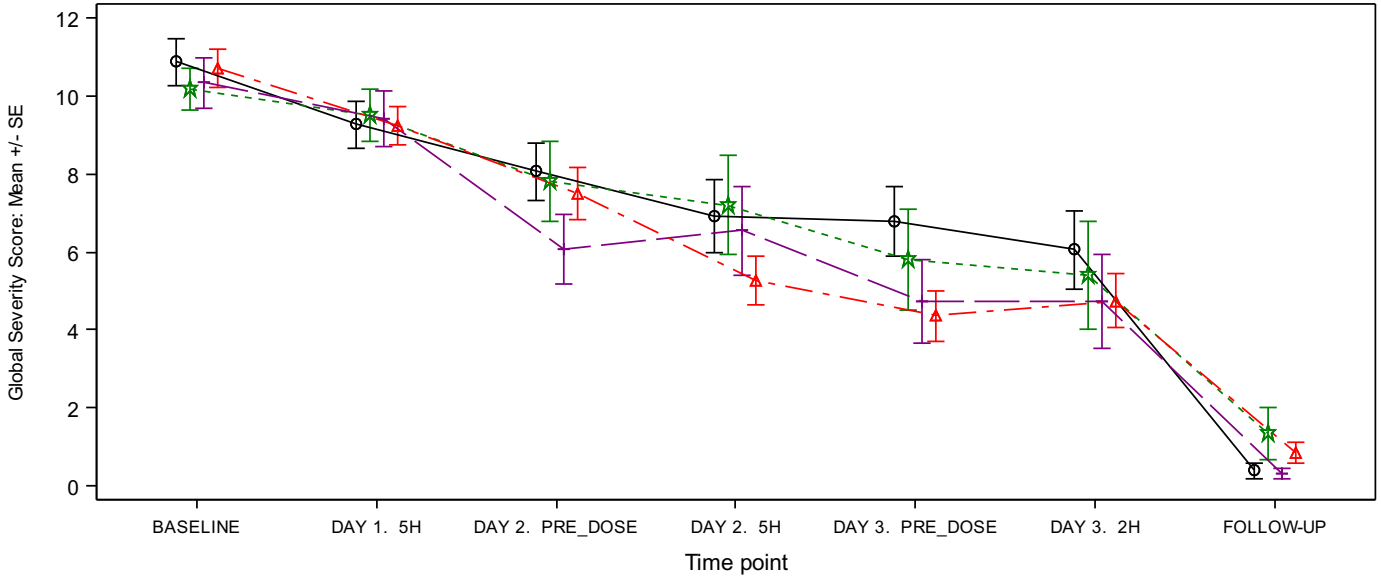
Predefined

- Baseline: Both **Inadequate oxygen and inadequate Feeding**
- Total of **50 subjects**
- Time-to-BQL of infectious virus (plaque assay)

		Placebo	ALX-0171 3 mg/kg	ALX-0171 6 mg/kg	ALX-0171 9 mg/kg
Severity subgroup		N=15	N=6	N=12	N=17
	Median Time-to-BQL in hours	94.4	25.1	14.7	4.8
	CI95%	(27.25 ; 190.43)	(4.98 ; 114.08)	(4.58 ; 46.00)	(4.15 ; 5.88)
Overall population		N=42	N=45	N=43	N=45
	Median Time-to-BQL in hours	46.1	14.2	5.1	5.1
	CI95%	(29.33 ; 94.42)	(5.17 ; 26.28)	(4.78 ; 24.72)	(4.97 ; 5.17)

RSV severity subgroup

Global Severity Score, actual values



PLACEBO	15	15	15	15	15	15	15
ALX-0171 3.0 mg/kg	6	6	5	5	5	5	6
ALX-0171 6.0 mg/kg	12	12	12	11	12	11	12
ALX-0171 9.0 mg/kg	17	17	16	16	16	16	15

RSV severity subgroup

Clinical Response/ Discharge

	Placebo N = 15	ALX-0171 3 mg/kg N = 6	ALX-0171 6 mg/kg N = 12	ALX-0171 9 mg/kg N = 17
Time to clinical Response (hours) Median (95% CI)	**76.4** (47.92; 91.13)	**102.6** (27.48; 173.82)	**37.7** (15.00; 99.58)	**68.4** (44.72; 77.22)
Time to adequate feeding	**48.3** (25.92, 89.13)	**78.4** (17.88, 166.63)	**27.6** (15.00, 74.88)	**20.3** (14.00, 32.22)
Time to adequate oxygenation	**76.4** (21.67, 91.13)	**102.6** (20.15, 173.82)	**15.0** (5.00, 98.00)	**68.3** (44.72, 77.22)
Days from first dose to discharge Median (95% CI)	**4.74** (2.82; 8.11)	**5.32** (2.87; 8.95)	**4.92** (2.92; 6.23)	**3.41** (2.82; 4.95)