Nabriva Therapeutics: One Of The Biggest Binary Events Of September

Summary:
- Nabriva is a single-asset company developing a novel pleuromutilin antibiotic, lefamulin (BC-3781), with IV/oral administration and low cross-resistance potential
- Lefamulin has shown comparable efficacy and improved tolerability to vancomycin in a Phase 2 trial of Acute Bacterial Skin and Skin Structure Infection (ABSSSI)
- Upcoming Phase 3 results for Community Acquired Bacterial Pneumonia (CABP) will likely pass efficacy criteria but have some risk of unexpected adverse events
- Despite stronger efficacy against some lung pathogens, lefamulin might not be as broadly effective as other antibiotics in CABP
- Overall, Nabriva could provide a much-needed new class of systemic antibiotic, but questions on potency and uncertainty on tolerability increase binary risk

Investment Thesis: *Despite some concerns on potency, in our view, there is still a good chance that lefamulin meets the non-inferiority endpoint in the LEAP 1 trial. Given that this will establish the first clinical proof of concept in CABP, we see substantial upside should it be successful. However, should it fail, we would expect equal or greater downside making this a high risk, high reward binary. Overall, with growing concerns on antibacterial resistance, there is a clear need for new antibiotics. If successful, a novel antibiotic like lefamulin should have a place in this evolving marketplace.*

Company Overview:
Nabriva Therapeutics (NASDAQ: NBRV) is a single-asset company focused on commercializing a novel antibiotic as a monotherapy in Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infection (ABSSSI). Lefamulin is anticipated to be used as a hospital-initiated IV therapy that switches to an oral therapy at home. A Phase 2 trial with positive results has already been completed in ABSSSI, and its use in other indications is currently in pre-clinical development. In April 2017, Nabriva announced that it would relocate from Austria to Ireland, where Nabriva Therapeutics AG shares were exchanged for Nabriva Therapeutics Plc. This move was strategically intelligent as it allows for a more favorable overall tax rate, plus it reduces costs associated with compliance.

Background and Context:
Lefamulin (also known as BC-3781) is a semi-synthetic pleuromutilin, a natural class of antimicrobial agents isolated from the fungus *Pleurotus mutilis*. Pleuromutilins were initially discovered in 1951 and structurally resolved in 1962. The first commercial pleuromutilins were for veterinary use (tiamulin (1997) and valnemulin (1999)). The first approved for human use was retapamulin (2007) which is indicated as a topical ointment for impetigo caused by *S. aureus* (MSSA only) or *S. pyogenes*. Nabriva hopes to be the first to produce an IV/oral pleuromutilin for systemic treatment in the hospital and at home.

Lefamulin has broad spectrum activity against both Gram-negative and Gram-positive bacteria, including multi-drug resistant strains and pathogens that cause “atypical” pneumonia. A comparison of MIC_{90} values (concentration of antibiotic needed to inhibit 90% of isolates *in vitro*, μg/mL) for common lung pathogens is shown in the figure below (from Paukner, et al.). Notably, it demonstrated potent activity against *S. pneumoniae*, and *M. catarrhalis*, but showed less potency against *H. influenzae*.

TABLE 4 Activities of BC-3781 and comparator antimicrobial agents against bacterial pathogens causing predominantly respiratory tract infections

Organism (no. tested) and antimicrobial agent	MIC^{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	CLSI %S/%R[a]	EUCAST %S/%R[a]
S. pneumoniae (1,473)					
BC-3781	0.12	0.25	≤0.008–1		
Azithromycin	≤0.25	>4	≤0.25–>4	62.6/36.6	61.7/37.4
Ceftriaxone	≤0.06	1	≤0.06–8	91.3/1.2	78.0/1.2
Cefuroxime	≤0.12	8	≤0.12–>16	73.3/24.0	72.0/26.7
Clarithromycin	≤0.25	>32	≤0.25–>32	63.2/36.6	63.2/36.6
Doxycycline	0.25	8	≤0.06–>8		73.9/25.2
Erythromycin	≤0.25	>4	≤0.25–>4	62.8/36.2	62.8/36.2
Imipenem	≤0.12	0.5	≤0.12–1	79.6/4.4	100.0/0.0
Levofloxacin	1	1	≤0.5–>4	98.9/1.0	98.9/1.1
Linezolid	1	1	≤0.12–4	99.9/−	100.0/0.0
Moxifloxacin	≤0.5	≤0.5	≤0.5–>4	99.0/0.7	98.7/1.3
Penicillin[b]	≤0.03	4	≤0.03–>4	88.5/0.5	
Penicillin[c]	≤0.03	4	≤0.03–>4	61.3/21.2	61.3/11.5
Tigecycline[d]	≤0.03	0.06	≤0.03–0.5	99.7/−	
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5–>4	68.3/23.2	74.0/23.2
Vancomycin	0.25	0.5	≤0.12–1	100.0/−	100.0/0.0
H. influenzae (360)					
BC-3781	1	2	0.015–8		
Ampicillin	≤1	>8	≤1–>8	74.4/23.3	74.4/25.6
Azithromycin	1	2	≤0.25–>4	98.3/−	0.8[e]/1.7
Ceftriaxone	≤0.06	≤0.06	≤0.06–0.5	100.0/−	99.2/0.8
Cefuroxime	1	2	≤0.12–>16	98.6/0.6	74.4/7.5
Ciprofloxacin	≤0.03	≤0.03	≤0.03–1	100.0/−	99.7/0.3
Clarithromycin	8	16	≤0.25–>32	81.3/2.5	0.3/1.1
Doxycycline	0.5	0.5	0.12–2		98.9/0.0
Erythromycin	4	8	0.25–>8		0.3/2.8
Imipenem	0.5	1	≤0.12–4	100.0/−	99.7/0.3
Moxifloxacin	≤0.5	≤0.5	≤0.5–1	100.0/−	99.7/0.3
Tigecycline[d]	0.25	0.25	0.06–1	90.6/−	
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5–>4	68.1/29.4	68.1/31.7
M. catarrhalis (253)					
BC-3781	0.12	0.25	≤0.008–0.5		
Azithromycin	≤0.25	≤0.25	≤0.25–2	99.6/−	99.6/0.4
Ceftriaxone	0.25	0.5	≤0.06–1	100.0/−	100.0/0.0
Cefuroxime	1	2	≤0.12–8	99.6/0.0	72.3/1.6
Ciprofloxacin	≤0.03	≤0.03	≤0.03–0.5	100.0/−	100.0/0.0
Clarithromycin	≤0.25	≤0.25	≤0.25–4	99.6/−	98.7/0.4
Doxycycline	0.12	0.25	≤0.06–4		99.6/0.4
Erythromycin	0.25	0.25	≤0.06–4	99.6/−	93.5/0.4
Imipenem	≤0.12	≤0.12	≤0.12–0.25		100.0/0.0
Moxifloxacin	≤0.5	≤0.5	≤0.5		100.0/0.0
Penicillin	>4	>4	≤0.03–>4		
Tigecycline[d]	0.06	0.25	≤0.03–0.5		
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	94.5/2.0	94.5/3.2

[a] %S, percentage of susceptible organisms; %R, percentage of resistant organisms. Criteria were as published by the CLSI (2012) and EUCAST (2011) (25, 26).
[b] Criteria as published by the CLSI (2012) for "Penicillin parenteral (non-meningitis)" (25).
[c] Criteria as published by the CLSI (2012) for "Penicillin (oral penicillin V)" (25).
[d] U.S. FDA breakpoints were applied (Tygacil drug information) (27).
[e] Percentage inhibited at ≤0.25 μg/ml (26).

Lefamulin also has potent bactericidal (bacteria-killing) effects against *M. pneumoniae*, a key differentiation feature shared only with the fluoroquinolones. *M. pneumoniae* is one of the "atypical" pneumonia-causing agents and is commonly treated with macrolides. However, macrolides and tetracyclines are only bacteriostatic (inhibit bacterial growth without necessarily killing them), which might reduce their efficacy in immunosuppressed populations that experience systemic infections. Additionally, there are macrolide-resistant strains that may support lefamulin as a first-choice option.

An important consideration for an antibiotic intended to treat lung infection is the concentrations achieved at the necessary site of action. Accordingly, lefamulin pharmacokinetics have been evaluated in plasma, soft tissue, and pulmonary epithelial lining fluid (ELF) following one 150 mg IV infusion for 1 hour. Lefamulin concentration in the ELF peaked at 1 μg/mL and then fell to 0.2 μg/mL over the course of 12 hours (shown below, from Zeitlinger, et al.). The median C_{max} was 0.7 μg/mL and T_{max} occurred 1 hour after the infusion. Given that the MIC_{90} values of the majority of lung pathogens tested were <0.5 μg/mL, lefamulin should effectively treat these infections.

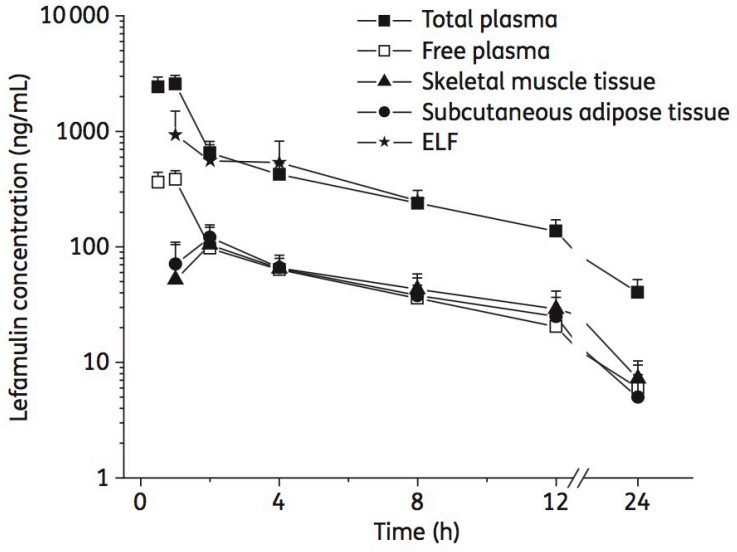

Figure 1. Mean ± standard deviation concentration–time curves of lefamulin in plasma (n=12), skeletal muscle tissue (n=10), subcutaneous adipose tissue (n=8) and ELF (n=3) after intravenous administration of 150 mg of lefamulin over 1 h. For free plasma concentrations, a protein-unbound fraction of 13% was estimated and used for calculations.

Community-Acquired Bacterial Pneumonia (CABP)

CABP is pneumonia that occurs in people that have little to no contact with the healthcare system or hospitals. The most common bacteria known to cause CABP include *S. pneumoniae*, *H. influenzae*, *C. pneumoniae*, and *M. pneumoniae*, although more than half of the cases of CABP are caused by unknown pathogens.

Current Clinical Trials:

Patients in the LEAP studies were selected based on pneumonia Patient Outcomes Research Team (PORT) risk classification (also known as the Pneumonia Severity Index, PSI). Scoring is based on various factors such as age, baseline health characteristics, and co-morbidities. Class I – III represent outpatients with less than 1% mortality rate, while Class IV and V represent inpatients with a 9.3% and 27% mortality rate respectively.

LEAP 1 is the first of two Phase 3 trials in CABP and tests the effect of IV-to-oral lefamulin administration in ~550 moderate to severe risk patients (PORT Risk Class III and at least 25% who are Class IV or V). Patients will be treated for 7 days with lefamulin or moxifloxacin +/- linezolid, with treatment being extended to 10 days for patients with MRSA. 150 mg of lefamulin will be administered via IV infusion 2 times daily for at least 3 days, and then participants will take 600 mg twice daily orally. This dosing is similar to the Phase 2 ABSSSI trial previously conducted by Nabriva (discussed below). Topline results of the LEAP 1 trial are expected in September 2017.

LEAP 2 is an oral-only Phase 3 trial in ~740 moderate risk patients (PORT Risk Class II and at least 50% who are Class III or IV). Topline results are expected Q1 2018. Regulatory filings are planned for the US and EU pending positive Phase 3 results, with a priority review request sent to the FDA for CABP. According to management and not surprisingly, potential partnerships for lefamulin seem to be pending successful CABP Phase 3 data.

For both trials, the primary endpoint for the FDA is the proportion of patients that achieve an Early Clinical Response 96 hours after the first dose with a non-inferiority margin to the comparator arm of

12.5% (LEAP 1) and 10% (LEAP 2). Secondary outcomes include 1) looking at Early Clinical Response in the Intent to Treat (ITT) population (meaning individuals who may have only done partial treatment), 2) including the investigator's personal assessment of "success" in treatment 5-10 days after the last dose of the drug is given, and 3) determining the safety profile based on adverse events reported from screening to 30 days after the first dose.

EMA approval is based on Investigator Assessment of Clinical Response (IACR) at Test of Cure 5-10 days after the last dose of the study drug, with a non-inferiority margin to the comparator arm of 10% (LEAP 1 and LEAP 2).

Acute Bacterial Skin and Skin Structure Infection (ABSSSI)
ABSSSI types that are studied in clinical trials include extensive cellulitus/erysipelas, wound infections, and major cutaneous abscesses with lesions that are at least 75 cm^2 in surface area. The most common bacterial causes of ABSSSI are *Streptococcus pyogenes* and *Staphylococcus aureus* including methicillin-resistant *S. aureus*.

Nabriva's Phase 2 data for lefamulin compared favorably to standard of care in both the Clinically Evaluable (CE) and Modified Intent-to-Treat (which included patients with detectable Gram positive pathogens) cohorts. Clinical success rates were 88.9% in the CE population and 82.4% in the MITT population. Vancomycin was the comparator arm and achieved similar clinical success rates (92.2% in CE; 82.4% in MITT). The safety profiles were also similar with slightly fewer AEs in the lefamulin arm.

Although the Phase 2 data in ABSSSI are supportive, Nabriva remains focused on the advancement of lefamulin in CABP. Nabriva will "seriously consider" starting a Phase 3 ABSSSI trial after the LEAP trials are completed. They anticipate only needing one additional registration trial for marketing approval.

Risks
While the IV dose being used in the LEAP 1 Phase 3 trial appears sufficient to achieve ELF concentrations that far exceed the MIC_{90} values for many known pathogens that cause CABP, it may not be sufficient for *H. influenzae*, which was the suspected causal agent in ~10% of CABP patients in one study based in Japan and 6% of patients in Norway. The MIC_{50} of lefamulin for *H. influenzae* is 1 μg/mL, the maximum concentration observed immediately after infusion. This particularly weak activity of lefamulin might limit its efficacy as a monotherapy in this subset of patients, which reflects a meaningful percentage of the known causes of CABP. Nabriva's failure to address the potential impact of this patient population could weaken potential readouts. Nabriva also potentially complicates its trial design by including an arm looking at moxifloxacin plus linezolid. Although Nabriva is trying to push lefamulin as a monotherapy and has shown strong activity against MRSA compared to linezolid, including its Phase 2 trial in ABSSSI, it is possible that a combo therapy will prove more effective than lefamulin alone in MRSA positive and negative patients, which could impact trial results.

Furthermore, although pleuromutilins have not been used extensively in humans and show low cross-resistance baseline to other antibiotics, it has been observed previously through the *cfr* gene, which confers resistance to lincosamides, oxazolidinones (excluding torezolid), streptogramin A, phenicols, and pleuromutilins. Resistance was only detected in four strains from four different states in the US, and in Germany, only six cfr-carrying staphylococcal strains were identified in animals over the past 17 years as of 2011. However, outbreaks have occurred, suggesting potential risk. Resistance can also be conferred through the *vga*(A) and *vga*(A)*v* genes in 6 *S. aureus* human isolates out of 5,676

total. Overall, resistance to antibiotics are expected to develop as use increases, and Nabriva's claim about an apparent lack of cross-resistance with other antibiotic classes might be overstated. Regardless, as a new class, pleuromutilins will likely experience few initial cases of resistance.

Adverse events are also a potential risk associated with the CABP trials since Phase 3 trials were initiated based on the strength of the ABSSSI trial, which is a very different patient population. In the ABSSSI Phase 2 trials, the safety profile for the IV dose was very similar to vancomycin, with no SAEs and limited AEs primarily related to headache and non-severe gastrointestinal issues such as nausea and diarrhea. Adverse events and efficacy are intertwined since it has been noted that although the bioavailability of the oral 600 mg dose on a fasted stomach is bioequivalent to the 150 mg IV administration, it was reduced after the consumption of a high fat/high calorie meal. This study also showed that on a fasted stomach, the adverse events were higher and virtually nonexistent if the antibiotic was taken after consumption of a high fat meal. However, the safety profile on a fasted stomach was still comparable to what was observed with the vancomycin treatment for ABSSSI. Also, there is reason to believe that although they are separate indications, the safety profile in ABSSSI can be used to project the safety profile in CABP. Paratek Pharmaceuticals (NASDAQ: PRTK) is also evaluating a new antibiotic in CABP and ABSSSI, and compared the safety profiles from their different trials side-by-side. Across the indications and treatment regiments (IV to oral or oral-only), safety profiles were comparable for both drugs, with the only difference being that oral-only treatment with omadacycline led to higher nausea and vomiting in ABSSSI patients. Although Nabriva's antibiotic is a different class, we are fairly confident in concluding that most likely, the safety profile will be similar.

Lastly, the departure of CMO Dr. Elyse Seltzer, who oversaw the development, regulatory strategy, and execution of the Phase 3 LEAP 1 and 2 trials, is surprising given how close they are to data release. Although she will continue to act as a consultant to Nabriva and will stay on through the announcement of the LEAP 1 results, the timing is somewhat concerning.

Competition:
General competition is intense in the antibiotics market as more companies try to modify known classes or discover new ones, but the number of newly approved antibiotics per year has been steadily declining since 1980, underscoring the difficulty of identifying new classes or successfully modifying existing ones. One direct competitor to Nabriva is Paratek Pharmaceuticals (NASDAQ: PRTK). Paratek is a clinical stage company focusing on next-generation tetracycline-derived antibiotics called aminomethylcyclines (click here for an in-depth report by AMP Biotech Research on Paratek). Aminomethylcyclines are modified to reduce drug efflux and ribosomal protection while maintaining their broad-spectrum activity. Recently, Paratek released Phase 3 data with omadacycline in both IV to oral treatment (OASIS-1) and oral-only treatment (OASIS-2) for ABSSSI showing comparable early clinical response, clinical success rates in the CE and MITT cohorts, and safety profiles compared to linezolid. Additional phase 3 results met the non-inferiority endpoint for IV to oral treatment in CABP (OPTIC) when compared with moxifloxacin. Because the need for antibiotics is large, Paratek has the advantage of a rolling NDA submission which they plan to start in December 2017.

Cempra (NASDAQ: CEMP) is also a competitor seeking to enter the CABP market. Cempra's lead candidate solithromycin is a next-generation macrolide (fluoroketolide subtype) that recently received a Complete Response Letter (CRL) from the FDA referencing potential hepatic toxicity issues. Additionally, solithromycin recently failed to meet the non-inferiority endpoint for a study in gonorrhea patients, suggesting it is unlikely to be a relevant competitor in the antibiotics space anytime soon.

Lastly, Achaogen (NASDAQ: AKAO) is also developing a new antibiotic, plazomicin (a next-generation aminoglycoside). However, Achaogen's interest is outside ABSSSI and CABP and is currently focused on developing plazomicin in complicated urinary tract infection (cUTI) and indications like hospital-acquired pneumonias that are caused by carbapenem-resistant Enterobacteriaceae. Also, while it has seen success in the clinic in patients with cUTI, it is only effective against gram-negative bacteria, limiting its total addressable market.

Financials:
Nabriva currently has about $53M in cash and a burn rate of $15M/Q as of June 30th 2017. This cash position gives them roughly ¾ - 1 year runway, which should be sufficient time to complete their LEAP 1 (topline data expected in September) and LEAP 2 (topline data expected Q1 2018) clinical trials. However, with positive data from either trial, you can expect a secondary offering shortly thereafter. As of September 7th, the market cap is ~$262M.

Market Opportunity:
In the US, CABP leads to over 1 million hospitalizations per year, with direct costs for a single community acquired pneumonia (CAP) hospitalization ranging from $3,000 - $13,000. In total this results in roughly $17 billion in healthcare costs per year. Furthermore, readmissions associated with pneumonia are high, with 140,000 hospital readmissions per year that result in $10 billion in healthcare costs. However, the proportion of readmissions that can be addressed by better treatment is unclear since a substantial portion of readmissions are due to comorbidities. Two drugs that comprise roughly a third of the CABP antibiotic usage each are azithromycin and levofloxacin. The peak sales of levofloxacin and azithromycin in 2010 for use in all skin, respiratory, and UTI indications were $3.4B and $1.8B respectively. Total script performance for CABP has also been slowly increasing, with 9.5M scripts being prescribed in 2013.

Summary:
Overall, lefamulin is a promising new antibiotic with first-in-class potential that comes with the advantage of having limited cross-over resistance potential with many currently used antibiotics. The upcoming Phase 3 readout for IV to oral lefamulin in CABP will likely pass its efficacy criteria and have an acceptable tolerability profile. Although there is some risk that lefamulin is not as effective against some bacteria that are known to cause CABP, we see this as unlikely to significantly affect lefamulin's clinical success rate. While there is no existing tolerability data in a CABP population, we don't expect anything outside the typical side effects associated with antibiotics. Despite these risks, we are optimistic that lefamulin will prove successful in its upcoming phase 3 readouts, and that the NBRV market cap will increase significantly with this success, even after a possible dilution event within the next 6 months.

Based on the above analysis, we have taken a conservative position in NBRV in our AMP hypothetical model fund and will likely hold it long-term.

At AMP we aim to differentiate ourselves with deeper analysis that leverages our years of scientific training and industry experience. Currently contributing are several PhDs and 1 MD.