BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

14th June 2017

Ablynx

Opportunity knocking at the door

Healthcare

Fair Value EUR22 vs. EUR18 (price EUR11.82) **BUY**

Bloomberg	ABLX BB
Reuters	ABLX.BR
12-month High / Low (EUR)	13.2 / 8.4
Market capitalisation (EURm)	722
Enterprise Value (BG estimates EURm)	866
Avg. 6m daily volume ('000 shares)	138.1
Free Float	66.0%
3y EPS CAGR	-18.4%

YE December	12/16	12/17e	12/18e	12/19e
Revenue (EURm)	81.60	39.63	37.68	89.35
EBIT (EURm)	-23.33	-58.17	-40.91	4.48
Basic EPS (EUR)	-1.13	-1.77	-1.45	-0.61
Diluted EPS (EUR)	-1.13	-1.77	-1.45	-0.61

Caplacizumab in aTTP should report Phase III results in H2 2017e. We would expect a positive readout from this trial to definitively shift investor focus from vobarilizumab, which still has a card to play in SLE, to: 1/ the change in the company's business model to become a biopharma and 2/ a promising pipeline, significantly undervalued at current levels and de-risked by both the presence of established partners as well as encouraging clinical results. For the latter, we see ALX-0171 in RSV-infected populations as a key value driver not reflected in the current share price. We reiterate our BUY rating and increase our FV from EUR18 to EUR22.

- **Caplacizumab (aTTP) Phase III results in H2 2017e should trigger a significant re-rating.** While the increase in our PoS for the product on positive Phase III results would add EUR4 to our FV, we expect the shift from a biotech to a biopharma business model as soon as 2018 (EU approval) to provide a key trigger for interest from investors and pharma.

- **RSV is a high unmet medical need and Ablynx has an overlooked and promising Phase IIb asset, ALX-0171** (results in H2 2018). We estimate that peak sales in excess of EUR1.5bn (RSV-infected infants and HSCT patients) are not fully reflected in the current share price. Positive Phase IIa results already released reinforce our positive stance on the drug and validate the rationale behind the company's Nanobody platform in our view. Ablynx aims to find a partner for the product in RSV-infected infants on the basis of Phase IIb, for a deal value that we estimate at up to EUR500m (plus double-digit royalties).

- **At current levels, we see vobarilizumab as free upside.** Interaction with potential partners is ongoing but it is our understanding that no deal will be made before Phase IIb results in SLE in H1 2018e and AbbVie's decision whether or not to take the RA programme forward.

- **We reiterate our BUY rating and increase our FV from EUR18 to EUR22 per share.** We lift our PoS linked to caplacizumab in Europe (80% vs. 50%) to reflect the recent filing to the EMA and include HSCT patient population for ALX-0171 in our valuation model.

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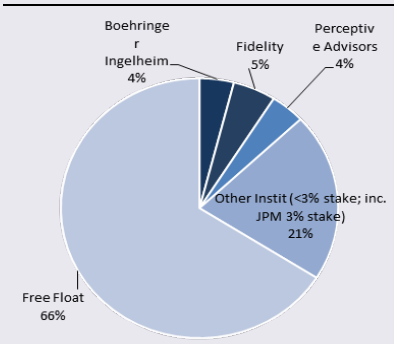

Company Overview

Ablynx NV is a Belgium-based biopharmaceutical company engaged in the discovery and development of Nanobodies, a class of therapeutic proteins based on single-domain antibody fragments, for a range of serious and life-threatening human diseases, including inflammation, thrombosis, oncology and Alzheimer's disease. The Company's portfolio consists of projects in the pipeline and Nanobodies in clinical development. Ablynx has research collaborations and significant partnerships with pharmaceutical companies, including AbbVie, Merck&Co and Boehringer Ingelheim to name a few.

Income Statement (EURm)	**2014**	**2015**	**2016**	**2017e**	**2018e**	**2019e**	2020e
Revenues	49.3	77.5	81.6	39.6	37.7	89.3	188
Change (%)	*37.2%*	*57.3%*	*5.2%*	*-51.4%*	*-4.9%*	*137%*	*111%*
Adjusted EBITDA	(14.7)	(15.6)	(21.9)	(57.5)	(40.2)	6.1	90.3
EBIT	(16.2)	(17.0)	(23.3)	(58.2)	(40.9)	4.5	87.0
Change (%)	*-8.1%*	*-4.4%*	*-37.6%*	*-149%*	*-29.7%*	*-%*	*1 840%*
Financial results	3.5	(37.6)	(37.6)	(37.6)	(37.6)	(37.6)	(37.6)
Pre-Tax profits	(12.7)	(54.5)	(60.9)	(95.8)	(78.5)	(33.1)	49.4
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Profits from associates	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Minority interests	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit	(12.7)	(54.5)	(60.9)	(95.8)	(78.5)	(33.1)	42.0
Restated net profit	(12.7)	(54.5)	(60.9)	(95.8)	(78.5)	(33.1)	42.0
Change (%)	*-34.6%*	*-328%*	*-11.7%*	*-57.2%*	*-18.0%*	*-57.8%*	*-%*
Cash Flow Statement (EURm)							
Operating cash flows	(32.3)	(69.0)	(108)	(119)	(85.3)	(22.2)	66.2
Change in working capital	0.0	85.1	(61.5)	(96.1)	(78.8)	(33.8)	40.5
Capex, net	(6.2)	(39.7)	(2.1)	(1.0)	(0.96)	(2.3)	(4.8)
Financial investments, net	39.7	101	0.0	0.0	0.0	0.0	0.0
Dividends	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net debt	(189)	(83.4)	152	143	143	154	175
Free Cash flow	1.1	(8.1)	(110)	(120)	(86.2)	(24.5)	61.4
Balance Sheet (EURm)							
Tangible fixed assets	16.0	18.8	19.4	19.7	20.0	20.7	22.2
Intangibles assets	0.44	0.34	0.34	0.34	0.34	0.34	0.34
Cash & equivalents	204	235	125	4.8	(81.4)	(106)	(44.5)
current assets	0.59	10.5	3.7	3.7	3.7	3.7	3.7
Other assets	1.5	1.0	1.0	1.0	1.0	1.0	1.0
Total assets	223	265	149	29.7	(56.3)	(80.1)	(17.2)
L & ST Debt	10.5	146	147	141	140	148	163
Others liabilities	137	90.9	35.3	17.6	10.5	12.0	18.1
Shareholders' funds	75.5	27.9	(33.0)	(129)	(207)	(240)	(198)
Total Liabilities	223	265	149	29.7	(56.3)	(80.1)	(17.2)
Capital employed	7.6	17.0	10.3	16.9	17.5	10.4	(3.0)
Financial Ratios							
Operating margin	(32.94)	(21.87)	(28.59)	(147)	(109)	5.02	46.23
Tax rate	0.0	0.0	0.0	0.0	0.0	0.0	(15.00)
Net margin	(25.82)	(70.35)	(74.65)	(242)	(208)	(37.06)	22.31
ROE (after tax)	(16.87)	(195)	185	74.37	37.87	13.77	(21.16)
ROCE (after tax)	NM	NM	NM	NM	NM	NM	NM
Gearing	NM	NM	NM	NM	NM	NM	NM
Payout ratio	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of shares, diluted	54.13	54.13	54.13	54.13	54.13	54.13	54.13
Data per Share (EUR)							
EPS	(0.24)	(1.01)	(1.13)	(1.77)	(1.45)	(0.61)	0.78
Restated EPS	(0.24)	(1.01)	(1.13)	(1.77)	(1.45)	(0.61)	0.78
% change	*-42.2%*	*-328%*	*-11.7%*	*-57.2%*	*-18.0%*	*-57.8%*	*-%*
BVPS	1.39	0.52	(0.61)	(2.38)	(3.83)	(4.44)	(3.67)
Operating cash flows	(0.60)	(1.27)	(1.99)	(2.20)	(1.58)	(0.41)	1.22
FCF	0.02	(0.15)	(2.03)	(2.22)	(1.59)	(0.45)	1.13
Net dividend	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Source: Company Data; Bryan, Garnier & Co ests.

Please see the section headed "Important information" on the back page of this report.

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1. Short-term re-rating from capla

Ablynx is currently running the HERCULES Phase III trial for caplacizumab in acquired Thrombotic Thrombocytopenic Purpura (aTTP), a rare blood clotting disorder, with a readout expected in H2 2017. We expect the results from this trial to be a major catalyst for the company, definitively shifting investor focus from last year's setback with AbbVie not opting-in for vobarilizumab in RA, to the commercial opportunity caplacizumab represents for the company, which is expected to go to market on a standalone basis.

1.1. Phase III results in H2 2017

Following positive Phase IIb results from the TITAN trial in June 2014, Ablynx filed for conditional approval in Europe in aTTP and initiated a Phase III trial, with the objective of 1/ gaining FDA approval and 2/ confirming European conditional approval expected towards mid-2018.

aTTP is linked to a high mortality rate of up to 30% in the first 30 days post-acute episode

aTTP is an auto-immune disorder, for which no specific therapeutic drug is currently approved. In patients with aTTP, the body makes antibodies (proteins) that block the activity of the ADAMTS13 enzyme, leading to an accumulation of ultra-large von Willebrand Factor (ULvWF) multimers, which bind to platelets and induce aggregation (thrombocytopenia). Episodes of TTP have been associated with a high mortality rate of up to 30%, most of them occurring within the first 30 days (*Benhamou Y et al. J Thromb Haemost 2015;13(2):293-302; Han B et al. Am J Hematol 2015;90(8):709-14; Benhamou Y et al. Haematologica 2012;97(8):1181-1186*). Current SoC following an aTTP event consists of daily plasma exchange (PEX) to remove ULvWF multimers and autoantibodies while replenishing ADAMTS-13 concomitant to the administration of immunosuppressants (e.g., corticosteroids, Rituximab) to inhibit auto-antibody formation. However, the SoC has a number of limitations, including:

Limitations of current SoC include:

- Risk of organ damage
- High relapse rate
- Refractoriness

- It takes 10 to 15 days on average before normalisation of the platelet count under the SoC and the longer it takes for platelet count to return to normal, the greater the risk of organ damage (especially the kidneys).
- The effect of the immunosuppressants generally kicks in around 30 days post-acute episode and initiation of SoC (PEX + immunosuppressants) is thought to have an impact on the relapse rate, with up to 30% of patients relapsing while on treatment.
- Refractoriness to SoC (i.e. lack of improvement of thrombocytopenia or failure to double platelet count within four days) is observed in approximately 17% of cases and is associated with poor prognosis of survival (*Chemnitz JM et al. Ann Hematol 2010;89(10):1029-33*).

Phase II demonstrated reduction in median time to platelet count normalisation

As mentioned, Ablynx reported positive Phase II results for caplacizumab in the treatment of aTTP, with caplacizumab on top of SoC successfully reducing the median time to platelet count normalisation (3.00 days, n=36) vs. SoC alone (4.92 days, n=39) with a p-value of 0.013. In the trial, caplacizumab was initially administered at the 10mg dose (IV bolus) followed by daily SC at the 10mg dose during PEX and 30 days after daily PEX had stopped with platelet count normalisation guiding the time to stop PEX. We also noted that 1/ exacerbations, which are the leading cause of morbidity and mortality in aTTP, occurred in 71% fewer patients in the active treatment group compared to sham-controlled group (3 vs. 11 pts) and 2/ complete remission up to 30 days after the end of the daily plasma exchange was 81% in the active group versus 46% for placebo.

Post-hoc analysis showed reduction in the frequency of major thromboembolic events and refractoriness to treatment

Lastly, post-hoc analysis of the Phase II trial showed that caplacizumab reduced the frequency of major thromboembolic events by 74% (11.4%, n=4 vs. 43.2%, n=16) and decreased refractoriness to treatment from 21.6% (n=8) in the placebo group to 5.7% (n=2) in the active treatment arm.

Fig. 1: Post-hoc analysis of TTP related to clinically relevant AEs

	Caplacizumab (N=35)		Placebo (N=37)	
	Events, n	Subjects, n (%)	Events, n	Subjects, n (%)
Embolic and thrombotic events (SMQ)				
Acute myocardial infarction	0	0	2	2 (5.4%)
Deep vein thrombosis	0	0	1	1 (2.7%)
Venous thrombosis	0	0	1	1 (2.7%)
Pulmonary embolism	1	1 (2.9%)	1	1 (2.7%)
Ischemic stroke	0	0	1	1 (2.7%)
Hemorrhagic stroke	0	0	1	1 (2.7%)
Thrombotic thrombocytopenic purpura[1]	3 [2]	3 (8.6%) [2]	13	11 (29.7%)
TTP-related mortality				
Deaths related to TTP	0	0	2	2 (5.4%)
TOTAL	**4**	**4 (11.4%) [3], #**	**22**	**16 (43.2%) [3], #**

[1] this preferred term consisted of recurrences of TTP during the treatment period, defined in the protocol as exacerbations of TTP; [2] one adverse event reported as 'Thrombocytopenia' was not considered in this analysis, as this event was reported as part of the presenting disease; [3] a subject may have experienced more than one event
Nominal p=0.006

Source: Journal of Haemostasis 26 April 2017.

Fig. 2: Post-hoc analysis of refractoriness to treatment (safety population of PhII)

Table 1. Post Hoc Analysis of Refractoriness to Treatment in the Safety Population of the TITAN Study.*

Definition of Refractoriness	Caplacizumab (N=35)	Placebo (N=37)
	number (percent)	
No platelet response after 7 days, despite daily plasma-exchange therapy†	2 (6)	8 (22)‡
Absence of platelet-count doubling after 4 days of standard treatment, with lactate dehydrogenase level >ULN§	0	4 (11)

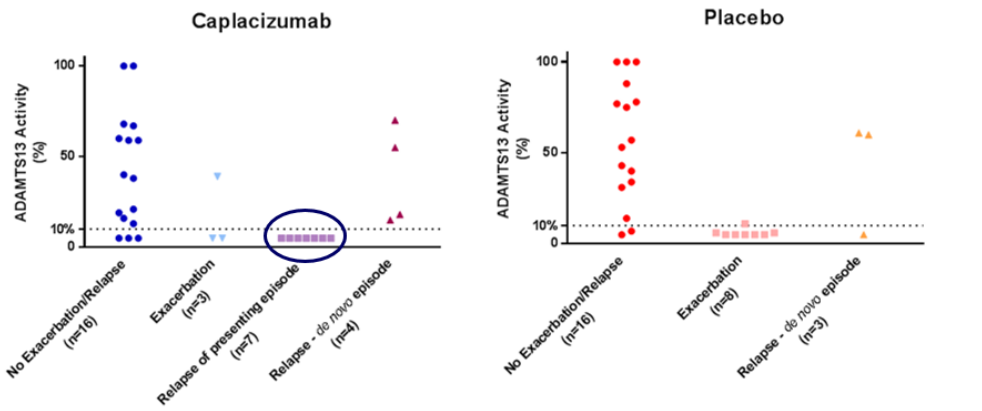
* ULN denotes upper limit of the normal range.
† Definition is from Sayani and Abrams.[2]
‡ Two patients in the placebo group who discontinued the study prematurely (<7 days) without reaching the platelet-count criterion (i.e., platelet count, $<150\times10^9$ per liter) were counted as having disease that was refractory to treatment.
§ Definition is from Soucemarianadin et al.[3]

Source: Company Data; NEJM letter to the editor (23rd June, 2016).

Filing for conditional approval in EU in February 2017

On the basis of these results, Ablynx filed for conditional approval in Europe in February 2017 as the EMA accepted the company's assumption that patients might need to spend more time on caplacizumab to avoid relapse (i.e. before the effect of immunosuppressants kicks in), until ADAMTS13 increases to above the 10% level, which is thought to be a reliable biomarker.

Fig. 3: Underlying activity based on ADAMTS13 activity (Phase II trial)



Source: Company Data.

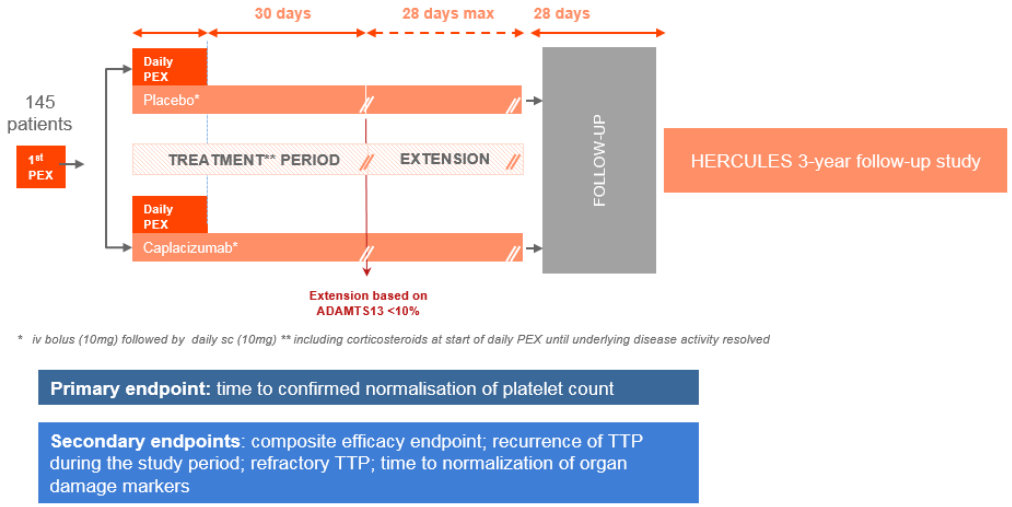
ADAMTS13 activity thought to be a reliable biomarker for monitoring relapse risk

While no conditional approval pathway exists in the US, Ablynx initiated the HERCULES Phase III trial. In contrast to the TITAN trial, the HERCULES trial includes the possibility for patients to prolong SC injection of caplacizumab or placebo beyond 30 days after discontinuation of PEX, if ADAMTS13 levels remain below the 10% threshold. We believe that including this option in the design of the Phase III trial should address potential FDA concerns as 15-20% of patients would need to be treated with caplacizumab for more than 30 days.

HERCULES Phase III trial to readout in Q3 2017

Note that the production of anti-drug antibodies in certain patients had no effect on pharmacokinetic and pharmacodynamics. Indeed, even if prolonged by 28 days (as depicted below), the window of treatment would be too short to observe an impact of anti-drug antibodies on the safety and efficacy of the drug in our view. Recruitment of the 145 patients in the HERCULES trial was completed at the end of April 2017 and we would expect top-line results in late H2 2017.

Fig. 4: Caplacizumab HERCULES Phase III trial design



Source: Company Data.

Fast recruitment made it possible to increase the enrolment target by 43%

Note that fast recruitment with the initial target of 92 patients reached in Q3 2016 enabled Ablynx to increase the enrolment target to 132 or more patients without delaying the readout of the HERCULES Phase III trial. This is in contrast to the delay in recruitment for the Phase II study as 20% of patients presenting at the hospital with an acute episode are in a coma and not all aTPP patients are referred to haematologists. Since TITAN phase II study, significant progress have been made: 1/ HERCULES study design allows patients in a coma to be enrolled (consent form through legal representative) 2/ the growing implications of centres participating in Ablynx trials, especially following the publication of results from the TITAN trial in the NEJM (February 2016) and 3/ the education that has already been done by the company although some still needs to be carried out in small to medium size hospitals.

Secondary endpoints more important than primary endpoint for regulators and payers

Increasing the enrolment target enabled the company to further increase the statistical power of the trial and especially of its key secondary endpoints. We believe that the secondary endpoints (cf chart above) will be of particular importance to regulatory agencies as they focus on the treatment's safety (thromboembolic events) and cost-effectiveness, which could be triggered only by reducing the number of exacerbations. Reducing the number of exacerbations would also be key for the company in justifying a value-based pricing.

1.2. Heading towards integrated biopharma status as soon as 2018

Ablynx should be able to include Phase III results from the HERCULES trial in its answers to the EMA's LoQ to secure conditional approval

While the EMA filing for approval based on Phase II results took place on 6th February 2017, we estimate that the list of questions (LoQ; 120 days) will be issued by the EMA in the second half of June 2017. Given that 1/ the results from the HERCULES Phase III trial are expected to be released in H2 2017e and 2/ the applicant, i.e. Ablynx, has from three months and up to six months to answer the EMA's LoQ, the company should be able to integrate findings from the HERCULES trial into its answers to secure approval in Europe. This approval could be either definitive or conditional.

EU approval in Q1 2018, US approval by 2018YE

In all, we would expect European approval for caplacizumab in aTTP by mid-2018 at the earliest. This takes into account the EMA's 277-day standard review process, to which two rounds of answers for Ablynx should be added of three to six months and three months, respectively. In the US, BLA submission should occur in H1 2018 and approval towards the end of 2018/early 2019.

~100 sales reps should provide access to 300 aTTP centers treating two-thirds of acute episodes

Ablynx has already recruited its Medical Science Liaisons since it is pursuing a standalone strategy for the marketing of caplacizumab in both the US and in Europe. We estimate that 100 sales representatives are to be hired either directly or via a contract sales organisation, and evenly split between the European and the US markets. These reps should provide the company with access to roughly 300 key reference centres that treat two-thirds of aTTP acute episodes. The latter number should be seen in the context of aTTP patients being frequently underdiagnosed (e.g. patients presenting in a coma, not all being referred to haematologists, etc.).

EU peak sales EUR170m, US peak sales EUR225m, Partnership in Japan

In Europe, Ablynx will pursue a two-step commercial strategy by first penetrating large UK, French and German centres (often involved in the global Phase III trial) before capitalising on its KOL network to address smaller centres. Caplacizumab benefits from Orphan Drug status both in the US and Europe, which should give the company pricing leverage to pursue value-based pricing and justify a price of EUR80,000 and USD180,000 in Europe and the US, respectively. In Japan, Ablynx is to initiate a PK study by the end of the year and following its completion, we do not rule out an out-licensing deal considering the different market access strategies. We estimate that such a deal could fetch up to EUR35m (of which a EUR15m upfront payment in 2018) alongside royalties in the 20-25% range.

We have retained the following prices assumptions in our model:

- In the US: list price of USD180,000 or USD144,000 after a 20% discount (i.e. EUR131,000)
- Europe and Japan: list price of EUR80,000 or EUR68,000 after a 15% discount

We estimate total peak sales for the product at EUR423m (see table below), 53% of which in the US. Note that patent protection lasts until 2035 and the company guides on estimated peak sales in excess of EUR400m.

Fig. 5: Caplacizumab sales estimates (in EURm)

Caplacizumab		**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Total Sales EU+US+JPN		**4**	**37**	**96**	**159**	**227**	**297**	**370**	**381**	**392**	**403**	**410**	**416**	**423**
			762%	162%	66%	43%	31%	24%	3%	3%	3%	2%	2%	2%
EU														
Population		563	572	580	589	598	607	616	625	634	644	654	663	673
Acute Events	0,001%													
Acquired TTP	90%													
Covered events	67%													
Total Addressable		4152	4214	4277	4341	4406	4473	4540	4608	4677	4747	4818	4890	4964
% Penetration		2%	10%	18%	26%	34%	42%	50%	50%	50%	50%	50%	50%	50%
Price EURk	68													
Sales EURm		**4**	**27**	**51**	**76**	**101**	**127**	**154**	**157**	**159**	**161**	**164**	**166**	**169**
North America														
Population		368	375	383	390	398	406	414	423	431	440	448	457	467
Acute Events	0,001%													
Acquired TTP	90%													
Covered events	67%													
Total Addressable		2712	2766	2821	2878	2935	2994	3054	3115	3177	3241	3306	3372	3439
% Penetration			3%	12%	22%	31%	41%	50%	50%	50%	50%	50%	50%	50%
Price USDk	144													
Price EURk	131													
Sales EURm		**0**	**9**	**44**	**81**	**119**	**159**	**200**	**204**	**208**	**212**	**216**	**221**	**225**
Japan														
Population		123	122	122	121	121	120	119	119	118	118	117	116	116
Acute Events	0,001%													
Acquired TTP	90%													
Covered events	67%													
Total Addressable		907	902	898	893	889	884	880	876	871	867	862	858	854
% Penetration					3%	10%	18%	26%	34%	42%	50%	50%	50%	50%
Price EURk	68													
Sales EURm		**0**	**0**	**0**	**2**	**6**	**11**	**16**	**20**	**25**	**29**	**29**	**29**	**29**

Source: Bryan, Garnier & Co ests.

2. ALX-0171 in RSV: an opportunity and important platform validation

2.1. The high unmet Medical Need

RSV infection is associated with high morbidity and mortality rates in those with underdeveloped or compromised immune systems

Respiratory syncytial virus (RSV) is a common and highly contagious virus that infects the respiratory tract of most children by age two. RSV can also infect adults. In most cases, the virus causes mild, cold-like symptoms that appear four to six days after infection and are resolved within one to two weeks with self-care.

However, RSV infection is associated with significant morbidity and mortality in those with underdeveloped or compromised immune systems. High-risk populations include premature babies, infants and adults with heart and lung disease, the elderly or anyone with a weakened immune system, including hematopoietic stem cell transplant (HSCT) patients as well as cancer patients receiving chemotherapy. There are currently no effective evidence-based therapeutic or preventive interventions and supportive care remains the cornerstone of clinical management (*Lower respiratory tract infection caused by RSV: current management and new therapeutics; Mazur et al. 2015*). As a result, repeat infections, lifelong susceptibility to RSV and poor outcomes remain common. Based on available epidemiology and health outcomes data, the global cost burden of RSV on an annual basis has been estimated at over USD80bn.

The global cost burden of RSV is >USD80bn

■ Infants & Children

RSV is the leading cause of hospitalisation in children under the age of one

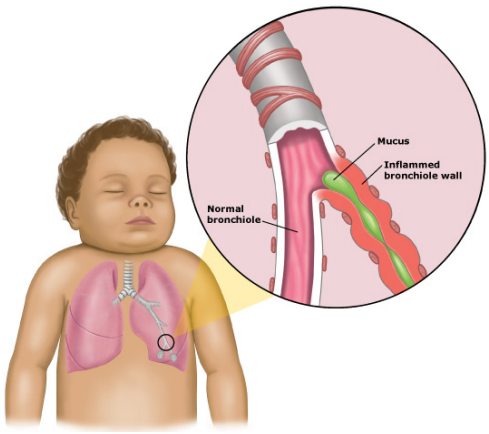
3,000 to 8,500 deaths per year in infants under two years of age

In the US, RSV is the leading cause of hospitalisation in children under the age of one. It causes 150,000 hospital admissions annually in children under two years of age and accounts for 18% of all emergency department visits in children under the age of five (*Lower respiratory tract infection caused by RSV: current management and new therapeutics; Mazur et al. 2015*). Globally, the annual burden of RSV infection is 34 million cases, resulting in 3-4 million hospitalisations and an estimated 3,000-8,500 deaths in infants under two years of age. RSV infection is the most common cause of lower respiratory tract infections (LRTIs), including bronchiolitis (inflammation of the small airways in the lung) and pneumonia (infection of the lungs), and is associated with nine times more deaths in infants than influenza on an annual basis. RSV infection accounts for more than half of all cases of bronchiolitis in children, with an estimated 50-80% of bronchiolitis hospitalisations during the winter and a similarly high percentage of bronchiolitis infant deaths associated with the virus. RSV bronchiolitis has been shown to play a causal part in the development of recurrent wheeze in children and is associated with the development of asthma and subsequent respiratory morbidity (*Lower respiratory tract infection caused by RSV: current management and new therapeutics; Mazur et al. 2015*).

Pneumonia, which can develop as a complication of RSV bronchiolitis, is the most common cause of mortality in children under five years of age, with an estimated 10% of episodes severe enough to be life-threatening and require hospital admission. The annual incidence of pneumonia in the US is estimated at 15.7/10,000 children, with RSV being the most common pathogen detected (28% of cases) and associated with the highest incidence among children under the age of two with pneumonia, the patient group most frequently affected by the disease (62.2/10,000; CDC). Since the consequences of RSV LRTI can extend into adulthood, the importance of developing effective preventive and therapeutic strategies for this vulnerable population cannot be understated.

Please see the section headed "Important information" on the back page of this report.

Fig. 6: RSV-induced bronchiolitis in infants



Source: https://www.chrisjohnsonmd.com/2011/11/08/its-time-once-again-for-bronchiolitis-and-respiratory-syncytial-virus-rsv/

Immunocompromised

RSV is the leading cause of severe infections in immunocompromised patients, with mortality rates as high as 80%

RSV is the leading cause of severe infections in immunocompromised patients, with mortality rates as high as 80%. Within this population, HSCT patients, solid organ transplant (SOT) patients and cancer patients receiving chemotherapy are at the highest risk for mortality from RSV infection. Additional risk factors vary depending on the cause of immunosuppression, lymphopenia, time to RSV diagnosis, history of lung disease, age (with younger patients at higher risk), and use of IV immune globulin (IVIG) for viral prophylaxis (*RSV infection in the immunocompromised host; Stewart et al, 2013*).

In immunosuppressed patients, RSV infection can rapidly progress from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI), and subsequently to RSV pneumonia. Progression to LRTI occurs in 50% of patients undergoing HSCT or receiving chemotherapy. The prolonged hospitalisation and increase in transfers to intensive care, along with the deterioration in overall outcomes, underscore the need for effective preventive and therapeutic options for this highly susceptible patient population as well.

Elderly

RSV responsible for 10,000 all-cause deaths per year in the over-64 age group

RSV infection has also been established as a significant cause of morbidity and mortality in elderly adults, with epidemiological evidence pointing to an impact similar to that of non-pandemic influenza, both in the community and long-term care settings. Attack rates in nursing homes range from 5-10% per year, with a high incidence of pneumonia (10-20%) and death (2-5%). RSV infection is estimated to cause some 10,000 all-cause deaths per year in the over-64 age group, which represents c.25% of deaths associated with Influenza A in the same age group (*RSV infection in elderly adults; Falsey et al., 2005*). While the complex comorbidities of this population create challenges in demonstrating the efficacy of experimental interventions in the clinic, the need for therapeutic options in particular is acute given general demographic trends and the growing utilisation of long-term care facilities.

2.2. Current preventive & therapeutic landscape

Lack of clinical evidence to support currently recommended interventions

Despite decades of R&D, the preventive and therapeutic options for RSV infection remain extremely limited. The lack of clinical evidence to support currently recommended interventions further underscores the high unmet medical need and the urgency to deliver new approaches that are safe and efficacious, particularly in highly vulnerable and medically complex patients.

Fig. 7: RSV: level of evidence per recommended intervention

	2014 American Academy of Pediatrics[4]	2008 Royal Australian College of General Practitioners[28]	2006 Scottish Intercollegiate Guidelines Network[29]	NICE Guideline 2015[30]
Inhaled bronchodilators	Level B: albuterol (salbutamol) should not be given	Level A: β, agonists not recommended Level D: trial β, agonists if older than 9 months, discontinue if no response Level A: ipratropium bromide not recommended	Level B: β, agonists not recommended Level X: nebulised ipratropium not recommended	Not recommended
Systemic corticosteroids	Level A: not recommended	Level A: not recommended	Level A: not recommended	Not recommended
Ribavarin	No recommendation	Level A: not recommended	Level B: not recommended	No recommendation
Antibiotics (only if indications for bacterial co-infection present)	Level B: recommended	Level A: not recommended Level D: consider for secondary bacterial infection	Level X: not recommended	Not recommended
Chest physiotherapy	Level B: should not be used	Level A: not recommended	Level A: not recommended	Not recommended if children do not have relevant comorbities
Maintaining hydration and fluid balance	Level X: nasogastric or intravenous fluids if unable to maintain oral hydration	Level D: maintain oral feeding unless feeding increases respiratory distress	Level D: nasogastric feeding if child cannot maintain oral intake	Nasogastric or orogastric tube recommended when children cannot take enough fluid orally Intravenous isotonic fluids recommended for children who do not tolerate nasogastric or orogastric fluids, or have impending respiratory failure
Supplemental oxygen	Level D: choice not to administer if SpO_2 >90%	No recommendation	Level D: should be given for SpO_2 ≤92% or severe respiratory distress or cyanosis Level X: CPAP should be considered for severe respiratory distress or apnoea	Recommended for SpO_2 <92%
Pulse oximetry	Level C: continuous pulse oximetry not recommended	Level D: continuous pulse oximetry if in prone position	Level C: should be performed for every child attending hospital with acute bronchiolitis Level X: monitor 8-12 h after discontinuation of supplemental oxygen therapy	No recommendation
Epinephrine	Level B: should not be given	Level A: nebulised adrenaline not recommended	Level A: not recommended	Not recommended
Nebulised hypotonic saline, Normal Saline	Level B: can be given during hospitalisation*	Level D: mist, steam, nebulised saline not recommended	No recommendation	Not recommended
Paracetamol or ibuprofen	No recommendation	Level D: may be given	No recommendation	No recommendation
Antitussives, expectorants, decongestants	No recommendation	Not recommended	No recommendation	No recommendation
Capillary blood gas	No recommendation	No recommendation	No recommendation	Consider in children with severe worsening respiratory distress or impending respiratory failure Not recommended as routine
Nasal suctioning	No recommendation	Level D: may be trialled	Level D: should be used for children who exhibit respiratory distress due to nasal blockage	Recommended if respiratory distress or feeding difficulties or apnoea

Guidelines compared from table 1 based on level of evidence for each intervention. Level A: well designed randomised controlled trials; Level B: randomised controlled trials with minor limitations or overwhelming evidence from observational studies; Level C: observational studies (case-control and cohort); Level D: expert opinion, case reports; Level X: validating study not possible but clear benefit or harm or recommended practice by development group. CPAP=continuous positive airway pressure. *4 trials published after the publication of the 2014 American Academy of Pediatrics guidelines found no benefit of hypertonic saline therapy.[31-34]

Table 2: **Level of evidence per recommended intervention**

Source: LRTI caused by RSV: current management and new therapeutics; Mazur et al. 2015.

No vaccine commercially available

No vaccine is commercially available, including for high-risk groups for whom an RSV infection can have dire health consequences beyond the short term. Within the medical community, there is general consensus that RSV is the most important missing indication in the vaccination schedule of newborns.

Only product approved has limited efficacy and its label has been narrowed significantly

A single product is commercially available for the prevention of RSV infection, which relies on passive immunisation and is restricted to a narrow segment of the infant population. Synagis (pavilizumab), an antibody-based immunoprophylaxis marketed by AstraZeneca and AbbVie, has shown limited efficacy in clinical practice, and less than 20% of infants are eligible based on very low birthweight and/or congenital conditions (see section 2.4.1.).

Ribavirin, an anti-viral agent with a controversial efficacy and safety profile, is the only option available for post-infection treatment. However, it has been shown to have teratogenic effects and as a result, its use has been restricted to severe high-risk cases in a similarly narrow patient population.

Please see the section headed "Important information" on the back page of this report.

2.3. ALX-0171: a novel anti-RSV Nanobody for post-infection treatment

ALX-0171 uniquely positioned in post-infection segment

We believe Ablynx has a unique positioning in the RSV landscape with ALX-0171 as the most therapeutic candidate currently in clinical development for post-infection treatment in high-risk populations. In our view, this is a potential commercial opportunity that has been largely overlooked by investors.

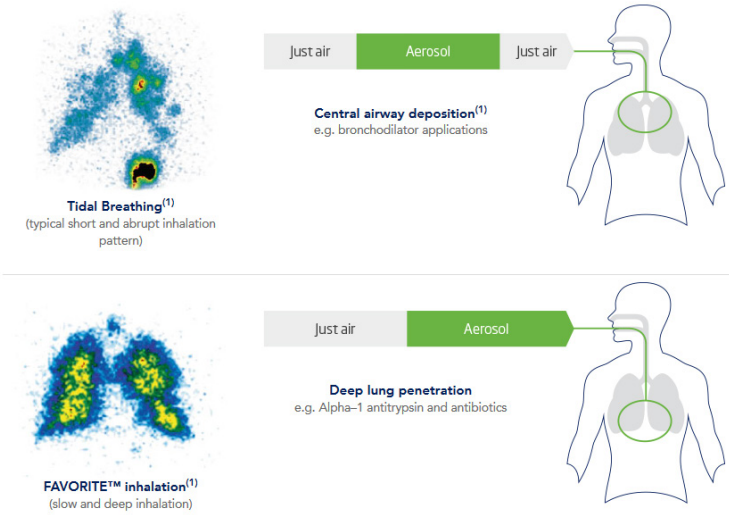
RSV is an enveloped, negative-sense RNA virus. The envelope, which is a host cell-derived lipid bilayer assembled during budding of the virus, contains three transmembrane viral proteins: F (fusion), G (attachment) and the small hydrophobic (SH) protein. The F and G proteins mediate host cell attachment, fusion and entry, elicit virus-neutralising antibodies and are the main targets for investigational preventive and therapeutic agents.

ALX-0171 is a trivalent Nanobody allowing the host's immune system to clear the virus faster

Leveraging Ablynx's powerful Nanobody technology, ALX-0171 is a first-in-class trivalent Nanobody i.e. three Nanobodies binding to the F-protein to increase both potency and stability. ALX-0171 thus neutralises RSV by blocking virus uptake into cells, thereby allowing the host's immune system to clear the virus faster. This has the potential to reduce the length of hospitalisation and the costs to payers.

Designed to meet the needs of even the most fragile patients, ALX-0171 is being developed in an inhaled formulation. Ablynx is the only company to have safely and successfully introduced a biologic into the lungs of infants, an important advantage in paediatric drug development. This novel, differentiated route of administration directly addresses the shortcomings of intramuscular injections and oral delivery, removing a key hindrance to broad use in some of the neediest patients. Ablynx has partnered with Vectura to gain access to its hand-held, self-contained and battery-powered FOX inhalation system (adapted for use in neonates and infants), which features the FAVORITE technology platform for nebulisation of ALX-0171, enabling deep lung penetration. Note that the product is CE marked and has 510(k) clearance.

Fig. 8: Vectura's FAVORITE inhalation technology



Source: Vectura Group Plc.; Mayer et al. 2001: Deposition von therapeutischen Aerosolen in der Lungenperipherie. Aerosole in der inhalationstherapie, ed. G. Scheuch. Vol. 5. 2001, Dustri-Verlag Dr Karl Feistle: München. 93–100.

2.4. Other approaches not convincing yet

Other approaches have yet to yield positive late-stage results

Growing understanding of the immunology and pathogenesis of RSV infection are driving continued R&D. Concerted efforts have also been made to establish suitable animal models. Replicating the results from animal models into the clinic is particularly challenging, however, and Ablynx has strongly benefitted from the robustness of its Nanobodies, enabling nebulisation and administration in lamb models that have a respiratory system close to that of infants.

The other main approaches being pursued include:

- Anti-RSV antibodies (passive immunisation)
- Anti-virals (post-infection treatment)
- Vaccines (active immunisation)

2.4.1. Anti-RSV antibodies for passive immunisation

The lack of a vaccine for active immunisation has made passive immunisation the only option for preventing and modifying RSV infection.

Synagis is the only available option…

Synagis (palivizumab), marketed by AstraZeneca and AbbVie, was launched in 1998 and is the only commercially available product in this category. Its narrow label, however, limits use only to children with very low birthweight and/or serious congenital diseases. It is not indicated for use in any other high-risk populations, leaving the medical need for RSV prevention and protection largely unmet.

Synagis is an immunoglobulin (IgG) directed against an epitope in the A antigenic site of RSV-F that gives patients "passive immunity" effectively mimicking the type of immunity a mother naturally passes to her baby during the last three months of pregnancy. Since many premature infants are born before the mother's antibodies can be passed along, however, and their lungs and immune systems are too immature, an RSV infection can prove deadly as the thick secretions can cut off a baby's air supply.

…yet its label has been significantly narrowed because of a lack of efficacy

AstraZeneca and AbbVie's failure to boost sales before patent expiry in 2015 is rooted in the cumulative revisions (we count five) of treatment guidelines from the American Academy of Paediatrics (AAP), which have been recommending less usage of the drug due to its limited demonstrated effect on reducing RSV hospitalisations and no effect on mortality rates from RSV or rates of subsequent wheezing or asthma. The AAP now recommends that prophylaxis be limited to infants born before 29 weeks of gestation, and to those with certain chronic conditions such as congenital heart disease or chronic lung disease. This downward revision from 35 weeks to 29 weeks or earlier reflects the falling rates of RSV hospitalisations due to advances in neonatal care since Synagis was launched in 1998, in addition to new data on the children at the highest risk of RSV hospitalisation who are most likely to benefit. Fewer than 20% of infants are now eligible for treatment with palivizumab, representing a shrinking commercial opportunity.

Sales dropped from USD1.9bn in 2013 to USD1.3bn in 2015

As a result, worldwide sales of Synagis, which is marketed by AstraZeneca in the US and AbbVie ex-US, dropped from USD1.9bn in 2013 to USD1.3bn in 2015 despite patent protection. The biggest impact was shouldered by AstraZeneca, which saw its sales plummet from over USD1bn to USD600 over the same period. Cost and method of administration have been further limiting factors. The course of treatment consists of a series of intramuscular injections once a month for five months with the first injection carried out before the outbreak of the RSV season, which varies every year and limits the

product's use in a real-life setting as repeated intramuscular injections are especially challenging in fragile infants. At the recommended dose of 15 mg/kg of body weight, the monthly cost is USD1,500-2,000 for an annual cost of up to USD10,000 (5 doses maximum).

Fig. 9: Synagis sales (USDm)

Synagis sales (USDm)	2011	2012	2013	2014	2015	2016	2017e	2018e	2019e	2020e
AstraZeneca	975	1038	1060	900	662	677	664	608	549	510
% change		6%	2%	-15%	-26%	2%	-2%	-8%	-10%	-7%
AbbVie	775	825	827	835	740	730	713	709	698	693
% change		6%	0%	1%	-11%	-1%	-2%	-1%	-2%	-1%
Total Sales	**1750**	**1863**	**1887**	**1735**	**1402**	**1407**	**1377**	**1317**	**1247**	**1203**
% change		**6%**	**1%**	**-8%**	**-19%**	**0%**	**-2%**	**-4%**	**-5%**	**-4%**

Source: Bloomberg (AbbVie); Bryan, Garnier & Co ests (AZN).

Motavizumab (MEDI524), a second-generation monoclonal antibody derived from palivizumab using affinity maturation techniques, was being developed by AstraZeneca/MedImmune. However, after failing to demonstrate superiority in Phase II trials and given evidence of side effects, the programme was discontinued in 2010.

To address the monthly dosage requirement that has hindered Synagis use, MedImmune has recently been developing a third-generation RSV-specific YTE mutant (amino acid substitutions M252Y/S254T/T256E) monoclonal antibodies. These include MEDI557 and MEDI8897 derived from motavizumab and D25, respectively.

MEDI8897 Phase III trial to be initiated in shortly

In March 2017, Sanofi entered an alliance with MedImmune to co-develop MEDI8897, paying EUR120m upfront and committing up to EUR495m in milestones. MEDI8897 has received FDA Fast Track designation and neutralises RSV by binding the RSV-F protein expressed on virions and infected cells. It has been engineered to have a long half-life, addressing a key shortcoming of Synagis, and requires only a single dose to provide protection for the entire RSV season. MEDI8897 is currently in a Phase IIb trial in preterm infants ineligible for Synagis. The development plan includes a Phase III trial in healthy full-term and late pre-term infants.

Regeneron's suptavumab Phase III to readout by 2017YE

The other clinical stage programme is Regeneron's suptavumab (REGN2222), a fully human monoclonal antibody directed against RSV-F, which is derived from RSV-F-immunised transgenic mice expressing human immunoglobulin germ line sequences. This is the only RSV-specific antibody to reach Phase III since motavizumab, with the ongoing clinical trials in premature infants expected to be completed by the end of 2017e.

An alternative approach being pursued is maternal immunisation with an RSV vaccine during pregnancy to boost pre-existing immunity and increase transplacental transfer of RSV-specific antibodies. This may be less effective for very premature infants, however, due to the limited RSV antibody transfer.

Novavax had the most advanced maternal immunisation candidate in the pipeline until a significant clinical setback was announced in September 2016. The RSV F-protein recombinant nanoparticle vaccine had failed to achieve both its primary and secondary objectives, and did not demonstrate vaccine efficacy in the Phase III RESOLVE trial.

GlaxoSmithKline has the other two maternal vaccines in clinical development, both based on the RSV-F protein subunit approach. GSK3003891A is currently in Phase II trials while a legacy Novartis programme is completing Phase I studies.

2.4.2. Anti-virals

The safety of the only anti-viral approved, Virazole, is of particular concern

A single agent, Virazole (ribavirin for inhalation solution), is currently indicated for the treatment of hospitalised infants and young children with severe RSV-LRTI. Ribavirin is a nucleoside analogue inhibitor of viral RNA synthesis and is also licensed for use in HSCT patients with RSV-LRTI. While recent data suggest it may play a role in reducing mortality in this cohort, the efficacy of ribavirin is still only supported by inconclusive evidence from small, under-powered studies. Its safety is of particular concern as significant teratogenic and/or embryocidal effects have been observed in all animal species exposed to ribavirin.

Recent efforts to develop RSV anti-viral drugs have primarily focused on fusion inhibitors:

- Presatovir (GS-5806; Gilead Sciences), currently in four Phase II clinical studies in HSCT patients with URTI, HSCT patients with LRTI, lung transplant patients (LT) with RSV infection and adults hospitalised with RSV infection

- AK0529 (Ark Biosciences; licensed from Roche), currently in Phase II studies in infants hospitalised with RSV infection

In February 2017, Aviragen's BTA585 failed to demonstrate an effect on viral load in a Phase IIa study in adults given an intranasal inoculation with RSV. The company has not yet announced whether it will pursue the development BTA585, pending data analysis. Using a different mechanism of action was Alnylam Pharmaceuticals' asvasiran (ALN-RSV01), a siRNA targeting the RSV nucleocapsid messenger RNA to be delivered via inhalation. The program was discontinued a few years ago, however, after missing the primary endpoint in a Phase IIb study in LT patients.

2.4.3. Vaccines… a graveyard

Although there has been significant new activity in vaccine development, very few programmes are currently in the clinic and lack of efficacy in later-stage clinical trials remains common.

The major stumbling block in developing an effective vaccine has proven to be the nature of the RSV virus itself, which in a weakened state does not stimulate an immune system response like other vaccines. Chemical inactivation, which is used in flu shots, has produced devastating results. One of the first candidate vaccines, formalin-inactivated RSV (FI-RSV), not only failed to protect children in early trials but enhanced virus-induced respiratory disease, leading to two deaths and a high hospitalisation rate. The vaccine-enhanced disease is thought to be caused by the induction of high levels of non-neutralising antibodies. Ideally, an effective vaccine would induce high levels of neutralising antibodies instead.

The other common method for viral attenuation, by passage, has also failed to produce satisfactory results. This is because the natural RSV virus does not induce high levels of immunity itself in contrast to other viruses. Other barriers include the very young age of most patients, the lack of a good animal model that recapitulates human RSV infection, and the virus' ability to both evade innate and adaptive immunity and re-infect patients.

Broadly speaking, the vaccine candidates in development today are based on three main platforms. Protein-based vaccines include subunit antigens, e.g. pre- and post-fusion F and G proteins or peptides. Gene-based and vectored approaches include nucleic acid vaccines, e.g. naked DNA and RNA. Replication-deficient vectors such as human and chimpanzee adenovirus vectors or MVA-vectored vaccines containing one or more RSV antigen inserts also fall in this category. Finally, intranasal administration of live-attenuated viruses has yielded some encouraging proof-of-concept data, likely because live-attenuated RSV inoculation closely resembles natural infection.

An encouraging development came from researchers at Emory University in Atlanta who recently successfully engineered RSV to weaken without losing its immunogenicity in laboratory tests. This was achieved by enhancing the production of the RSV fusion protein (RSV-F), which allows RSV to enter cells and makes the virus more stable while also removing or weakening other viral genes that promote infection and suppress the immune system (*Christopher C. Stobart et al. A live RSV vaccine with engineered thermostability is immunogenic in cotton rats despite high attenuation, Nature Communications Dec. 21st, 2016*).

Despite such promising developments, however, an effective vaccine for RSV remains years away as the late-stage pipeline remains thin. Should a vaccine candidate prove to be successful in late stage clinical trials, we anticipate the following limitations will leave room for other approaches and, in particular, post-infection ones:

Perfect immunisation does not exist

- Perfect immunisation would not be possible even if an effective vaccine became available, hence the need for post-infection therapeutic options.

Time required to build immunity

- On-the-spot protection prior to hospitalisation is not possible via a vaccine as immunity requires time to develop, leaving a window during which a patient might still contract RSV.

Vaccines do not cover 100% of the population

- The preventive protection offered by vaccines, while effective, does not cover the entire population. While some populations would be unaware of or have no access to such protection as it takes time for a new vaccination scheme to be implemented countrywide, others could be reluctant to adopt it for a number of reasons, including safety concerns, religious beliefs, etc.

Need for a booster?

- The issue of the need for a booster to extend immunity remains open. Note that RSV infection is again becoming a significant health concern for elderly populations.

2.5. Breathe in, ALX-0171 is working

ALX-0171 is currently in a Phase IIb study in infants hospitalised for RSV-LRTI, with top-line data expected in H2 2018. A clinical trial in HSCT patients is on track to be initiated in year-end 2017e.

2.5.1. Encouraging Phase IIa results

Positive results from Phase IIa validates the platform

The completed Phase I/IIa study in 53 infants aged one to 24 months confirmed the safety profile of ALX-0171, in addition to generating promising early indications of efficacy. While the minimum age for participation was initially set at three months, a review by the data safety board enabled the lowering of the minimum age to one month, and the subsequent enrolment of 18 infants towards the lower end of the age range. No treatment-related serious adverse events were detected and viral load fell faster in the treatment arm than the placebo group although the measure was not powered for statistical significance. Similar trends were observed in the time to undetectable virus and performance on the Global Severity Score, a composite measure to assess respiratory difficulty, medical intervention and feeding. Given that as little as a one-log difference in virus titer can lead to a significant difference in

both disease severity and hospitalisation in infants, these findings represent encouraging indicators of drug activity.

Fig. 10: ALX-0171, Phase IIa results (safety)

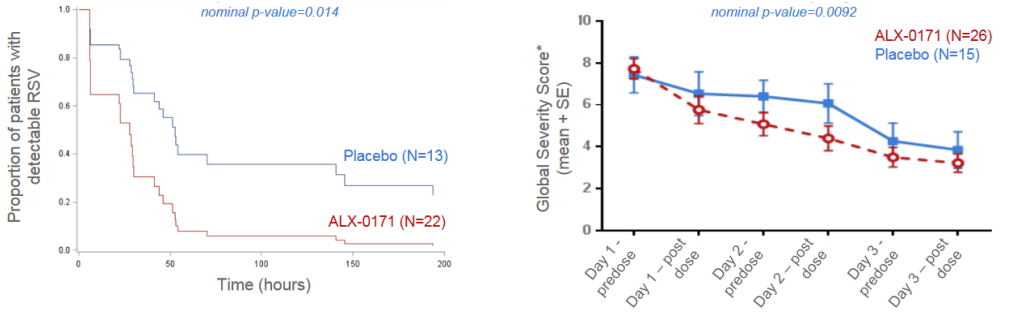
	Open-label group ALX-0171 (N=5)	Randomised group ALX-0171 (N=30)	Randomised group Placebo (N=16)
Adverse events (AEs)			
- number (%) of subjects with an AE	4 (80.0)	9 (30.0)	4 (25.0)
- number (%) of subjects with a treatment-related AE	1 (20.0)	2 (6.7)	0 (0.0)
Serious adverse events (SAEs)			
- number (%) of subjects with an SAE	3* (60.0)	1** (3.3)	0 (0.0)
- number (%) of subjects with treatment-related SAEs	0 (0.0)	0 (0.0)	0 (0.0)

* 1 of whom discontinued ** subject discontinued

- Most common AEs were infections and respiratory disorders
- 3 AEs related to ALX-0171: mild cough, mild rhinorrhoea, mild fever 11 days after last dose
- 5 SAEs reported: hypo-responsiveness, hypotonia, pneumonia (2) and atelectasis

Source: Company Data.

Fig. 11: ALX-0171, Phase IIa results (early efficacy signals)



Source: Company Data.

2.5.2. Phase IIb to readout in H2 2018

Nebulised Nanobodies to treat RSV validates the rationale behind the Nanobody platform

The promising Phase IIa results, beyond prompting the company to initiate a Phase IIb trial, are an important validation of the Nanobody platform's low immunogenic potential with no Fc region known to stimulate phagocytic or cytotoxic cells that could lead to cytokine release syndromes, as well as its robustness and stability, in our view. We are not ruling out the possibility that this could prompt Ablynx or one of its eight partners to explore other routes such as oral, topical or ocular.

1/ median time to undetectable virus >24 hours quicker with ALX-0171 and 2/ difference in effect on clinical score supportive for Phase IIb.

For its Phase IIb study, Ablynx set anti-viral effect at 14 days after the first dose as a primary endpoint i.e. viral drop below assay quantification limit determined by PCR. This reflects promising early findings from the Phase IIa study, which showed 1/ a median time to undetectable virus >24 hours quicker with ALX-0171 vs. placebo and 2/ a statistically significant difference in effect on clinical score (composite including feeding intolerance, medical intervention, respiratory difficulty/frequency, apnoea, general condition and fever – cf. table above).

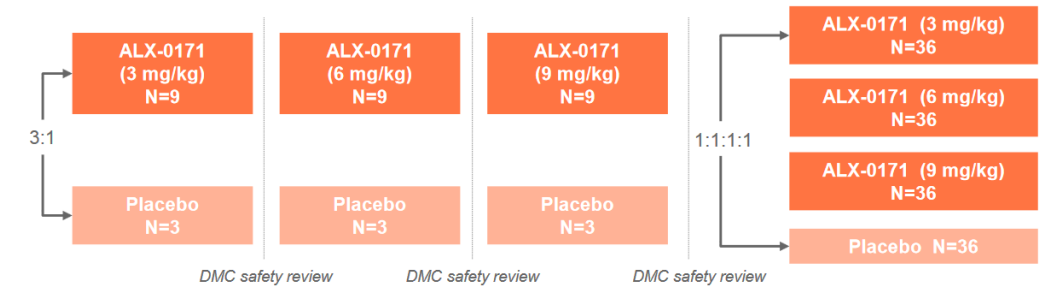
It is important to note that there is currently no consensus among experts on what the best endpoint for a post-infection treatment in RSV is. Following 1/ advisory boards with KOLs, 2/ discussions with regulatory authorities as well as interactions with market access experts to understand what would be most important for payers, anti-viral effect via nasal swabs has been chosen as the primary endpoint over the reduction in days of hospitalisation. Indeed, the latter would have given too much subjectivity to the trial and been limited by the different treatment approaches from one country to next.

Results from Phase IIb in H2 2018

Safety of ALX-0171 prompted Ablynx to use higher dose

180 infants aged 28 days to two years old are expected to be enrolled in the Phase IIb trial, initiated in January 2017 and being conducted in 36 centres mainly located in Europe and Latin America. The location of the centres enables Ablynx to follow the RSV season. In the first part of the trial also known as dose escalation, ALX-0171 is administrated at the 3mg/kg, 6mg/kg and 9mg/kg doses once a day for three consecutive days vs. placebo. Since the 1.5mg/kg dose tested in the Phase IIa trial did not show any safety concerns, Ablynx decided to have more room to potentially manoeuvre the efficacy side for the Phase IIb and increased the doses (3mg/kg, 6mg/kg and 9mg/kg). The second part of the trial will assess the efficacy of the product candidate on anti-viral effect at the three doses in larger population samples vs. placebo. We expect the RESPIRE trial to readout in H2 2018. Despite having no US sites participating in this trial, we believe that the way forward in the US could be fast for Ablynx should the Phase IIb trial be successful and in the light of all the safety data generated so far. A Phase II trial is expected to be initiated in Japan by the end of the year.

Fig. 12: Phase IIb RESPIRE study design



Source: Company Data.

2.5.3. Strong upside potential from HSCT patients and use in the prevention setting

Standalone market strategy in HSCT patients

BGe EUR450m peak sales

By the end of 2017e, Ablynx should initiate a Phase II trial in RSV-infected Haematopoietic stem cell transplant (HSCT) patients, a population with mortality rates as high as 30-40%. Market access is easier as these patients are more concentrated, which bodes well for a standalone marketing strategy for the company. We believe that if the results of the upcoming trial are positive (results in 2019 BGe), Ablynx would be able to file for approval in Europe. Moreover, commercialising the product candidate in this very specific patient population would help the company obtain a higher price (BGe ~USD80k).

Further upside potential in the prevention setting: a few "puffs" before hospitalisation

Interestingly, this would also enable Ablynx to trigger interest from physicians for the use of ALX-0171 earlier in the treatment paradigm, i.e. before hospitalisation in a preventive setting. Indeed, infants and the elderly can potentially be given a few "puffs" before hospitalisation given the high likelihood of RSV infection and/or the lack of vaccine protection. In the elderly population, however, we note that comorbidities can have confounding effects on the ability to demonstrate clinically meaningful efficacy.

Nevertheless, the trial in HSCT patients to be initiated in late 2017 has the potential to unequivocally demonstrate the efficacy of ALX-0171 in highly fragile populations.

2.5.4. ALX-0171… a multi-billion product

■ **ALX-0171 in RSV alone has a >EUR1bn sales potential**

Fig. 13: ALX-0171 sales model in RSV (BGe, EURm)

ALX-0171 in RSV		2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Total sales (EURm)		**36**	**271**	**502**	**729**	**954**	**1175**	**1167**	**1159**	**1151**	**1143**
			642%	**85%**	**45%**	**31%**	**23%**	**-1%**	**-1%**	**-1%**	**-1%**
EU											
Infant (in m)	-0,7%	15,6	15,5	15,4	15,3	15,2	15,1	15,0	14,9	14,8	14,7
% hospitalisation	0,52%										
price (EURm)	9000	9000	9000	9000	9000	9000	9000	9000	9000	9000	9000
% penetration		2%	11%	21%	31%	40%	50%	50%	50%	50%	50%
Sales (EURm)		**11**	**81**	**151**	**219**	**287**	**354**	**351**	**349**	**346**	**344**
North America											
Infant (in m)	-0,7%	18,7	18,6	18,5	18,4	18,2	18,1	18,0	17,8	17,7	17,6
% hospitalisation	0,52%										
price (EURm)	15000	15000	15000	15000	15000	15000	15000	15000	15000	15000	15000
% penetration		2%	11%	21%	31%	40%	50%	50%	50%	50%	50%
Sales (EURm)		**22**	**163**	**301**	**438**	**573**	**706**	**701**	**696**	**691**	**686**
Japan											
Infant (in m)	-0,6%	5,1	5,1	5,0	5,0	5,0	5,0	4,9	4,9	4,9	4,8
% hospitalisation	0,52%										
price (EURm)	9000	9000	9000	9000	9000	9000	9000	9000	9000	9000	9000
% penetration		2%	11%	21%	31%	40%	50%	50%	50%	50%	50%
Sales (EURm)		**4**	**27**	**49**	**72**	**94**	**116**	**115**	**115**	**114**	**113**

Source: Bryan, Garnier & Co ests.

■ **Use in HSCT patients pushing ALX-0171 to the next level**

Fig. 14: ALX-0171 sales model in HSCT patients (BGe, EURm)

ALX-0171 in HSCT		2022	2023	2024	2025	2026	2027	2028	2029	2030
HSCT/year		53864	54672	55492	56325	57169	58027	58897	59781	60678
infection rate %	35%									
penetration		2%	7%	13%	19%	24%	30%	30%	30%	30%
US price (EURk)	73									
EU & JPN price (EURk)	44									
WW sales ALX-0171		**21**	**100**	**182**	**267**	**354**	**443**	**450**	**457**	**463**
% growth			**387%**	**82%**	**46%**	**33%**	**25%**	**1%**	**1%**	**2%**

Source: Bryan, Garnier & Co ests.

3. Rest of the pipeline

3.1. Best-in-class IL-6R, vobarilizumab, has a card to play in SLE

AbbVie's opt-in in SLE would force it to take forward the development of vobarilizumab in RA

Following AbbVie's decision not to opt-in for the Rheumatoid Arthritis (RA) indication in Q4 2016, Ablynx initiated discussions with potential partners to take over the development of the product candidate in this indication. However, it is our understanding that a potential deal is not likely to happen before mid-2018. Indeed, AbbVie's potential opt-in for the systemic lupus erythematosus (SLE) indication based on Phase II results in H1 2018 would force it to take forward the development of the drug in RA. AbbVie sees SLE as a potential lever for vobarilizumab's inclusion in formularies as competition is too fierce in RA to have a product for this indication only. We believe that this view is shared by other potential partners.

We assign no value to the drug in SLE

Phase II results in Q1 2018

94% of patients in the trial have rolled over in the extension trial

At present, we assign no value to the Phase II trial of the product candidate in SLE. 312 patients have been recruited in the trial, which will evaluate the efficacy of vobarilizumab at 4 different doses over a 48-week treatment course. The primary endpoint of this trial, the BICLA (*BILAG*-Based Composite Lupus Assessment), is a broadly accepted, sensitive and clinically meaningful composite measure of SLE disease activity. It is based on an intention to treat or withdraw medicines as the fundamental basis and measures individual parameters based on nine scored organ domains (not present, improving, same, worse, or new) and compares the disease activity to the prior month. The BILAG is considered to be the most comprehensive of the SLE activity measures.

AbbVie might position voba as a last line treatment upon opt-in decision by mid-2018

In terms of positioning in the RA indication, it is likely that the product will be promoted as a last line therapeutic option as positioning it earlier in the treatment paradigm might cannibalise AbbVie's JAK inhibitor in our view. We see companies that have no JAK inhibitors as potential partners, should AbbVie decide not to opt-in for SLE by mid-2018.

3.2. IO deal with Merck & Co well on track

First PoC achieved in IO

The USD5.7bn immuno-oncology collaboration with Merck & Co is well on track. As a reminder, Ablynx achieved pre-clinical proof of concept in late 2015. Although the size of the milestones, at EUR3.5m, was not significant for Ablynx, it was a clear positive signal from Merck that Nanobodies are at least as good as a combination of antibodies in inhibiting tumour growth.

First Nanobody in IO to reach the clinic by end-2017e should put the platform in the spotlight

The first programme should reach the clinic by the end of the year. Upon positive results from the caplacizumab Phase III trial in Q3 2017, we would expect the first Nanobody from the Merck & Co agreement to reach the clinic by year-end and put a spotlight on Ablynx's platform. In IO, Nanobodies that can be easily linked to target different pathways have significant potential in our view. Indeed, the combination of different targets should not fully block the pathways and increase efficacy while enabling it to work at smaller doses to lower toxicity.

4. FV increased to EUR22/share

We have made the following adjustments to our valuation model. As a result, our Fair Value increases by EUR4 to EUR22 per share (vs. EUR18):

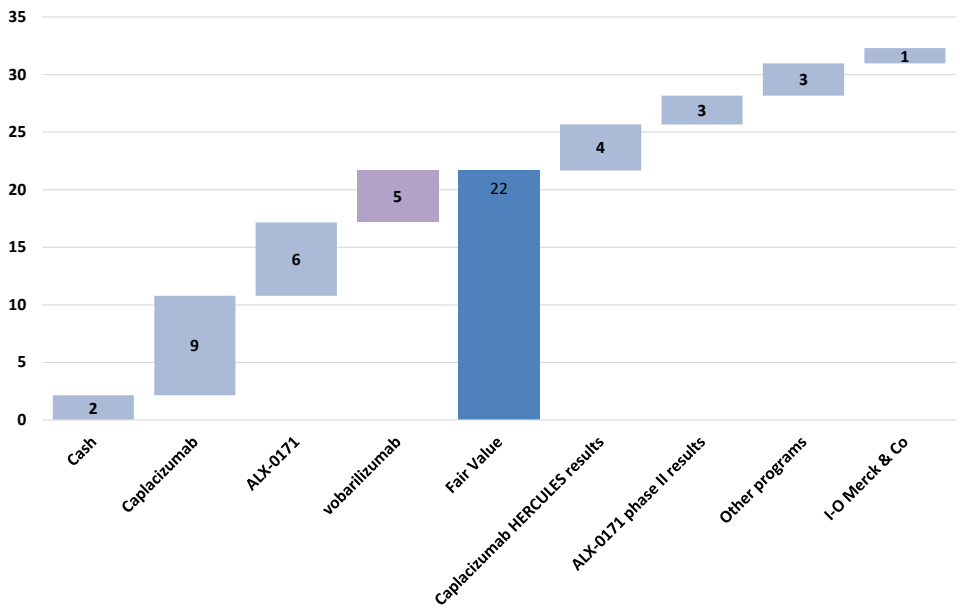
- **Caplacizumab in aTTP:** We have separated the US and Japanese market opportunities from the European one to reflect the more advanced development stage of the product in Europe following the recent filing to the EMA. We have subsequently increased our European PoS to 80% vs. 50% previously. This led to a EUR1 increase in our FV.

- **ALX-0171 in RSV:** We have included the HSCT patient population targeted by Ablynx on a standalone basis, which adds EUR3 to our FV.

Current share price supported by caplacizumab alone

Current share price of EUR11.8 per share is almost fully supported by caplacizumab alone. Once caplacizumab's HERCULES Phase III trial reads out in H2 2018, we anticipate significant re-rating as investor focus shifts to Ablynx's evolving business model and the potential its Nanobody platform has in overcoming conventional Mabs' limitations.

Fig. 15: BGe valuation (per share)



Source: Bryan, Garnier & Co ests.

Price Chart and Rating History

Ablynx

Ratings		
Date	**Ratings**	**Price**
27/10/15	BUY	EUR11.94

Target Price	
Date	**Target price**
05/01/17	EUR18
21/10/16	EUR16
03/05/16	EUR18
06/04/16	EUR17
05/01/16	EUR18
27/10/15	EUR17
21/07/15	EUR16
26/02/15	EUR14
18/06/14	EUR11.5

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Stock rating

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Distribution of stock ratings

BUY ratings 47.9% NEUTRAL ratings 36.2% SELL ratings 16%

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Please see the section headed "Important information" on the back page of this report.

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