THE RACE FOR THE SUPERIOR CORRECTOR – AN AGGRESSIVE TRIPLE COMBO STRATEGY

Vertex – TRAFFIC AND TRANSPORT studies leave room from improved outcomes in patients. Key gaps include:

- Modest clinical benefit – The difference between active treatment and placebo with respect to the mean absolute improvement in the percentage of predicted FEV1 ranged from 2.6 to 4.0% points (P<0.001), which corresponded to a mean relative treatment difference of 4.3 to 6.7% (P<0.001).
- Orkambi's limited clinical benefit is limited to homozygous patients – Implies at least 40% of the commercial opportunity is currently untapped
- Dropout rates (between 30% to 15%) and compliance (between 80% to 70%) on Orkambi suggests room for improved safety profile

The challenge here is all the drugs need to bind to the same target without interacting and increasing the possibility of adverse events. Logically, one can either fix each dose on its own, in a sequence. However, since triple combo is the play here, the Galapagos program is in trouble if the third component affects the binding of the first two.

Galapagos has two correctors in development, which include:

- C1- 2222, its and backup;
- And C2 – 2737

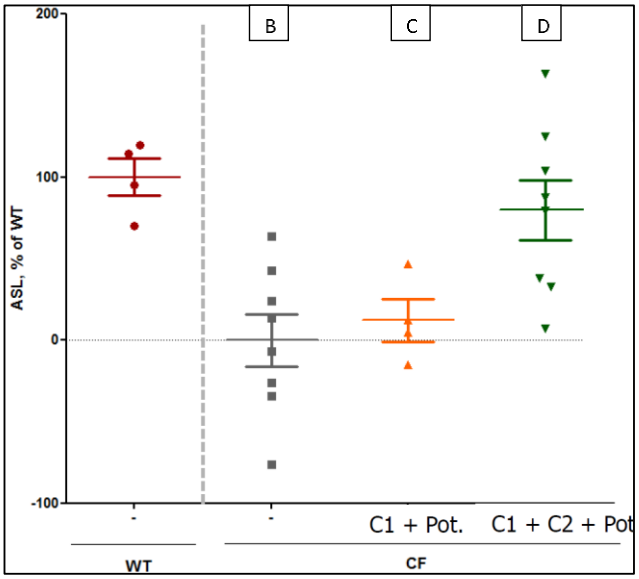
Note, C1- 2222 healthy volunteer study is complete and a PK study in CF patients will be initiated later this year.

Importantly, 2222 was well-tolerated in healthy volunteers. Key take-aways from the randomized, double blind, placebo-controlled healthy volunteer study:

- SAD doses ranged from 50 - 800 mg
- MAD doses ranged from 150 - 600 mg qd. for 14 days
- PK supports once daily dosing regimens for future development
- Favorable & rapid absorption in patients was noted
- Phase 1 in combination with potentiator to start after the SAPHIRA 1 and 2 read out

Also note, healthy volunteer phase 1 with C2 – 2737 is likely to commence during 4Q16. As a note of caution highlighting the risks (unfavorable drug-drug interactions) of aggressively developing multiple programs targeting the same target, a previous corrector 2665 has been discontinued in favor of 2737. C2 -2737 selection was likely based on lung penetration and 2665 had a negative impact on the competitive binding to the CFTR protein when combined with P+C1). -2737 is currently in preclinical toxicological studies, which is rate limiting in the race for a triple combo *vs.* VRTX.

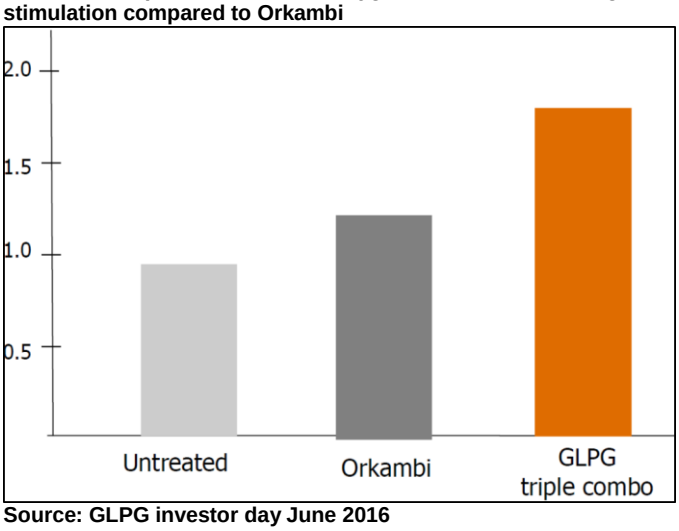
Exhibit 33: *In vitro* data: (A) Control cell line – healthy (100%); (B) Untreated delta F508 homozygous cell line; (C) Corrector + potentiator; and (D) Triple therapy, C1+C2+potentiator drives recovery close to normal cells.



Source: GLPG investor day June 2016

While Kalydeco provides significant clinical benefit for 10% of the CF patients, and Orkambi provides a modest clinical benefit for ~45% of the 508del homozygous patients, ~40% of the market (heterozygous patients) remains underserved. In vitro data suggests potential benefit for the heterozygous patients might be within the scope with the emerging focus on triple combo. As highlighted in the assay on organoids, the Galapagos triple combo appears to provide a benefit over Orkambi. However, these are in vitro assays, and will need to be translated into the clinic.

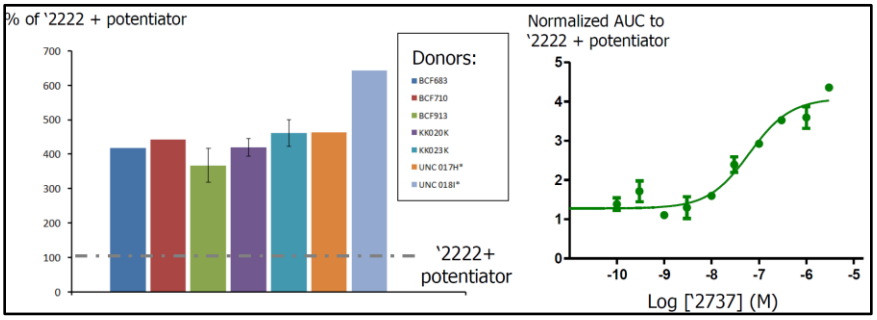
Exhibit 34: Triple combo in heterozygous G542X/F508del organoids - Lumen area after stimulation compared to Orkambi



Source: GLPG investor day June 2016

Note, Galapagos has had to make some changes to its original development strategy, dropping a previous corrector in favor of new and potentially better one, highlighting the risks of an aggressive development strategy. C2 – 2737 was selected because it has a higher lung penetration (compared to 2665), and it has the least impact on binding of potentiator and C1. C2 – 2737 delivers between 400% to 600% increase of ion currents over the membrane compared to dual therapy (left panel, exhibit 25). Additionally, C2 – 2737 has nanomolar EC50, implying less drug.

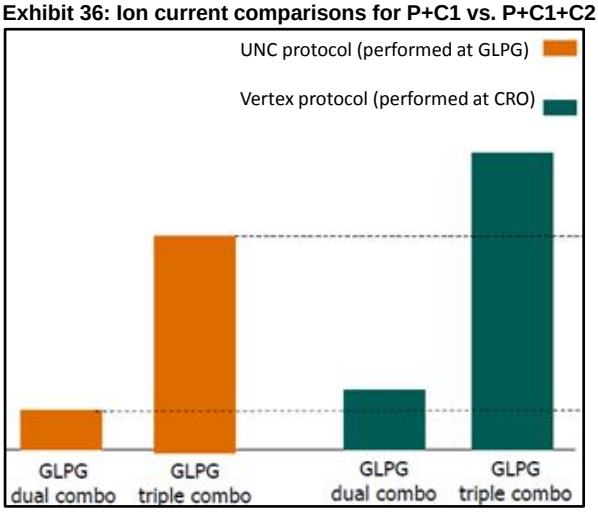
Exhibit 35: Triple combo delivers robust correction across multiple patient F508del/F508del donor cells: C2 – 2737, is the most advanced corrector



Source: GLPG investor day June 2016

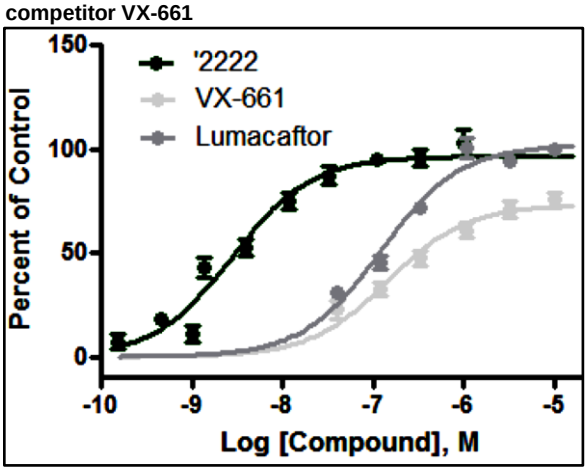
-2222, it's an early binder like Kalydeco and VX-661 and appears to be more potent and hence, dosing and potentially lower SAE 's could be an advantage. Also, the maximal efficacy (Emax) with -2222 appears to be similar to that of Kalydeco (both of which are consistently higher than -661) and if this holds up in the clinic then -2222 could well be a superior corrector than VX-661.

Exhibit 36: Ion current comparisons for P+C1 vs. P+C1+C2 based on assay



Source: GLPG investor day June 2016

Exhibit 37: Corrector -2222 appears to be an early binder and might be an advantage over competitor VX-661



Source: GLPG investor day June 2016

P+C1 combination studies in healthy volunteers will be initiated only after SAPHIRA and phase 1 data from 2451 becomes available. Current timelines imply a 1H17 P+C1 combo study initiation in healthy volunteers.

Exhibit 38: CF U.S revenue build and rNPV

			2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Mutation	Age														
F508del Homozygous	12+		8,500	8,602	8,705	8,810	8,915	9,022	9,131	9,240	9,351	9,463	9,577	9,692	9,808
Growth rate			1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
GLPG adoption							7.0%	9.8%	12.7%	14.7%	16.1%	17.2%	18.1%	18.6%	18.8%
Growth rate GLPG								40.0%	30.0%	15.0%	10.0%	7.0%	5.0%	3.0%	1.0%
Compliance			80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
Drop out			15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%
GLPG patients							624	884	1163	1354	1507	1632	1734	1807	1847
GLPG Price per patient							375,000.00	393,750.00	413,437.50	434,109.38	455,814.84	478,605.59	502,535.87	527,662.66	554,045.79
Price increase				5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
GLPG revenue							187,223,461	278,521,110	384,743,491	470,152,699	549,542,684	624,820,140	697,130,574	762,994,077	818,865,081
Mutation	Age	Population													
F508del Homozygous	6 to 11		2,460	2,490	2,519	2,550	2,580	2,611	2,643	2,674	2,706	2,739	2,772	2,805	2,839
Growth rate			1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
GLPG adoption							5.0%	6.5%	7.8%	8.6%	9.2%	9.6%	9.9%	10.2%	10.3%
Growth rate GLPG							60.0%	30.0%	20.0%	10.0%	7.0%	5.0%	3.0%	3.0%	1.0%
Compliance			80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
Drop out			15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%
GLPG patients							129	170	206	229	248	264	275	287	293
GLPG Price per patient							375,000.00	393,750.00	413,437.50	434,109.38	455,814.84	478,605.59	502,535.87	527,662.66	554,045.79
Price increase				5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
GLPG revenue							38,703,337	53,464,016	68,173,036	79,684,735	90,600,110	101,085,260	110,635,594	121,088,223	129,955,030
Mutation	Age	Population													
F508del Homozygous	0 to 5		2,050	2,075	2,099	2,125	2,150	2,176	2,202	2,229	2,255	2,282	2,310	2,337	2,365
Growth rate			1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
GLPG adoption							15.0%	17.3%	19.0%	20.3%	21.7%	22.8%	23.5%	24.2%	24.4%
					41.2%	42.0%	42.6%	43.0%	43.4%	43.7%	43.9%	44.1%	44.2%	44.3%	44.5%
Growth rate GLPG								15.0%	10.0%	7.0%	7.0%	5.0%	3.0%	3.0%	1.0%
Compliance			80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
Drop out			15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%
GLPG patients								375	418	452	490	521	543	566	578
GLPG Price per patient							375,000.00	393,750.00	413,437.50	434,109.38	455,814.84	478,605.59	502,535.87	527,662.66	554,045.79
Price increase				5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
GLPG revenue							-	118,237,728	138,203,351	157,134,722	178,659,351	199,335,598	218,168,426	238,780,543	256,265,487
			2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Mutation		Population													
G551D, 2117H, etc			4000	4048	4080	4113	4146	4179	4213	4246	4280	4314	4349	4384	4419
Growth rate			1.2%	1.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
GLPG Adoption							15%	16%	19%	23%	23%	24%	25%	26%	26%
GPLG growth rate								30%	20%	10%	7%	5%	5%	3%	1%
Comliance							80%	80%	80%	80%	80%	80%	80%	80%	80%
Drop out							15%	15%	15%	15%	15%	15%	15%	15%	15%
GPLG patients							529	568	687	762	822	870	921	956	974
GPLG price per patient							375000.00	386250.00	397837.50	409772.63	422065.80	434727.78	447769.61	461202.70	475038.78
Price increase			3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
GLPG revenue							158,581,872	175,622,445	218,805,897	249,890,338	277,607,375	302,634,235	329,917,317	352,809,355	369,963,793
GLPG gross revenue			$ -	$ -	$ -	$ -	$ 304,500,670.70	$ 625,046,300.13	$ 809,925,775.95	$ 956,862,484.92	$ 1,096,409,519.30	$ 1,227,875,232.64	$ 1,355,051,910.78	$ 1,475,672,190.20	$ 1,575,049,390.33
GLPG royalty rate							16%	17%	18%	19%	20%	20%	20%	20%	20%
Net revenue			0	0	0	0	61,521,387	106,393,701	145,786,640	181,803,874	219,281,904	245,575,047	271,170,382	295,134,440	315,009,878
R&D expenditure			(35,000,000)	(35,000,000)	(30,000,000)	(30,000,000)	(15,000,000)								
Milestone				250,000,000	150,000,000	50,000,000	50,000,000	50,000,000	50,000,000						
Net revenue			$ (35,000,000.00)	$ 215,000,000.00	$ 120,000,000.00	$ 20,000,000.00	$ 96,521,387.31	$ 156,393,701.02	$ 195,786,639.67	$ 181,803,874.04	$ 219,281,903.86	$ 245,575,046.53	$ 271,170,382.16	$ 295,134,439.64	$ 315,009,878.07
Probabbility of success			85%	75%	50%	30%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Probability adjusted revenue			$ (29,750,000.00)	$ 161,250,000.00	$ 60,000,000.00	$ 6,000,000.00	$ 19,304,277.46	$ 31,278,740.20	$ 39,157,327.93	$ 36,360,774.81	$ 43,856,380.77	$ 49,115,009.31	$ 54,234,076.43	$ 59,026,887.93	$ 63,001,975.61
Discount rate	9%														
rNPV	$333,367,374.20														
FDSO	39,076,000.00														
rNP/share	$ 8.00														

Source: Janney Montgomery Scott LLC estimates

Exhibit 39: CF ROW revenue build and rNPV

			2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Mutation	Age	Population													
F508del Homozygous	12+		12,000	12,144	12,290	12,437	12,586	12,737	12,890	13,045	13,202	13,360	13,520	13,683	13,847
Growth rate			1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
GLPG adoption							7.0%	9.8%	12.7%	14.7%	16.1%	17.2%	18.1%	18.6%	18.8%
Growth rate GLPG								40.0%	30.0%	15.0%	10.0%	7.0%	5.0%	3.0%	1.0%
Compliance			80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
Drop out			15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%
GLPG patients							881	1248	1642	1911	2128	2304	2448	2552	2608
GLPG Price per patient							112,500.00	115,312.50	118,195.31	121,150.20	124,178.95	127,283.42	130,465.51	133,727.15	137,070.33
Price increase				2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
GLPG revenue							79,294,643	115,153,266	155,283,027	185,236,347	211,360,229	234,591,043	255,508,353	272,989,979	286,004,231
Mutation	Age	Population													
F508del Homozygous	6 to 11		3,540	3,582	3,625	3,669	3,713	3,758	3,803	3,848	3,894	3,941	3,988	4,036	4,085
Growth rate			1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
GLPG adoption							5.0%	6.5%	7.8%	8.6%	9.2%	9.6%	9.9%	10.2%	10.3%
Growth rate GLPG								30.0%	20.0%	10.0%	7.0%	5.0%	3.0%	3.0%	1.0%
Compliance			80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
Drop out			15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%
GLPG patients							186	244	297	330	358	380	396	413	422
GLPG Price per patient							112,500.00	115,312.50	118,195.31	121,150.20	124,178.95	127,283.42	130,465.51	133,727.15	137,070.33
Price increase				2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
GLPG revenue							16,708,514	22,531,264	28,046,016	32,001,346	35,518,646	38,685,666	41,332,500	44,160,429	46,265,689
Mutation	Age	Population													
F508del Homozygous	0 to 5		2,950	2,985	3,021	3,057	3,094	3,131	3,169	3,207	3,245	3,284	3,324	3,364	3,404
Growth rate			1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
GLPG adoption							15.0%	17.3%	19.0%	20.3%	21.7%	22.8%	23.5%	24.2%	24.4%
Growth rate GLPG								15.0%	10.0%	7.0%	7.0%	5.0%	3.0%	3.0%	1.0%
Compliance			80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
Drop out			15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%
GLPG patients							464	540	601	651	705	749	781	814	832
GLPG Price per patient							112,500.00	115,312.50	118,195.31	121,150.20	124,178.95	127,283.42	130,465.51	133,727.15	137,070.33
Price increase				3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
GLPG revenue							41,771,285	49,828,757	56,856,106	63,105,218	70,041,176	76,286,397	81,505,836	87,082,384	91,233,862
Mutation		Population													
G551D, 2117H, etc			5000	5060	5121	5182	5244	5307	5371	5435	5501	5567	5633	5701	5769
Growth rate			1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
GLPG Adoption							20%	26%	31%	34%	37%	39%	40%	42%	42%
GPLG growth rate								30%	20%	10%	7%	5%	5%	3%	1%
Comliance							80%	80%	80%	80%	80%	80%	80%	80%	80%
Drop out							15%	15%	15%	15%	15%	15%	15%	15%	15%
GPLG patients							892	1173	1424	1586	1717	1824	1939	2021	2065
GPLG price per patient/month							112500.00	115312.50	118195.31	121150.20	124178.95	127283.42	130465.51	133727.15	137070.33
Price increase			3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
GLPG revenue							80,238,626	108,200,985	134,684,258	153,678,779	170,569,768	185,778,621	202,343,572	216,187,717	226,494,034
GPLG product sale			0	0	0	0	218,013,067.72	295,714,271.89	374,869,408.38	434,021,690.08	487,489,817.94	535,341,726.86	580,690,261.52	620,420,508.53	649,997,815.43
royalty							16%	17%	18%	19%	20%	20%	20%	20%	20%
Net revenue							34,882,090.84	50,271,426.22	67,476,493.51	82,464,121.12	97,497,963.59	107,068,345.37	116,138,052.30	124,084,101.71	129,999,563.09
Probabbility of success			85%	75%	50%	30%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Probability adjjusted revenue			0	0	0	0	8,720,522.71	12,567,856.56	16,869,123.38	20,616,030.28	24,374,490.90	26,767,086.34	29,034,513.08	31,021,025.43	32,499,890.77
Discount rate		9%													
rNPV		$88,147,071.25													
FDSO		39,076,000.00													
rNP/share	$	2.00													

Source: Janney Montgomery Scott LLC estimates