Antibe Therapeutics

Hydrogen Sulfide-Releasing Anti-Inflammatory ATB-346 Leads a Suite of High-Value GI-Protective Pain Drugs – Spec BUY

ATE-TSXV: $0.48
Speculative Buy
$1.40 Target

Event: We are formally initiating coverage on Toronto-based Antibe Therapeutics with a **Speculative BUY rating and price target of $1.40**. Antibe is a diversified pharma firm, with a clinical arm investigating the development of gastrointestinal (GI)-protective nonsteroidal anti-inflammatory drug (NSAID) derivatives, led by a patented hydrogen sulfide-releasing derivative of the NSAID naproxen called ATB-346. The fact that '346 can release hydrogen sulfide in the gut is core to its gastro-protective potential, specifically for reducing frequency/severity of gastro-duodenal ulcers (and bleeding associated with them) that can arise from chronic NSAID use.

The full chemical name for ATB-346, just for the record, is [2-(6-methoxynapthalen-2-yl)-propionic acid 4-thoicarbamoyl phenyl ester] and the '4-thiocarbamoyl phenyl ester' moiety is the part of the molecule that releases hydrogen sulfide in the gut (the rest is naproxen itself). The structure of ATB-346 is as shown in Exhibit 1. Similarly derivatized analogs of other NSAIDs like ketoprofen (ATB-352) or alternative pain drugs like acetylsalicylic acid (ATB-340) are separately in development, though not yet as advanced as ATB-346, and for now, our investment thesis will be predominantly '346-focused. The firm is not a pure play drug developer however, and operates a revenue-generating regenerative medicine subsidiary called Citagenix, with its core product portfolio of both therapies and devices targeting bone regeneration, primarily in dental markets.

Creating even greater value, and greater safety, from what is still a market-leading NSAID in naproxen: Naproxen was genericized long ago, but the most recognizable existing brands of underivatized drugs are probably Bayer's (BAYN-EU, NR) Aleve and Atnahs Pharmaceuticals' (Private) branded generic formulation of Syntex's (part of Roche since 1994) original Naprosyn formulation, with Horizon Pharma (HZNP-Q, NR) separately marketing a branded naproxen-esomeprazole delayed-release formulation called Vimovo (co-administration of a proton pump inhibitor like esomeprazole [which AstraZeneca sells as Nexium] would be an alternative way to mitigate upper GI ulcer symptoms arising from chronic NSAID use) and Takeda marketing a naproxen-lansoprazole formulation branded as Prevacid Naprapac. However, this combination approach with proton pump inhibitor (PPI) drugs presents its own limitations, particularly with increasing awareness within the medical community on adverse events that are independently associated with PPI use.

But an alternative approach is to modify naproxen itself in ways that preserve its core pain-mitigating pharmacologic activity (primarily through inhibition of cyclooxygenase enzymes COX-1/COX-2) while mitigating its impact on gastric epithelium that gives rise to the GI ulcers in some patients. Historically, this has been a drug development challenge that Antibe appears to have overcome with ATB-346, and perhaps with other candidates in its pipeline.

Hydrogen sulfide-releasing drugs have long been expected to confer additive benefits to drugs modified to release it, and ATB-346 GI ulceration rate data supports this thesis: That hydrogen sulfide has therapeutic potential in GI health would certainly come as a surprise to anyone who has ever inhaled trace amounts of the noxious gas. The rotten-egg-smelling colourless, flammable, water-soluble gas uncharitably referred to as swamp gas or sewer gas, can be fatally toxic if inhaled at concentrations at or higher than 1,000 parts per million (or about 0.1% of partial pressure of inhaled gas volume), but it has dramatic anti-inflammatory,

Projected Return: 192%
Valuation: NPV, 20x EPS, 12.5x EV/EBITDA (F2025 forecasts)

Market Data

Basic Shares O/S (M)	199.0
FD Shares O/S (M)	259.5
Market capitalization ($M)	95.5
Enterprise Value ($M)	91.8
Adj pro forma cash ($M, most rec Q)	5.0
LT debt ($M, most rec Q)	1.3
52 Week Range	$0.08-$0.79
Avg. Daily Volume (M)	7.2947
Fiscal Year End	Mar-31

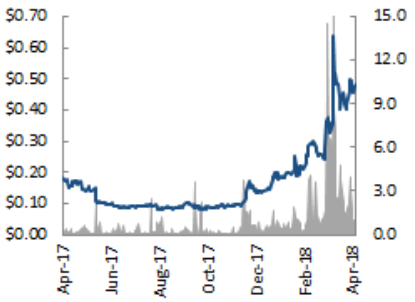
Key Milestone

Phase II data, ATB-346 dose-ranging study	CQ119
Commence ATB-346 dose-ranging study	CQ218
Phase II, ATB-346, GI ulceration rate data (completed Mar/18)	CQ118
Phase II, open-label knee osteoarthritis data (completed Aug/16)	CQ316

Financial Metrics

In C$	2018E	2019E	2020E
Total Revenue ($000)	8,402	8,822	9,264
EBITDA ($000)	(5,248)	(5,647)	(8,279)
Adj net inc ($000)	(7,101)	(7,194)	(9,826)
EPS (basic)	($0.04)	($0.04)	($0.05)
EPS (FD)	($0.03)	($0.03)	($0.04)
P/E	NA	NA	NA
EV/EBITDA	NA	NA	NA

Antibe is a clinical stage drug developer, with lead clinical asset - hydrogen sulfide-releasing naproxen analog ATB-346 - focused on knee osteoarthritis as initial pain market. Ketoprofen-based ATB-352 & aspirin-based ATB-340 are in preclinical testing



Source: Consensus Data - Capital IQ, Forecasts/Estimates - Echelon Wealth Partners

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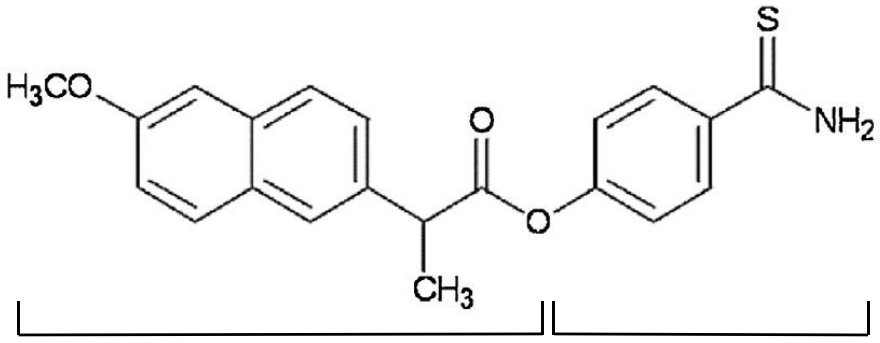
cytoprotective, and pro-healing activity when released in the GI tract or in the bloodstream, and at much lower concentrations than those conferring lethal effects when inhaled.

This activity has long been known and is well-characterized in the medical literature, but the challenge until recently has been how to design hydrogen sulfide-releasing analogs of pharmacologically active agents that actually release hydrogen sulfide, that do so in a way that confers measurable and not just theoretical impact on disease processes, and that preserve the core activity of the agent being modified. We now have strong Phase II data showing that ATB-346 embodies all three elements, enhancing naproxen's medical utility in the process.

The NSAID naproxen is a prudent pain therapy both commercially and pharmacologically for testing utility of Antibe's hydrogen sulfide-releasing chemistry: Naproxen itself has been approved for prescription sale in the US since 1976 and for over-the-counter use since 1994. The US National Institutes of Health estimates that over 10 million prescriptions for naproxen are filled each year, excluding over-the-counter sales that are likely equally substantial. As stated, the highest profile naproxen brand currently, other than those co-formulated with esomeprazole, is Bayer's consumer brand Aleve, which continues to generate strong sales despite some recent softness. Bayer reported sharp declines in sales of its branded naproxen formulation Aleve last year, citing US competition from alternative pain therapies, and with annual F2017 sales of €375M falling from €416M last year and €413M in F2015. FQ417 sales of €103M were correspondingly down from €115M in FQ416 and €105M in FQ415, but still strong in absolute terms, in our view, and still providing a solid foundation onto which a superior formulation like ATB-346 could be layered.

Exhibit 1 – Molecular Structure of ATB-346



Source: Pharmacological Research (2016). Vol. 111, pp. 652-658

Highly positive Phase II gastro-duodenal ulcer rate data are already available that support ATB-346 ability to confer naproxen-like pain relief without naproxen-like side effects: Antibe already has generated safety data from a 244-patient Phase II gastro-duodenal ulceration rate that showed that ATB-346, at a dose that conferred naproxen-like pain relief in a small Phase II pain study completed back in FQ217 (Aug/16, described below), exhibited not just lower but dramatically lower GI ulceration rate at two-week follow-up when compared to naproxen itself (42.1% GI ulcer frequency [53 of 126 patients] at two weeks for naproxen, administered at the dose usually indicated for knee osteoarthritis pain, 500mg twice-daily, vs. 2.5% GI ulcer frequency [3 of 118 patients] for ATB-346-treated patients at dose previously shown by Antibe to confer naproxen-like pain relief in knee osteoarthritis, 250mg once-daily).

The specific naproxen formulation to which ATB-346 was compared was not identified by Antibe or its collaborating CRO Topstone Research, but control naproxen could have been supplied by any of several Canadian manufacturers, including Teva Canada (TEVA-NY, NR), Pharmascience [Private; PMS-Naproxen], Mylan [MYL-Q, NR; Mylan-Naproxen], Apotex [Private; APO-Naproxen], or Bayer [Aleve], among others). Any of these would work well as control therapy regardless of which specifically was incorporated into the trial. We would intuitively consider data that so clearly differentiated a control therapy from an experimental therapy to at least be clinically meaningful if not statistically significant, and indeed it was with a p-value of less than 0.001. We see these data, even though they did not directly

assess magnitude of knee osteoarthritis pain relief that will clearly need to be explored in larger Phase II/III studies, as hugely validating for Antibe's patented hydrogen sulfide-releasing chemistry and thus hugely positive for the platform (and specifically ATB-346) to advance through clinical/regulatory activities and to commercial launch, which our model assumes could transpire under best-case scenario by FH223.

Lower ATB-346 dose tested in new Phase II GI ulceration rate trial did not impact liver physiology as dramatically as higher doses previously explored: Importantly, Antibe reported the impact on liver physiology for ATB-346 at the dose tested, by which we mean that incidence (and presumably magnitude) of elevation in blood plasma of the liver enzymes alanine transaminase and aspartate transaminase was comparable to published values for commonly prescribed NSAIDs. Antibe did not provide any specific data on this observation and we will thus be interested to see just how it compares by this measure on impact on liver function. Recall that in the highest dose level of the multiple ascending dose portion of the Phase I trial that Antibe conducted back in F2014/15, elevated liver enzymes in the blood in patients to whom up to 1,500mg daily of ATB-346 was administered compelled Antibe to suspend the trial and to redefine the dose range over which ATB-346 could be safely administered to humans – it appears that 250mg daily dosing falls within that range, whatever it turns out to be.

Exhibit 2 – Income and Financial Summary for Antibe

(C$000, except EPS)	2017A	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
Product Sales, Citagenix	9,054	8,402	8,822	9,264	9,727	10,213	10,724	11,260	11,823	12,414	13,035	13,686
Royalty revenue, ATB-346	0	0	0	0	0	0	0	70,895	172,879	249,816	303,713	355,780
Total revenue	**$9,054**	**$8,402**	**$8,822**	**$9,264**	**$9,727**	**$10,213**	**$10,724**	**$82,155**	**$184,701**	**$262,230**	**$316,748**	**$369,466**
Revenue growth (%)	*104%*	*($7%)*	*5%*	*5%*	*5%*	*5%*	*5%*	*666%*	*125%*	*42%*	*21%*	*17%*
EBITDA	**($3,700)**	**($5,248)**	**($5,647)**	**($8,279)**	**($5,223)**	**($4,543)**	**($2,145)**	**$66,453**	**$165,599**	**$241,089**	**$294,495**	**$346,648**
EBITDA growth (%)	50%	42%	8%	47%	(37%)	(13%)	(53%)	(3198%)	149%	46%	22%	18%
EBITDA margin (%)	*(41%)*	*(62%)*	*(64%)*	*(89%)*	*(54%)*	*(44%)*	*(20%)*	*81%*	*90%*	*92%*	*93%*	*94%*
Net income, fully-taxed	($5,746)	($7,101)	($7,194)	($9,826)	($6,770)	($6,089)	($3,692)	$45,434	$114,836	$167,680	$205,063	$241,571
Fully-taxed EPS (basic)	($0.05)	($0.04)	($0.04)	($0.05)	($0.03)	($0.03)	($0.02)	$0.21	$0.52	$0.77	$0.94	$1.10
Fully-taxed EPS (fd)	**($0.03)**	**($0.03)**	**($0.03)**	**($0.04)**	**($0.02)**	**($0.02)**	**($0.01)**	**$0.16**	**$0.41**	**$0.60**	**$0.73**	**$0.86**
P/E (basic)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*2.3x*	*0.9x*	*0.6x*	*0.5x*	*0.4x*
EV/EBITDA	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*1.4x*	*0.6x*	*0.4x*	*0.3x*	*0.3x*
S/O, basic (M)	*113.0*	*163.0*	*199.0*	*209.0*	*219.0*	*219.0*	*219.0*	*219.0*	*219.0*	*219.0*	*219.0*	*219.0*
S/O, fd (M)	*166.1*	*243.3*	*259.5*	*269.5*	*279.5*	*279.5*	*279.5*	*279.5*	*279.5*	*279.5*	*279.5*	*279.5*

Source: Historicals - Company Information, Forecasts/estimates – Echelon Wealth Partners

We were initially cautious on Antibe's Phase II GI-Safety study design just based on relatively short study duration, but multiple published studies showed us that two-week duration was sufficient to reveal differences in GI ulceration rate: By the way, we were initially cautious on how dramatic the ulceration rate would be in either study arm after only two-week follow-up, but there is in fact abundant evidence in the medical literature that naproxen-induced gastroduodenal ulcers, if they occur at all, usually occur within a two-week window, if not earlier. In one 2010 study in *Alimentary Pharmacology & Therapeutics* published by University of Illinois researchers, a lipophilic naproxen prodrug analog called naproxen etemesil (also called LT-NS001) was compared to naproxen itself (coincidentally, also tested here at 500mg twice-daily) in a 120-patient Phase II trial and in that trial, the primary endpoint was manifestation of endoscopically confirmed gastroduodenal ulcers at an even earlier time point of one week. Interestingly, a lower proportion of naproxen etemesil-treated patients (3.3%) developed gastroduodenal ulcers (quantified by a modified Lanza score) than did naproxen-treated subjects (15.8%, lower than in Antibe's study but possibly due to differences in patient inclusion/exclusion criteria), but to our knowledge, this naproxen analog is no longer in clinical testing (a 534-patient knee osteoarthritis pain trial was separately completed in 2010, but data were not published in peer-reviewed format).

Next clinical trial should focus on more precisely defining dose range over which optimal combination of high pain relief/low GI ulceration rate can be identified: On that theme, Antibe was clear in its recent press release that next steps in ATB-346 clinical testing will focus on precisely defining the range of ATB-346 dosages that can be safely

administered to humans without sacrificing the reduction in ulceration rate seen so clearly in the 250mg daily dosing trial just concluded and of course without sacrificing the impact on reducing knee osteoarthritis pain that naproxen at its admittedly higher indicated dose engenders. Accordingly, we believe that the firm is already contemplating a multi-arm (including placebo control this time) Phase II efficacy trial, perhaps testing patients diagnosed with imaging-confirmed knee osteoarthritis pain and not healthy volunteers, and probably testing ATB-346 daily dosages at or below 250mg daily as tested in the now-completed 244-patient Phase II GI-Safety trial.

As a guess, the firm will probably enroll about 50 patients per study arm (so, 200-250 patients in total, depending on how many ATB-346 treatment arms are randomized) and we would expect the trial to enroll patients in at least 10 pain centres/hospitals and not through just 4 facilities as in the just-completed Phase II GI-Safety trial. If the new efficacy Phase II trial can commence by end-of-FQ218 as we believe is feasible, and if duration of follow-up is two weeks again as it was in the Phase II trial and in the 12-patient open-label Phase II knee osteoarthritis trial completed back in FQ316 (well, was 10 days actually, but certainly similar in duration). Assuming patient enrollment can conclude in a quarter or two, it seems reasonable to us to assume that final two-week multi-dose data could be available by FH219, and pivotal US-based Phase III testing could commence by FH120.

We already have data showing that ATB-346 test dose exhibiting low GI ulceration rate could confer naproxen-like pain relief in future Phase III knee osteoarthritis testing: We have long been cautious not to overinterpret Antibe's legacy Phase II knee osteoarthritis data just because it has not to this point been compared to placebo within a randomized placebo-controlled trial and placebo effects are particularly striking in pain studies as our own coverage history has endured. But still, we are encouraged by how well ATB-346 did perform in a 12-patient 10-day Phase IIA single-dose ATB-346 trial that Antibe concluded back in FQ316, establishing 250mg once-daily as a reasonable dosage strength to explore in the Phase II trial just completed. Recall that in the Phase IIA trial completed in Aug/16, Antibe did see time-dependent improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-quantified pain intensity at 250mg daily, with patients on average experiencing a 4.3-point reduction in WOMAC pain score at day four, and then declining further to 7.6 at day ten, with high levels of statistical significance in these values compared to baseline, though not to placebo as described.

Exhibit 3 – Valuation Scenarios for Antibe Therapeutics

NPV, discount rate	20%	30%	40%	50%	60%	70%
Implied value per share	$3.52	$2.05	**$1.18**	$0.76	$0.47	$0.30
Price/earnings multiple, F2025	**10x**	**15x**	**20x**	**25x**	**30x**	**35x**
Implied share price[1]	$0.76	$1.15	**$1.53**	$1.91	$2.29	$2.67
EV/EBITDA multiple, F2025	**5x**	**10x**	**12.5x**	**15x**	**17.5x**	**20x**
Implied share price[1,2]	$0.55	$1.10	**$1.37**	$1.65	$1.93	$2.20
One-year Antibe target price (C$) [1]			**$1.36**			

[1] Based on F2025 fd fully-taxed EPS of $0.41; EBITDA of $165.6M, discounted at 40%, FD S/O of 259.5M, but FD S/O of 279.5M embedded in our model

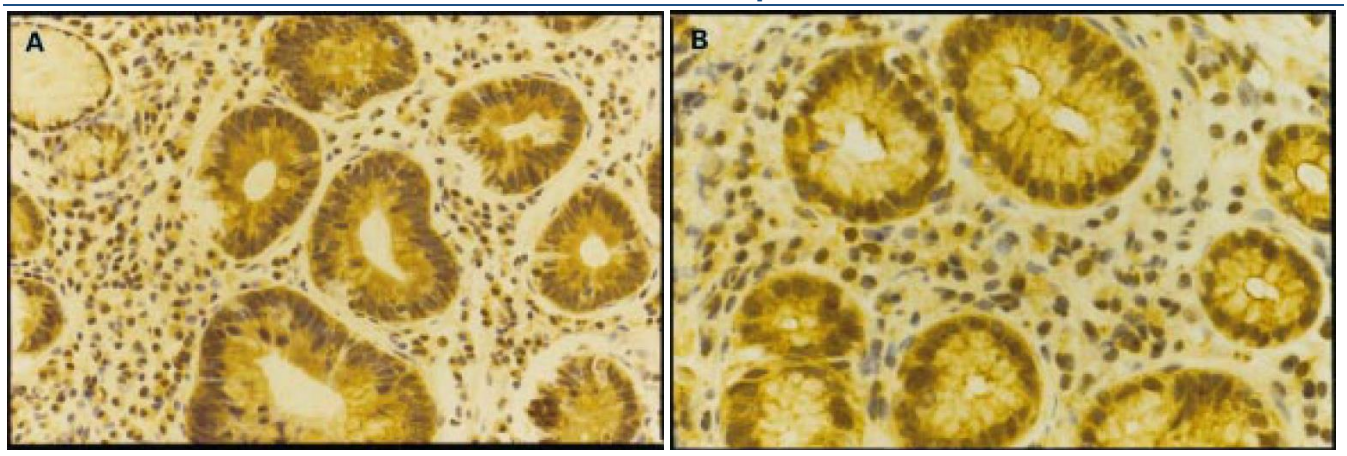
[2] Pro forma cash after Apr/18 warrant exercise of $5.0M (FQ318 cash $1.95M, $4.0M from warrant exercise, less YTD operating cash loss), FQ318 total debt after convertible debt conversion of $1.29M

Source: Echelon Wealth Partners

It is a bit early to precisely define how regulators will request that ATB-346 be tested in Phase III, but peer group Phase III programs provide us with reference points to consider: With ATB-346 solidly de-risked in our view through already completed Phase I/II studies, our model will assume that pivotal US-based Phase III knee osteoarthritis testing can commence by FH219. Based on other Phase III clinical programs funded for other pain therapies we have followed in recent years, we assume that Antibe will be requested by the FDA to fund two distinct placebo-sponsored knee osteoarthritis pain trials, each probably 500 to 600 patients in size, and probably with 12-week impact on WOMAC-assessed pain intensity as primary endpoint, both compared to baseline and to placebo. The FDA may also request that ATB-346 be compared to naproxen, but the agency does not normally request that experimental pain therapies be compared to an active study arm.

For comparison, we know through prior coverage that ON-based drug developer Nuvo Research (NRI-T, NR) eventually received FDA approval for DMSO-based diclofenac formulation Pennsaid 2% based on a 12-week 700-patient five-arm knee osteoarthritis trial completed back in FQ405 that did include oral diclofenac dosing in a distinct study arm, but that was unusual in comparison to more recent Phase III pain studies we reviewed and we do not believe that regulators (either the US FDA or the European EMA) will require a trial this complex or one that incorporates an active control into Antibe's future Phase III programs. Alternatively, hydrocodone formulation developer Zogenix (ZGNX-Q, NR) conducted two Phase III pain studies, one a 510-patient lower back pain trial completed in 2011 and a second 424-patient chronic pain trial completed in 2012, with both comparing Zogenix's experimental therapy (an extended-release acetaminophen-free hydrocodone formulation Zohydro ER) to placebo and not to alternative hydrocodone formulations. Zogenix's Phase III program is thus similar to the Phase III scenario for ATB-346 we describe above.

Exhibit 4 – Localisation of COX-1 and COX-2 in Gastric Epithelium in Patients with Gastric Ulcer



Source: Gut (2000). Vol. 47, pp. 762-770. Cyclooxygenase-1 (COX-1) staining in left panel; Cyclooxygenase-2 (COX-2) staining in right panel

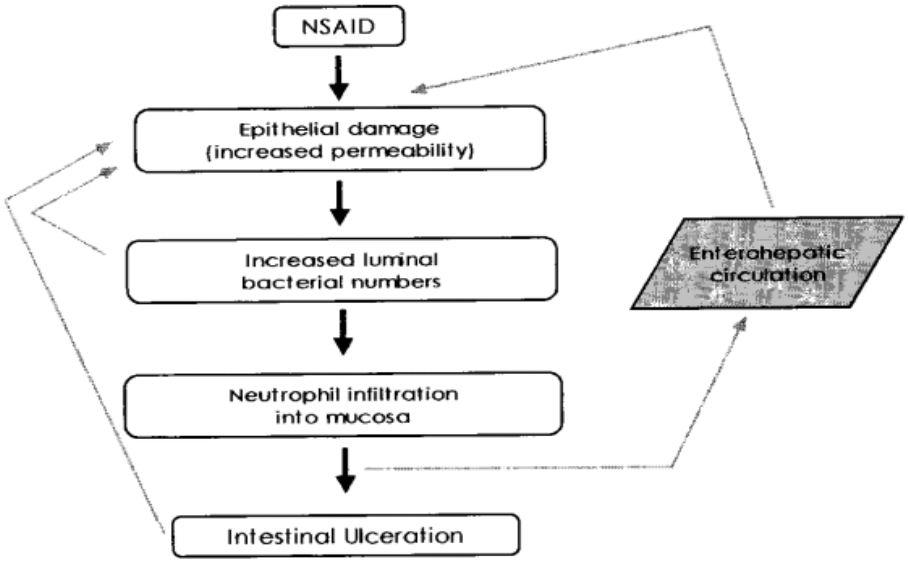
Recent warrant exercise provided substantial capital to fund new Phase II ATB-346 dose-ranging studies contemplated this year: Antibe substantially mitigated financial risk for new Phase II ATB-346 clinical studies described above through exercise of warrants ascribed to previous unit offerings consummated in F2017/18, a summary of which Antibe provided in its FQ318 MD&A and though dated, we will reproduce below to feature just where plausible source of warrant capital was derived. The key takeaway of course is that the firm now has $4M in new equity capital, bring pro forma cash to about $5M currently (FQ318 cash balance was $1.9M, and so the firm is telling us that FQ418 operating cash loss, likely from residual Phase II costs from the now-completed 244-patient GI ulceration rate trial, was about $0.9M). Cash to this level is sufficient to fund a new Phase II dose-ranging study as described above, for which cumulative costs to date are projected by Antibe at $2.6M.

In a separate transaction that substantially reduced outstanding debt, all convertible debt ($3.0M) on the balance sheet was separately converted to common shares, adding 13.9M shares in the process (conversion price was $0.22). In its Apr/18 investor presentation, Antibe stated that current basic S/O is 199M, obviously derived from considering 163M S/O at the end of FQ318, full conversion to shares of convertible debt (13.9M new shares as described above), and by inference, conversion of about 22M warrants to shares. Antibe did not specify which warrants were converted to shares, but if we assume that all warrants that expired this year were converted, a reasonable assumption when considering average exercise price in comparison to current price level, we would calculate total new shares of 23.6M and total cash generated on conversion of $4.2M. We suspect that the delta between the 22M shares now added to capital structure and $4.0M raised is in warrants that expire in late Dec/18 ($0.22 exercise price).

Antibe indicated in its updated Apr/18 investor presentation that there are now 38M warrants outstanding (were 59.3M at end of FQ318), and so when considering this, the 13.9M new shares from debt conversion and 21.0M outstanding options that we will assume are unchanged as published in the FQ318 MD&A, we calculate fully-diluted shares outstanding of about 257.2M. Actual fully-diluted shares outstanding, after considering partial exercise of warrants ascribed to convertible debt and errors due to rounding data indicated above, is now 259.5M and we will

use fully-diluted shares as the basis for our share-based forecasts. Former debt partner Knight Therapeutics (GUD-T, NR) holds marketing rights for Antibe's small-molecule pipeline, not limited to ATB-346, but the relevant markets held by Knight (Canada, Israel, Russia, sub-Saharan Africa) would not be overly impactful on our financial forecasts anyway.

Exhibit 5 – Proposed Pathogenesis of NSAID-Induced Small Intestinal Injury



Source: Gastroenterology (1997). Vol. 112, pp. 1000-1016

Next steps in ATB-346 development should in our view drive through imminent Phase II dose-ranging testing and into pivotal Phase III knee osteoarthritis trials as early as C2019: In summary, we are highly positive on the medical prospects for Antibe's full suite of hydrogen sulfide-releasing NSAID analog drugs and their potential for conferring GI-protective activity without sacrificing magnitude of pain relief, and in multiple pain markets not limited to knee osteoarthritis. But with capital markets expressing more profound caution on ATE valuation than we believe is warranted just based on ATB-346 Phase II GI ulceration rate data and thus on ATB-346's medical prospects alone, we will for now solely base our valuation on our projections for ATB-346 revenue/EBITDA potential and overall economics. We will as an initial thesis assume that most discretionary capital will be deployed to ATB-346 Phase II/III knee osteoarthritis testing once the 200-250-patient Phase II dose-ranging ATB-346 trial currently contemplated generates final data within the next three to four quarters. That said, we remain positive for how well ketoprofen-based ATB-352 and acetylsalicylic acid-based ATB-340 could perform in other acute/chronic pain markets, and both drugs provide substantial upside to our ATB-346-specific forecasts.

Several Phase III pain studies have been conducted by Antibe's peers that give us reference data for predicting clinical costs for driving ATB-346 to approval: There are many firms developing Phase III-stage knee osteoarthritis pain drugs, but many of them have diverse pipelines for which osteoarthritis-specific R&D expense is difficult to extract from financial statements. Examples include Regeneron (REGN-Q, NR)/Teva's Phase III anti-nerve growth factor biologic fasinumab (which by the way is being tested in a controlled Phase III knee osteoarthritis trial where naproxen is an active control therapy), Pfizer (PFE-NY, NR)/Eli Lilly's (LLY-NY, NR) own anti-NGF mAb tanezumab, and Mitsubishi Tanabe's (4508-JP, NR) own Phase III anti-NGF mAb drug MT-5547 (that all three are anti-NGF biologics is secondary, of course, to the fact that all three are being developed by firms that do not disclose clinical costs by product).

We know for example that Zogenix conducted two Phase III pain studies for its abuse-deterring hydrocodone formulation Zohydro ER, including a 510-patient chronic lower back pain study conducted in F2010/11 and a separate 424-patient chronic pain study conducted over a similar time period, and cumulative R&D expense in those two years was US$61.7M (the drug was FDA-approved in FQ413). Egalet's (EGLT-Q, NR) cumulative F2015/16 R&D expense while it was developing lead extended-release abuse-deterring morphine formulation Arymo ER was US$60.8M but it

had other products in the portfolio, including now-Phase III-stage oxycodone formulation Egalet-002 and another oxycodone formulation Oxaydo, among others, so R&D expense to that level was not specific to any one Phase III pain program. Another reference point for us is Collegiuim Pharmaceuticals (COLL-Q, NR), which received FDA approval for its abuse-deterring oxycodone drug Xtampza in FQ216 but for which cumulative R&D expense during F2013/14 when Xtrampza Phase III clinical activities would have been most robust were US$29.2M.

Exhibit 6 – Potential Adverse Effects of Long-Term PPI Treatment

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
Risk of fracture	Randomized trials, observational studies, systematic review and meta-analysis	Weak, OR < 2	Reduced calcium absorption in the duodenum and proximal jejunum as a consequence of achloridria
Hypomagnesaemia	Systematic review and meta-analysis of observational studies	Weak, OR < 2	Poorly defined (gastrointestinal malabsorption and renal wasting)
Vitamin B12 deficiency	Observational studies	Weak	Reduced acid-activated proteolytic digestion in the stomach related to reduced absorption
Dementia	Observational studies	Uncertain	High levels of amyloid-β and deposition of amyloid-β peptides in brains of animal models
Cardiovascular risk	Meta-analysis of observational studies and of RCT	Weak, OR < 2 for mortality and myocardial infarction (not significant when only RCT were included)	Competitive metabolism effect on cytochrome P450
Renal disease	Observational studies	Modest	Unclear (deposit of PPIs or their metabolites in the kidney's tubulo-interstitium stimulating immune response)
C. difficile infection	Meta-analysis of observational studies	Weak, OR < 2	Reduce gastric acidity may promote bacterial colonization in the GI tract
Pneumonia	Meta-analysis of observational studies, case–control studies	Weak, OR < 2	Potential micro-aspiration or translocation into the lungs from upper GI bacterial overgrowth
Fundic gland polyps	Observational studies	Consistent	Trophic effect of high gastrin levels on GI mucosa
Gastric cancer	Meta-analysis of observational studies	Uncertain, OR < 2 for gastric cancer, not significant for pre-neoplastic lesion	Possible synergic effect of PPI treatment and *Helicobacter pylori* infection
Colon cancer	Observational studies	No clear clinical association	Trophic effect of high gastrin levels on colon cancer cells *in vitro*

Source: Gastroenterology & Hepatology (2017). Vol. 32, pp. 1295-1302.

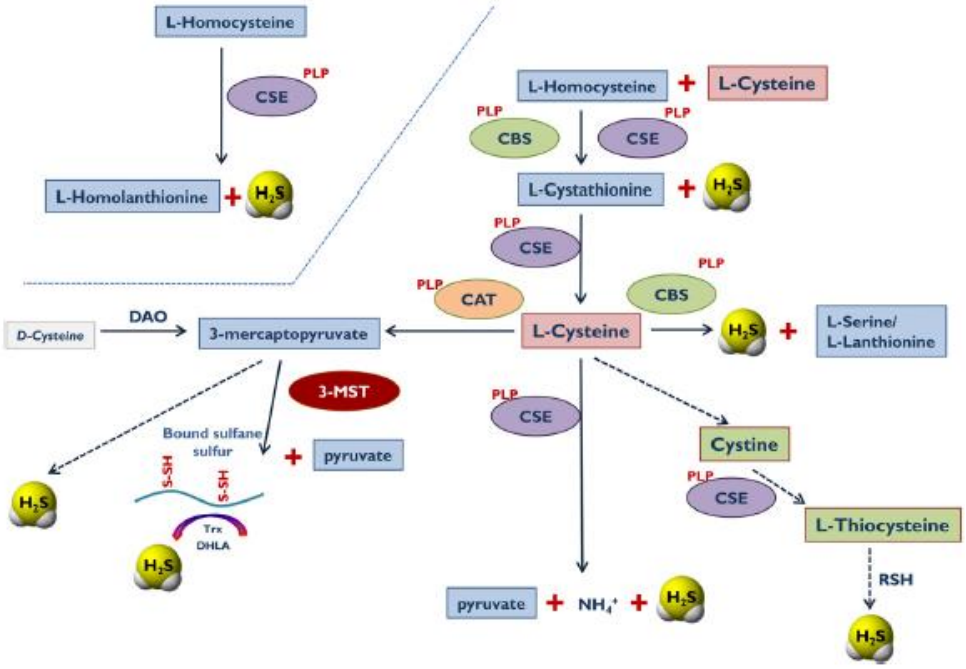
Our model will assume that future Phase III ATB-346 knee osteoarthritis studies could be funded through a combination of new equity and partnership capital: For another comparison, we know that MA-based hyaluronic acid supplement therapy Anika Therapeutics (ANIK-Q, NR) conducted Phase III testing for lead drug Cingal during F2017, commencing enrollment in a 576-patient Phase III knee osteoarthritis pain trial in FQ117 and completing enrollment in FQ417, and we know that the firm's R&D expense escalated from F2016 (US$10.7M) to F2017 (US$18.8M) and most of the delta was this trial. The trial still needs to conclude six-month follow-up by end-of-year,

thus the trial is undoubtedly still incurring clinical costs, but still infer that cumulative Phase III knee osteoarthritic costs for this one trial will exceed US$10M.

Our model will assume that Antibe can adequately fund two Phase III knee osteoarthritis studies (two placebo-controlled pain studies have been typically requested by the FDA to support new drug applications (NDAs) for novel pain therapies) for about US$25M ($30M) or so, though we will assume that cash-contributing partners can be identified after Phase II activities conclude to offset Antibe's own Phase III cash obligations. As shown in Exhibits 2 and 20, our model assumes that Antibe will generate royalty revenue for ATB-346 (and for ATB-352 [ketoprofen-based] and ATB-340 [acetylsalicylic acid-based] down the road) from future marketing partners, from which Antibe could receive royalties on net ATB-346 sales. Our model assumes that Antibe could partially fund ATB-346 Phase II/III development through new partnership capital but also through capital markets and our model will assume that capital raises in F2020/21 could be consummated at or near our one-year PT.

ATB-346 already has a strong profile in the medical literature even though it is still at a comparatively early stage of development. Most of the key insights into the drug's pharmacology are, predictably, published by University of Calgary researcher and Antibe Founder JL Wallace, but not exclusively as we will show. And even though ATB-346 has been a clinical-stage asset in Antibe's portfolio for many years now, many studies characterizing ATB-346's pharmacology and mechanism of action are quite recent, as we will describe.

Exhibit 7 – Hydrogen Sulfide Production Actually Occurs Non-Pharmacologically Through Several Distinct Pathways Originating with Sulfur-Containing Amino Acids



Source: Pharmacological Reviews (2017). Vol. 69, pp. 497-564.

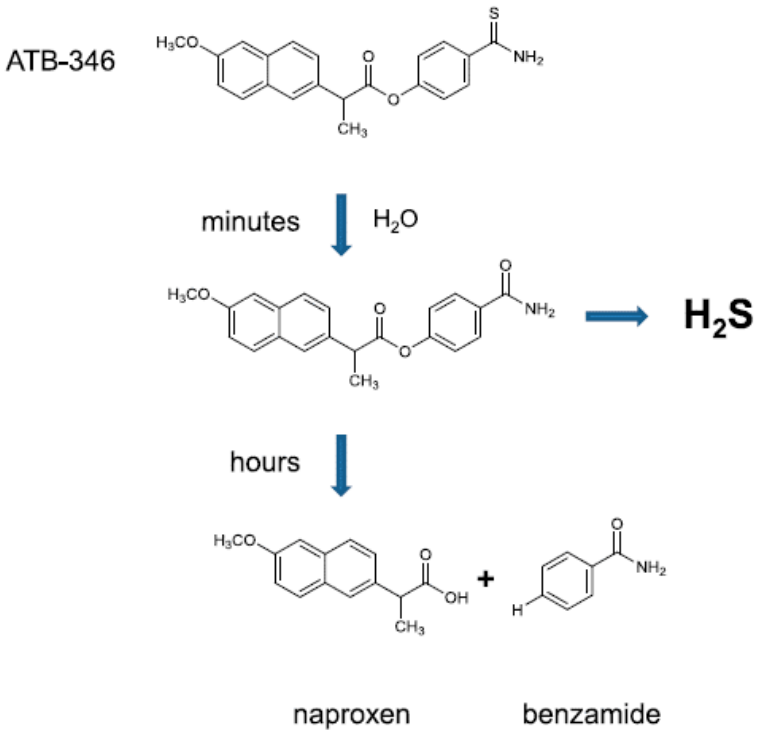
Of course, at this juncture in ATB-346's clinical history, clinical data actually demonstrating clinical benefit trumps preclinical/pharmacologic data predicting future clinical benefit, and we have obviously crossed that chasm (at least in part) through the GI ulceration rate data just reported. But still, pharmacologic underpinnings in support of clinical benefit are still useful to review and so below we summarize a few key characteristics of the drug that could be relevant to its medical prospects.

- **Preclinical data has long predicted ATB-346's gastro-protective activity:** For example, in a preclinical study published last year in the *Journal of Physiology & Pharmacology* that indirectly predicted ATB-346's impact on GI ulceration rate, University of Calgary researchers showed in a rodent model for gastric lesions (lesions are induced with a technique called water-immersion and restraint stress [WRS]) that ATB-346 (or alternatively,

naproxen co-administered with sodium hydrosulfide, a source of hydrogen sulfide when dissolved in water) generated far fewer gastric lesions than did naproxen itself at equivalent mole ratio dosage. Researchers separately showed that ATB-346 did not lead to production of all of the stress-induced pro-inflammatory cytokines that naproxen frequently does, such as various interleukins, interferon-gamma, or tumour necrosis factor-alpha, but it did upregulate anti-inflammatory markers like nuclear factor erythroid-derived 2)-like 2 [Nrf-2] or heme oxygenase-1 [HO-1], both known to be cyto-protective in ways that would be consistent with preserving gastric mucosa architecture and thus mitigate against lesion generation.

- **Other preclinical studies show potential for ATB-346 beyond pain management and into other inflammatory diseases:** A cellular assay study published by collaborators at the University of Naples and again the University of Calgary showed that ATB-346 could even be useful at inducing programmed cell death (apoptosis) in human melanoma cells, apparently through inhibiting pro-survival signalling pathways mitigated by the immune response cytokine NF-κB and through the Akt pathway, both relevant to multiple cancer forms and not just melanoma. Our model has no overt expectations that Antibe will fund any future melanoma testing (or any oncology testing at all), but we will watch for any academic advances that further de-risk any future oncology-focused programs that Antibe may choose to fund or out-license down the road.

Exhibit 8 – Non-Catalytic Hydrolysis Seems to Explain How ATB-346 Generates Hydrogen Sulfide in the GI Tract, and Benzamide Itself Could Have Cytoprotective Activity as Well



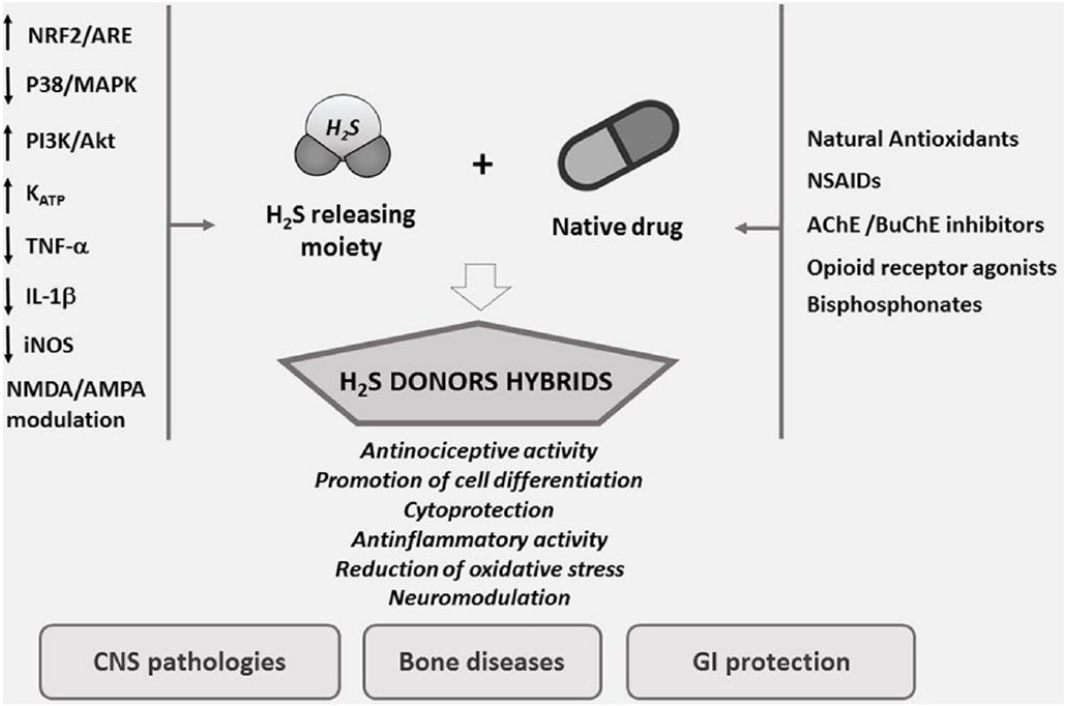
Source: Pharmacological Reviews (2017). Vol. 69, pp. 497-564.

- **And yet another set of preclinical studies show potential for ATB-346 for addressing inflammation in neurodegenerative disease:** A 2016 animal study published in the *Canadian Journal of Physiology & Pharmacology* by Alexandria University researchers showed that ATB-346 could also impact cognitive disorders by reducing the inflammation and oxidative stress associated with disease. Specifically, researchers used the glucosamine-nitrosourea alkylating agent streptozotocin to induce cognitive impairment in test animals (the drug is also toxic to pancreatic beta cells and is often used to induce diabetes in test animals), and almost without exception, ATB-346 was superior to naproxen itself at enhancing memory function in rat models as measured by the retention latency of passive avoidance task (the test measures whether or not test animals can learn to avoid

walking into a space with which an adverse event [electric shock grid] is associated) and by changes in biomarkers predicted to be associated with cognition, such as inflammation (lower interleukin-6 release) or neurotransmission (lower levels of the enzyme that breaks down the neurotransmitter acetylcholine in the hippocampus of test animals). As with melanoma above, cognitive disorders are not overly emphasized in our model either, but existing data is sufficiently compelling in our view to justify further academic study.

Antibe and collaborators showed that ATB-346's NSAID component and its hydrogen sulfide-releasing component need to be covalently linked together in one pharmacologic agent: As shown in Exhibit 1, it is fairly well-known from pharmacokinetic studies that ATB-346's thiocarbamoyl moiety (the part with the attached sulfur atom) converts fairly rapidly in water into an amide, replacing the sulfur atom with an oxygen atom from water, and creating hydrogen sulfide in the process. The naproxen-conjugated amide left behind does not on its own have any gastro-protective activity (Antibe checked this and published the findings before), and interestingly, if one were to alternatively co-administer naproxen itself with 4-hydroxy-thiobenzamide (basically ATB-346 but without the naproxen part and the sulfur-containing part chemically bonded together), one does not see any gastro-protection either, suggesting that spatial and temporal proximity of naproxen to hydrogen sulfide in the gut is essential to mitigate the GI lesions that naproxen would otherwise cause.

Exhibit 9 – Hydrogen Sulfide Release in Vivo has Long Been Recognized as Conferring Multiple Benefits for Multiple Therapies in Multiple Medical Markets



Source: Frontiers in Chemistry (2017). Vol. 5, pp. 1-7.

JL Wallace's group did in fact explore this possibility in the original 2010 paper in the *British Journal of Pharmacology* that described ATB-346 specifically (Wallace had described hydrogen sulfide's gastro-protective activity before, but the *BJP* paper was the first reveal on ATB-346's pharmacology that was published). The creation of hydrogen sulfide from ATB-346 does not appear to be enzymatically-driven. A separately interesting observation that makes ATB-346 chemistry even more relevant beyond its hydrogen sulfide-creating capabilities is that over longer periods of time, the drug breaks down into naproxen itself and benzamide (Exhibit 8) which appears to have its own cyto-protective and anti-inflammatory effects, possibly through inhibition of the enzyme poly(ADP-ribose) polymerase (PARP; interestingly, the same enzyme that is inhibited by AstraZeneca's [AZN-L, NR] olaparib/Lynparza, Clovis Oncology's [CLVS-Q, NR] rucaparib/Rubraca, and Tesaro's [TSRO-Q, NR] niraparib/Zejula).

We know of at least one other hydrogen sulfide-releasing acetylsalicylic acid formulation that has undergone rudimentary testing: The analog was code-named ACS14 and the hydrogen sulfide-releasing moiety is a cyclic sulfur-containing ring called a thioxodithiol instead of the thiocarbamoylphenyl group incorporated into ATB-346, and baseline characterization of this drug was published in 2014 in the journal *PLoS ONE* by University of Saskatchewan researchers (the paper demonstrated in cellular assays that ACS14 could reduce oxidative stress as quantified through attenuation of methylglyoxal and inducible nitric oxide synthase production). An earlier cellular study published by JiaoTong University researchers in 2012 in the *European Journal of Pharmacology*, showed therein that ACS14 could separately reduce inflammation by inhibiting interferon-induced migration of macrophages in ways that acetylsalicylic acid itself did not, presumably because of hydrogen sulfide release. But to our knowledge, this drug has not advanced into formal clinical testing.

Hydrogen sulfide's cyto-protective activity had been well-validated in other drug analogs as well, though ATB-346 is the most advanced clinical asset we have reviewed: We believe that ATB-346's now-documented ability to mitigate side effect profile for a market-leading branded pharmaceutical, in this case naproxen, expands potential for other hydrogen sulfide-releasing drug conjugates to advance into more substantive preclinical/clinical testing. The concept of hydrogen sulfide's cytoprotective activity has in fact been around for many years and the literature is well-populated by studies espousing its virtues, independent of Antibe or ATB-346 specifically. We observe with interest, for example, that hydrogen sulfide's potential to mitigate cardiac injury associated with anthracycline use in cancer chemotherapy has been well-studied and was summarized in a 2018 *Frontiers in Pharmacology* paper published by researchers at Beijing-based Capital Medical University. The review article cited no less than nine peer-reviewed studies that universally revealed that hydrogen sulfide exhibited protection against anthracycline-associated cardiotoxicity, which is still a major limiting factor in longer-term anthracycline use in cancer chemotherapy. Our model does not assume that Antibe will explore oncology applications for its hydrogen sulfide chemistry expertise, but we see clear upside to the platform if it chooses to work with partners on this theme.

Company History

Antibe has been focused on developing gastro-protective hydrogen sulfide-releasing NSAIDs throughout its corporate history: Antibe was formally incorporated as of May/09, and formally became Antibe Therapeutics Inc. as of Dec/09. In Jun/13, the firm went public on the TSX Venture Exchange, and pursued an OTCQX Exchange listing in Sep/14. The Company's present corporate structure sees shareholders owning 92.5% while Antibe Holdings (AH) owns 15.0M common shares, representing 7.5% of the Company's outstanding common share balance. The nuances of Antibe's corporate structure are not overly impactful on our scientifically/clinically-driven investment thesis but we offer details as background describing the entity driving clinical initiatives forward.

Of interest, AH has a material relationship with Antibe Therapeutics. Since 2009, AH has in place a patent relationship with Antibe Therapeutics. The two firms have in place an agreement that:

- Antibe Therapeutics will pay royalties of 4% to AH on all net sales upon first commercial sale;
- If a sublicense agreement is in place with Antibe Therapeutics, then the firm will pay 15% on royalty revenue earned;
- Apart from the patent agreement, AH is also a recipient of milestone payments at various points of Antibe's clinical development. AH will have the option to choose and receive the following:
    - The greater of $150,000 or 10% of any milestone payment from a sublicense upon enrollment of the first patient in the first Phase II trial, and likewise for the first Phase II and Phase III clinical trials initiated;
    - The greater of $250,000 or 10% of any milestone payment from a sublicense upon the filing of the first NDA;
    - The greater of $750,000 or 10% of any milestone payment from a sublicense upon the first regulatory registration authority.

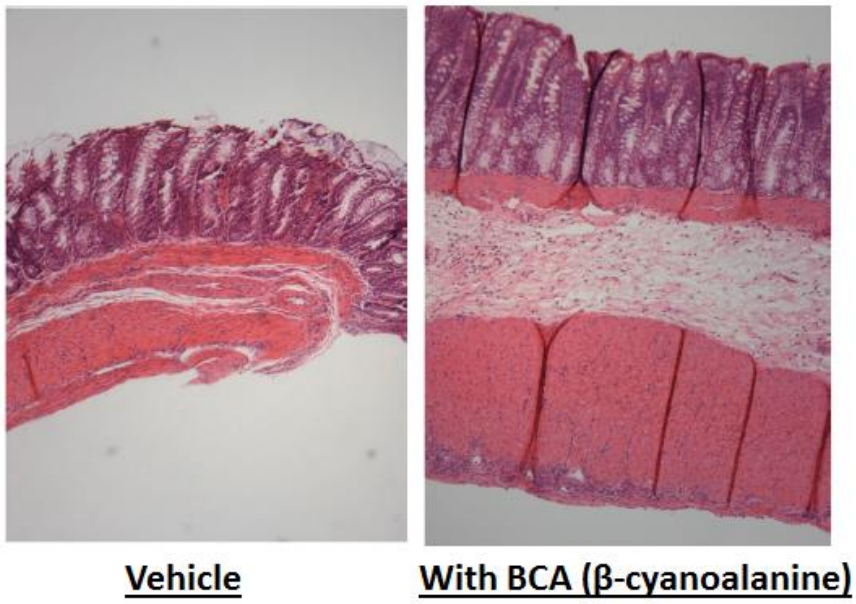
Insofar, only the milestone payments for the enrollment of the first patient in Phase I and Phase II clinical trials have been incurred. Given that there were no partnerships undertaken prior to both milestones, it would be safe to presume that $0.3M has been received by AH.

In 2015, the firm acquired Montreal-based Citagenix, cumulatively valued at $4.9M consisting of $0.4M in cash and the issuance of 25.9M ATE shares at $0.15/shr, as well as the issuance of an additional tranche of 2.9M ATE shares valued at $0.20/shr in Feb/16.

Backgrounder on NSAIDs – Still a Leading Pain Therapy Despite Well-Known GI Side Effects that ATB-346 can Overcome

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications for use in managing pain and inflammation across a number of conditions including osteoarthritis, gout, dental pain, and headache as examples. Commonly prescribed NSAIDs that readers might be familiar with include aspirin and ibuprofen (brand names: Motrin and Advil).

Exhibit 10 – Microscopic Appearance of Colitis-Induced Rats Treated with Vehicle (Control) or with β-cyanoalanine (an Inhibitor of CSE, and thus an Inhibitor of Hydrogen Sulfide)



Source: Gastroenterology (2009). Vol. 137, pp. 569–578

COX inhibition by NSAIDs are non-specific, leading to adverse effects. As explained by Ong and colleagues in a review published in *Clinical Medicine & Research* (2007), NSAIDs typically inhibit a prostaglandin (a type of lipid involved in the generation of inflammatory response) known as pro-inflammatory enzyme cyclooxygenase (COX). COX exists in two forms: COX-1 and COX-2, which serve different physiological functions. In *Prostaglandins & Other Lipid Mediators* (2002), Morita distinguishes the function of COX-1 and COX-2. COX-1 is expressed in most tissues and cells (including the gastrointestinal tract). COX-2, on the other hand, is particularly responsive to mediators of inflammation and found on most sites of inflammation. Of note, COX-1 levels do not change in the presence of inflammation, but COX-2 levels increase dramatically alongside prostaglandin production. The inverse shows COX-1 involved in the resolution of inflammation in ulcer healing.

As a class, the NSAIDs non-selectively inhibit COX-1 and COX-2, and selectively inhibit COX-2 inhibitors. While COX inhibition leads to efficacy in managing chronic or acute pain conditions, non-selective inhibition of COX can lead to deleterious effects on the GI system, given the inhibition of COX-1 in the gastric mucosa.

Of note, a study of COX-1 and COX-2 expression and localisation in the gastric mucosa was performed by Jackson and colleagues and published in *BMJ Gut* (2000). Researchers performed immunostaining on samples derived from 30 patients with histologically confirmed gastric ulcers (20 from gastrectomy, 10 from patients with active gastric ulcers at endoscopy). In patients with gastric ulcers, active inflammation was noted in all 30 samples, with COX-2 levels highly recorded in cells around the ulcer margin though no significant change in COX-1 levels were observed. In healthy epithelial cells surrounding the ulcer, lower COX-1 and COX-2 levels were found at 43% compared to levels found in normal tissue (COX-1 at 93% and COX-2 at 80%).

NSAIDs and gastric damage: In another review elucidated by Antibe's current Chief Scientific Officer John Wallace (*Gastroenterology* 1997), NSAID use goes beyond gastric damage, and could have implications for the small intestine and colon. In the case of the small intestine, NSAID use affects the small intestine differently from that of the stomach. Wallace proposes that NSAIDs create an increase in the permeability of the epithelium. The permeability allows plasma proteins to leak into the lumen, allowing luminal bacteria to flourish, resulting in the recruitment of neutrophils and exacerbating the inflammatory conditions in the small intestine, and ultimately leading to intestinal ulceration.

We also make reference to another study by Nippon Medical School researchers as published in *European Journal of Clinical Investigation* (2010 June) on the impact of NSAID use in healthy volunteers. 55 healthy male volunteers were recruited and then put on a NSAID regimen for 14 days alongside proton pump inhibitors. After 14 days, subjects were then evaluated via capsule endoscopy. Results indicated that the rate of mucosal lesions rose dramatically in subjects from baseline. Specifically, the rate in which mucosal lesions were detected rose from 11% (6 mucosal lesions in 6 subjects) to 60% (636 lesions in 32 subjects) in 53 evaluable subjects. The number of ulcers also increased to 23 in 8 subjects.

Common mitigation strategies are ineffective or considered too toxic. The adverse events range from an increased risk in developing peptic ulcers to serious upper GI complications such as hemorrhage (bleeding), perforation, and obstruction.

Although therapies that were COX-1 sparing and highly selective for COX-2 inhibition did emerge, cardiovascular risks involved with usage of such therapies were found later on. According to Hawkley in a review on NSAIDs published in *BMJ Gut* (2003), the risk of hospitalisation for GI complications associated with NSAID use is between 1.3 and 2.2 events per 1,000 patient years.

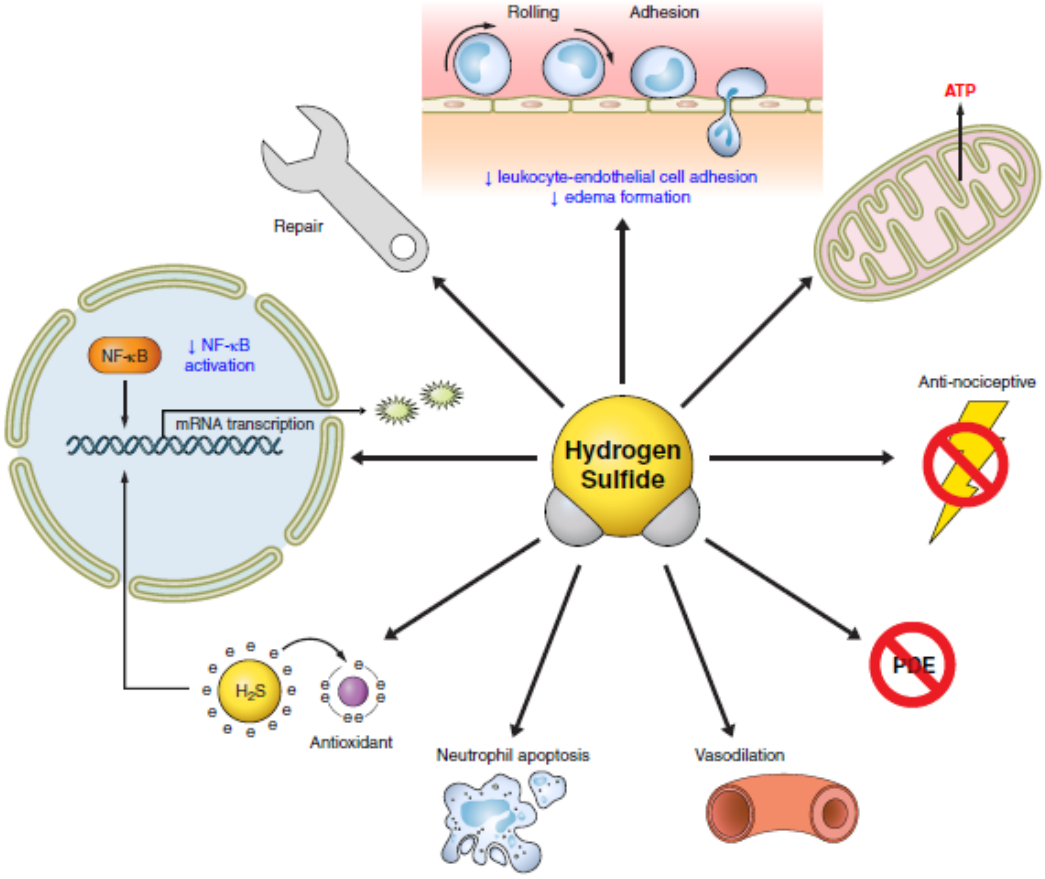
Notably, Merck's (MRK-NY, NR) COX-2 inhibitor rofecoxib (brand name: Vioxx) was taken off the market in 2004 following the outcome from the 2,586-patient APPROVe (Adenomatous Polyp Prevention on Vioxx) trial, in which the data safety monitoring board recommended the trial be stopped after observing that treated patients with a history of colorectal adenomas experienced an elevated risk for heart attack and stroke (46 patients in the treated group versus 26 patients in the placebo group). The observation was particularly evident in patients who were on the drug for more than 18 months.

Separately, another COX-2 inhibitor celecoxib (brand name: Celebrex) was able to remain on the market but only after a joint meeting with the Arthritis Advisory Committee and the Drug Safety & Risk Management Advisory Committee, which voted to allow the therapy to stay on the market. This also resulted in a change in Celebrex's label noting that Celebrex and all NSAIDs pose serious cardiovascular risks.

The risks imposed by Celebrex were then deemed to be in line with other NSAIDs following results from a 24,081-patient safety study known as the PRECISION (Prospective Randomized Evaluation of Celebrex Integrated Safety vs. Ibuprofen or Naproxen) trial that was conducted by Pfizer and published in *NEJM* (December 2016). Researchers Nissen and colleagues randomly assigned patients to be on a celecoxib, naproxen, or ibuprofen regimen. Results indicated that a primary outcome event (or first occurrence of an adverse event) occurring in the celecoxib group were marginally lower at 2.3% than the naproxen group at 2.5% and the ibuprofen group at 2.7%. The risk of GI events was considered lower with celecoxib than with naproxen or ibuprofen, although the risk of renal events was no different with Celebrex and naproxen. And while the study was able to demonstrate that celecoxib was similar in terms of safety compared to other common NSAIDs, researchers did note that higher doses of celecoxib in prior trials

did demonstrate a higher risk of cardiovascular events. Researchers also noted that adherence and retention were lower in most trials evaluating for cardiovascular outcomes. Although the study in this case implies that risks associated with Celebrex appear to be in line with that of other NSAID peers, it also does continue to highlight that the adverse GI and cardiovascular events associated with NSAIDs still persist.

Exhibit 11 – The Anti-Inflammatory Effects of Hydrogen Sulfide



Source: American Journal of Physiology & Gastroenterology (2013). Vol. 305, pp. G467–G473

In order to address the risk of developing NSAID-associated GI events, a co-therapy is often administered to mitigate such risks. In most cases, this involves the use of a proton pump inhibitor to inhibit acid secretion, with the explicit aim of promoting healing of NSAID-related gastric ulcers. However, risks associated with the long-term use of proton pump inhibitors are also increasingly becoming recognized by the scientific community, and thus hinder the opportunity for longer-term concomitant therapy with NSAIDs.

Of note, we refer to a paper published in *BMJ Gut* by researchers Cheung and colleagues. Researchers found that long-term use of proton pump inhibitors was associated with a doubling of risk of developing stomach cancer, despite *Helicobacter pylori* eradication therapy and with *H. pylori* absent during the course of PPI therapy. Findings were considered significant given that the bacteria is considered a cause of gastric cancer. Although only 0.24% of the 63,397 eligible patients developed gastric cancer, PPI use was nonetheless associated with an increase in gastric cancer.

To further develop this line of thought, we also refer to a review done by Eusebi and colleagues as published in the *Journal of Gastroenterology and Hepatology* (2017 June). Reviewers noted that proton pump inhibitor usage was increasingly being over-prescribed and inappropriately used, resulting with emerging evidence on a range of adverse effects with PPI therapy.

Other common mitigation strategies in place include the use of histamine H2-blockers to reduce the risk of developing dyspepsia in patients, although there still remains the underlying risk of developing serious GI bleeding. Another common strategy is the use of oral prostaglandins to prevent NSAID-associated peptic ulcer disease, but side effects also reduce its use.

Exhibit 12 – Antibe's Intellectual Property Strongly Covers ATB-346, its Composition-of-Matter & Methods of Use in Conferring Gastroprotective Pain Relief

Inventor(s)	Assignee	Issuance Date	Patent Number	Title	Description of Claims
Wallace, JL; Cirino G; Santagada V; Caliendo G	Antibe Holdings Inc. & Antibe Therapeutics Inc.	14-May-13 18-Nov-13 5-Dec-13 9-Jan-14 19-Aug-10 31-Mar-10 10-Dec-09 13-May-09 12-May-09 13-Apr-09	BR PI0714466 DK 2057139 PT 2057139 ES 2437223 US 20100210607 ZA 2009/00422 IL 196229 EP 2057139 MX MX/a/2009/000750 KR 1020090036115	Hydrogen Sulfide Derivatives Of Non-Steroidal Anti-Inflammatory Drugs	Derivatives of NSAIDs with improved anti-inflammatory properties for the treatment of inflammation, pain and fever; hydrogen sulfide-derivatized NSAIDs also produce anti-inflammatory compounds with reduced side effects
Wallace, JL; Cirino G; Caliendo G; Santagada V; Sparatore A; Fiorucci S	Antibe Therapeutics Inc.	2-Jun-11 28-Apr-11 21-Nov-11 22-Sep-09	US 20110130368 US 20110098257 ES 2368650 IL 196228	Derivatives of 4- or 5-aminosalicylic acid	Derivatives of 4- or 5-aminosalicylic acid aimed at the treatment of inflammatory bowel disease, and irritable bowel syndrome as well as the treatment/prevention of colon cancer; derivatives contain a hydrogen sulfide releasing moiety
Wallace, JL; Cirino G; Santagada V; Caliendo G	Antibe Therapeutics Inc.	16-Jun-11 4-Sep-12 22-Jul-09 3-Mar-09	US 20110144188 BR PI0712417 CN 101489986 KR 1.02009E+12	Salts Of Trimebutine And N-Desmethyl Trimebutine	Salts of trimebutine and N-monodesmethyl trimebutine which work to improve analgesic properties aimed at the treatment of visceral pain, particularly in abdominal pain
Wallace, JL; Cirino G; Santagada V; Caliendo G	Antibe Therapeutics Inc.	31-Mar-10 22-Jul-09 12-May-09 24-Apr-09 1-Apr-09	ZA 2009/00230 CN 101490029 MX MX/a/2009/000749 KR 1020090040428 EP 2041108	4-Hydroxythiobenzamide Derivatives Of Drugs	H2S-releasing moiety 4-hydroxythiobenzamide that is either covalently linked to a drug or forms a salt with S drug, which could both enhance activity and reduce side effects

Source: WIPO

Antibe's Lead Clinical Asset is ATB-346, for Which Technology-Validating Phase I/II Data are Already Available

Antibe's ATB-346 formulation is a hydrogen sulfide-releasing derivative of naproxen. The formulation aims to bypass a number of serious side effects involved with NSAIDs, namely that of GI events related to gastrointestinal ulceration and bleeding. While the therapy is currently being evaluated for safety, the firm ultimately hopes to advance this into indications related to chronic pain, including that of osteoarthritis and other related conditions in which NSAIDs are typically prescribed, including rheumatoid arthritis and ankylosing spondylitis.

By itself, naproxen is an orally ingested NSAID with analgesic and anti-inflammatory properties and commonly used in a number of arthritis conditions including osteoarthritis and rheumatoid arthritis. As we've discussed in the prior section, NSAIDs including naproxen are often accompanied with higher gastrointestinal risks.

Commonly, naproxen is available via OTC at a recommended dosage of 220mg per tablet every 8-12 hours, with a maximum dose of 660mg for up to 7 days of treatment. Higher doses (275mg and 550mg) are typically available by prescription.

Just to briefly reflect on the clinical evidence of naproxen and for comparison ATB-346, we note a review by Brigham and Women's Hospital researchers (published in *Osteoarthritis and Cartilage*; 24 (2016) 962-972) stated that median duration for NSAID treatment was typically 13 weeks, with the size of such treatment arms ranging from 25-481 subjects with a mean WOMAC (a measure that is typically employed as an endpoint of efficacy across most arthritis trials) baseline pain of 52 points. Median reduction along the WOMAC Pain scale was -18 points and was comparable to that achieved by opioids.

Hydrogen sulfide has dual roles in mediating gastrointestinal inflammation: The use of hydrogen sulfide as a gaseous mediator is thought to confer gastro-protective properties to overcome gastrointestinal effects associated with NSAID use. Its role is suggested in part from the observation that hydrogen sulfide is a gas that is connected to the gastrointestinal system, as per a review by Linden in *Antioxidants & Redox Signaling* (2014 Feb). The history of hydrogen sulfide was first systematically studied by Swedish chemist Carl Wilhelm Scheele in 1777, observing that hydrogen sulfide was generated copiously from the intestines after death despite being anaerobic. The biological origin of hydrogen sulfide gas was then solidified by Gayon when describing the ability of isolated bacteria to generate the gas from albuminous material, triggering a cascade of studies on the enzymatic production of hydrogen sulfide by intestinal bacteria.

However, Linden notes that in the case of intestinal inflammation, the role of hydrogen sulfide remains complex and at times contradictory. In extreme cases, it is currently proposed that luminal hydrogen sulfide is a causative factor for chronic intestinal inflammation, as well as in ulcerative colitis. On the other hand, studies performed using hydrogen sulfide outside the colon indicates an anti-inflammatory role for the gas. This role is documented across a number of animal studies including:

- Zanardo and colleagues in *FASEB journal* (2006) evaluated the role of hydrogen sulfide in inflammatory processes through a rat model. Researchers found that inducing fluid accumulation in the paw (edema; through carrageenan) was suppressed by hydrogen sulfide donors and enhanced by an inhibitor of hydrogen sulfide synthesis;
- Zayachkivska and colleagues in *PLoS One* (2014) evaluated the impact of hydrogen sulfide in rat model, wherein rats were fed with drinking water and fructose before being subjected to water-immersion stress to induce esophagitis (a condition mimicking acid reflux or gastroesophageal reflux disease), then evaluated for conditions with hydrogen sulfide inhibition or presence. Results indicated that treatment with hydrogen sulfide was able to mitigate the severity of esophageal injury and inflammation, while reducing inflammation (observed through the reduction of serum cytokine levels), and thus implying the role of hydrogen sulfide as a regulator of inflammation in the esophageal mucosa.

Among specific medical literature assessing the impact of NSAID-induced gastric injury, John Wallace is currently considered among one of the most prolific authors in the field. Herein we summarize a few of his notable studies.

- In a 2005 study published in *Gastroenterology*, Wallace and Fiorucci demonstrated that in rats where hydrogen sulfide was drastically reduced through the use of an inhibitor (indirectly; specifically by using a cystathionine-γ-lyase [CSE]-inhibitor known as DL-propargylglycine to reduce levels of hydrogen sulfide from the cardiovascular system), gastric mucosal injury was exacerbated by the oral administration of aspirin.
- Wallace further evaluated the impact of both endogenous and exogenous hydrogen sulfide through a 2009 paper published in *Gastroenterology* (2009;137:569–578). In the study, researchers chemically induced colitis in rats and assessed the ability of the colon to synthesize hydrogen sulfide as well as the residual effects once the two key hydrogen sulfide-related enzymes were inhibited. As with the prior paper published in 2005, researchers identified that the elevated levels of hydrogen sulfide observed in the inflamed colon were attributed to the enzyme CSE, as well as another enzyme known as CBS. By inhibiting these two enzymes, researchers noted that hydrogen sulfide synthesis declined in healthy colonic tissue by 50%, and greatly reduced in rats with colitis by 75-98%. Between the two enzymes, CBS was pinpointed as the major source of hydrogen sulfide under both conditions (healthy and inflamed colon). Our purpose here is not to point out which enzymes are implicated in hydrogen sulfide, but it is useful to know of hydrogen sulfide's dual functions in modulating the inflammatory conditions within the colon. Separately, researchers evaluated the impact in healthy rats to evaluate the GI impact on the absence of hydrogen sulfide. Healthy rats that were treated with a CSE inhibitor (to suppress hydrogen sulfide) were found to have inflammation in both the colon and small intestine.
- To further evaluate how hydrogen sulfide could potentially mediate the gastrointestinal environment, Chan and Wallace in the *American Journal of Physiology Gastrointestinal and Liver Physiology* (2013 Oct) provided a review

of how hydrogen sulfide confers its anti-inflammatory effects and regulates inflammation. Hydrogen sulfide of note can either exert pro-inflammatory or anti-inflammatory effects depending on the model or design, though researchers point out that a balance of the evidence presently point to hydrogen sulfide as exerting anti-inflammatory properties, along with a reduction in edema formation. In the GI mucosa, hydrogen sulfide is a vasodilator and contributes to mucosal defense by reducing the blood flow to the gastric mucosa caused by NSAID-induced gastric injury. Hydrogen sulfide was also demonstrated to aid in the healing of gastric and colonic ulcers as per animal studies. It is thought that hydrogen sulfide may help in enhancing mucosal blood flow to the ulcer margins and drive angiogenesis, a process needed for ulcer repair.

Prior clinical history: Early stage results appear to be in support of revised dosing regimen. Starting with prior animal studies, one of the more recent studies was published by Ianaro, Cirino and Wallace in *Pharmacological Research* (2016). In that study, mice were administered a carcinogen that developed into a form of cancer (known as aberrant crypt foci or ACF) that mimicked human colon cancer. Under those conditions, untreated mice will develop tumours. In this mice model, ATB-346 was able to demonstrate beneficial effects at lower doses than naproxen, at the same time being able to demonstrate a significant reduction in ACF at one-tenth of the minimally effective dose of naproxen. Physiologically, naproxen caused small intestinal damage and bleeding while ATB-346 did not.

Moving into formal clinical trials, a Phase I clinical trial initially hit a snag back in Jan/15 when the trial was suspended following observation of significant elevation of liver enzymes in subjects in both the highest (1,500mg) and higher dose (750mg) cohorts. Animal studies, such as the abovementioned study, did not demonstrate any signs of potential liver toxicity prior. Following a review of the trial data in Mar/15, management noted that dosing was the issue behind the observed elevation in liver enzyme levels, and thus moved forward with a much lower dose of 250mg.

At this dosage, the firm announced in Aug/15 that ATB-346 was found to be safe and well tolerated over a period of 14 days. In an *in vivo* study involving 600 blood samples from the Phase I trial, ATB-346 was able to markedly inhibit the COX enzyme (and also at doses as low as 75mg) and persisted for 24 hours after administration.

Following the adjustment to dosing, a 12-patient Phase II clinical trial in patients with knee osteoarthritis was carried out over the course of 10 days. Results confirmed the observation that the 250mg dose was safe. On efficacy, the WOMAC pain scale indicated a reduction of pain score of 4.3 units on day 4 and 7.6 units on day 10. In contrast, prior clinical evidence indicates twice daily NSAIDs typically reduce pain scores by 4 units over the course of a week or more, with no improvement beyond that level with continued treatment.

Interestingly, Wallace's University of Calgary team in collaboration with University of Naples researchers published in 2016 in the journal *Pharmacological Research* that ATB-346 was also effective as an anti-melanoma therapy, at least in *in vitro* cell culture assays. And as reported last month, we know that ATB-346 performed well on GI ulceration rate at a dose that we predict could be at or near that which could be effective at conferring approvable WOMAC-quantified pain relief in knee osteoarthritis. Confirmation of effective dose awaits pending Phase II dose-ranging studies currently contemplated by the firm.

Patent coverage: On patent coverage, our search on available patent documents note strong geographic coverage across four key patents in exhibit 12 above (for brevity, we provide a sample of such geographic coverage below, and not the full scope of the firm's patents). We did note that one of the key authors on Antibe's patents had a key relationship with a member of the board. Giuseppe Cirino, a published author on Antibe's patent, is noted to have conducted post-doctoral studies in the UK with Professor Rod Flower on a key mechanism of action on corticosteroids. Dr. Flower is also presently a director of Antibe. John Wallace, who is also named across all of Antibe's patents, is also on the firm's board, and as discussed earlier, is its Chief Scientific Officer.

ATB-352: An Analogous Hydrogen Sulfide-Releasing Ketoprofen Analog that has Strong Potential in Ketoprofen's Major Markets in Acute Pain

ATB-352 is a hydrogen sulfide-releasing derivative of ketoprofen, an NSAID that is prescribed for use in acute pain. According to a review by Italian researchers in *Reumatismo* (2010), ketoprofen works as an analgesic by inhibiting COX-1 and COX-2 enzymes as well, and is rapidly distributed into the central nervous system and passes the blood brain barrier within 15 minutes. Another property encouraging its use is good penetrability into the joint space. As such, ketoprofen is typically used in traumatic disorders, as well as orthopedic and rheumatic disorders. The review also concluded that pain relief between ketoprofen and opioid drugs was similar when evaluating studies on patients undergoing orthopedic surgery, implying a potential role in reducing reliance on opioid therapies and thereby reducing addiction that is typically associated with opioid therapies.

However, ketoprofen use is not without its limitations. In a review by Carbone and colleagues in the *Journal of Pharmacology & Pharmacotherapeutics* (2013 December), Italian researchers noted that ketoprofen has several known adverse events including cardiovascular reactions and gastrointestinal issues (vomiting and stomach bleeding). Researchers noted that the elderly are especially vulnerable to side effects from medications. In the review, it was noted that one of the common adverse events from ketoprofen use involved the digestive system (ulceration and bleeding). Since an adverse reaction can also cause a disease, a 'prescribing cascade' occurs in which a patient is prescribed a new drug to the existing regimen, which then adds to the risk of developing additional adverse events. Italian researchers noted that access to the drug is now limited, or completely withdrawn from the market.

Since the drug will be intended for use in acute pain, it would be useful to know the situations in which acute pain might be presented. In North America, acute pain is among the leading reasons for visiting emergency departments. In 2007, a study published by North American researchers Todd and colleagues in *The Journal of Pain* (2007 June, Vol 8 Issue 6, pp. 460-466) found that 83% of all cases assessed (equivalent to 842 patients) resulted in pain assessments (though prior literature indicated the figure was smaller at 78%).

At the same time, while looking at possible pharmacotherapies that might be deployed in acute pain situations, we note that the magnitude of opioid use in hospital visits for pain has increased over time. We refer to a 10-year study (2000 to 2010) published in the *American Journal of Emergency Medicine* (May 2014 Volume 32 (Issue5) Page, pp. 421-431) indicating that 45.4% of emergency department visits were associated with a primary symptom of pain or diagnosis of pain. Numerically, this translated into 35M visits in 2000 to 48.2M visits in 2010. At the same time, changes in patients presenting with severe pain increased from 25% to 40%. From 2000 to 2010, the number of patient visits for opioid treatment rose from 9.6M in 2000 to 23.6M in 2010, and non-opioid treatment raised marginally from 9.9M in 2000 to 10.4M in 2010.

As it remains early days for the therapy, clinical history of this asset remains limited. The most recent from Antibe's body of published data on ATB-352 is a study evaluating the impact of periodontitis in rats, published by Italian researchers in *Pharmacological Research* (2017 December 26, pii: S1043-6618(17)30990-8). On the study, rats were induced with periodontal disease using a lipopolysaccharide injection. Following the induction of the disease, rats were then treated with ATB-352, in which treatment with the therapy was able to demonstrate a reduction in the inflammatory process, and also exert positive effects on damage associated with the disease, primarily in bone resorption and tissue damage.

At last update in Apr/17, the firm confirmed that preclinical studies are now under way to advance ATB-352 into formal clinical trials. Animal data just published last year in *Pharmacological Research* by scientific founder and University of Calgary researcher JL Wallace & his collaborators at the University of Messina showed that ATB-352 could also be effective in mitigating symptoms of periodontitis, specifically on reducing associated inflammation arising from up-regulation of pro-inflammatory markers in this model (disease was induced by injection of bacterial lipopolysaccharide).

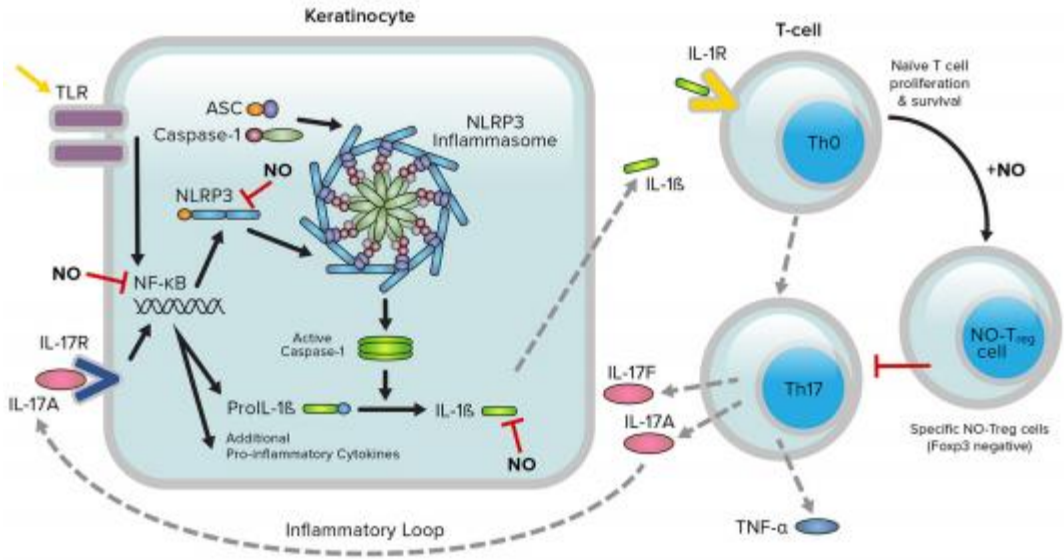
ATB-340: A Hydrogen Sulfide-Releasing Acetylsalicylic Acid Analog with Strong Cardio-Protective Activity, but with Potential to Confer Superior GI Side Effect Profile

Also following the same line of hydrogen sulfide-releasing range of therapies, ATB-340 is a hydrogen sulfide-releasing low-dose aspirin. The therapy is expected to be deployed as a preventative therapy, as it relates to the prevention of cardiovascular disease and cancer chemoprotection.

Given that aspirin is also an NSAID, the propensity of developing gastrointestinal adverse events is notably heightened as well. We won't go into too much detail here, but already a review of literature published by Lanas in *Current Medical Research and Opinions* (2007 Jan;23(1):163-73) indicated that the risk of developing upper GI complications was elevated when on prophylactic low-dose aspirin. While protective measures such as the use of proton pump inhibitors or eradication of *H. pylori* appeared to reduce the risk of such side effects, there appears to be no other credible and safer alternatives to aspirin prophylaxis. In a more recent update by Lanas in 2015 and published in *Current Pharmaceutical Design* (2015;21(35):5094-100), researchers noted that low dose aspirin not only affects the upper GI tract as per his prior review, and with newer endoscopic techniques, have demonstrated that low-dose aspirin also is liable in developing lesions in the lower GI tract. Lanas again cautions the full withdrawal of low-dose aspirin as risks of cardiovascular or cerebrovascular morbidity/mortality might be heightened.

In the US, a paper published by Stuntz and Bernstein in *Preventative Medicine Reports* (2017 Mar; 5: 183–186) indicated that self-reported low-dose aspirin use was noted by 23.3% of 90,558 respondents, primarily as it relates to cardiovascular prevention. At the same time, aspirin use for the purpose of cardiovascular protection has been on a slight decline, decreasing from 32.6% to 30.0% in the 2012 to 2015 timeframe. Of note, as well aspirin use was highest in the population aged 65 years and older. At present, we have not identified any recent press coverage on bringing ATB-340 forward in the clinical pipeline.

Exhibit 13 – SB204 Mechanism of Action



Source: Thiboutot et al, "Assessment of Pharmacokinetics and Safety of Investigational Nitric Oxide-Releasing SB204 Gel in Adolescents With Acne Vulgaris", World Congress of Pediatric Dermatology (2017)

Competitive Landscape

Peer Analysis: Treatments Incorporating Gaseous Mediators

Publicly listed drug development firms focused on advancing gaseous mediators within their respective pipelines are currently few and far between in the space. Insights available were predominantly garnered from two notable firms, primarily with nitric oxide-releasing therapies. We find parallels to use with hydrogen sulfide-releasing therapies in part because of several diseases that have been implicated in the deficiency or absence of nitric oxide.

NicOx S.A

French firm NicOx S.A (COX-EU, NR) is among one of the more established names in terms of gaseous mediators, and of which John Wallace was a co-founder of this company. The firm and licensing partner Bausch + Lomb/Valeant (VRX-T, NR) recently achieved approval for the nitric oxide-donating prostaglandin F2-alpha analog ophthalmic solution formulation latanoprostene bunod (commercial name: Vyzulta) in Nov/17.

The two firms have been partners since 2010, working on the then-known PF-03187207/NCX 116 with the aim of receiving approval in patients with primary open-angle glaucoma and ocular hypertension. Under the original terms of the agreement, NicOx would receive an upfront payment of US$10M, and milestone payments valued in total at US$169.5M. Previously, NCX 116 was partnered with Pfizer, which terminated the agreement after the therapy failed mid stage trials back in 2009. With the recent regulatory approval, Pfizer was still eligible for a US$15M payment. NicOx announced in Mar/18 that terms with Bausch + Lomb were recently amended on more favourable terms, which will see NicOx receive royalties of 10-16% in four tiers (previously 10-15%) depending on net sales, as well as potential milestone payments increasing by US$20M to US$165M (from US$145M previously).

Bausch + Lomb/Valeant experienced two complete response letters relating to manufacturing issues prior to achieving approval of Vyzulta. Thus, Vyzulta represents the first approved product for the firm. Previously, NicOx's pipeline had other nitric-oxide releasing therapies that saw development discontinued following failure during clinical trials. Of note, NicOx's HCT 3012/naproxcinod entered three Phase III trials aimed at the treatment of knee osteoarthritis. In 2010, the drug failed to garner support during the Arthritis Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee meeting, on the basis that sufficient evidence was not available at that time to support approval of naproxcinod for the relief of signs and symptoms of osteoarthritis, and ahead of the firm's PDUFA date in Jul/10. Ultimately, the drug failed to receive formal approval, on the grounds that additional data be conducted to assess cardiovascular and gastrointestinal safety of the therapy. In 2012, the firm announced the decision to shelve development plans for naproxcinod at least until a formal partner has been identified. Three years later, NicOx formally licensed naproxcinod to Fera Pharmaceuticals (Private) in a US$35M transaction as of Nov/15. NicOx will additionally be eligible for 7% royalties on net sales in the US. Fera will re-focus on developing the therapy for its original indication in the signs and symptoms of osteoarthritis.

Novan

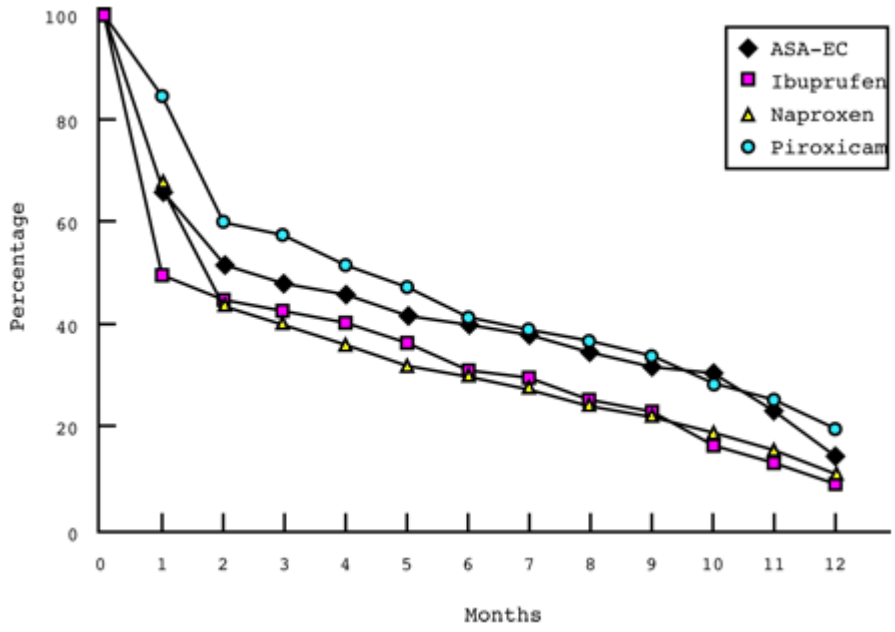
While not only focusing on the treatment of osteoarthritis, Novan (NOVN-Q, NR) is also focusing on nitric oxide applications, albeit in the dermatology front. Within the firm's broader pipeline, the partnered topical nitric-oxide releasing gel formulation of SB204 is advancing through Phase III trials. SB204 stores nitric oxide within the polymer backbone of a polysiloxane macromolecule (which the firm and its respective researchers coin as NVN1000). The mechanism of action is thought to target *Propionibacterium acne* (as its namesake indicates, it refers to the bacteria that is implicated in the pathology of acne) through the inhibition of an inflammatory signal (the NLRP3 inflammasome) which decreases the downstream cascade of other inflammatory recruiting signals (IL-1β and IL-17).

As of Nov/17, the firm announced that an undisclosed third party will take over SB204's remaining clinical development and potentially establish a new entity in order to advance and market SB204 globally (ex-Japan where Novan is partnered with Sato Pharmaceutical (Private) in that geography through a US$11M transaction), though financial terms were not disclosed.

Sulfagenix

Hydrogen sulfide-releasing pharmacology is manifested in at least one other clinical-stage asset in heart failure-targeted SG1002: Antibe has one peer firm, the private OH-based drug developer Sulfagenix, which features a sodium polysulthionate formulation SG1002 in its pipeline that is being developed as a heart failure (HF) therapy and for which a 50-patient Phase II placebo-controlled study is pending. The drug is actually already sold as a medical food under the brand Sulfzix. Data from an exploratory 15-patient Phase I/II SG1002 study are already available and published by Sulfagenix and collaborators at LSU Health Sciences Center back in 2015 in the journal *Cardiovascular Therapeutics*, showing therein that gas chromatographically-confirmed increases in serum hydrogen sulfide were apparent in SG1002-treated HF subjects and this was correlated in a dose-dependent fashion with simultaneous reduction in serum levels of the stress-responsive peptide brain natriuretic peptide (BNP). Interestingly, John Wallace has featured SG1002 in review articles on hydrogen sulfide pharmacology. But we see no evidence that Sulfagenix is advancing SG1002 into more comprehensive Phase II heart failure testing, and regardless, heart failure is not a medical market to which we ascribe value for any of Antibe's hydrogen sulfide-releasing small-molecule pain therapies.

Exhibit 14 – Discontinuation Rates of Four Oral NSAIDs Over a Twelve-month Period



Source: Annals of the Rheumatic Diseases (2002). Vol. 61, pp. 767-773.

Preclinical/Laboratory-Stage Hydrogen Sulfide-Releasing Drugs

Independent of SG1002 (and ATB-346, of course), there have actually been quite a few hydrogen sulfide-releasing analog drugs that have been described in the medical literature, many of which were described in a 2017 *Frontiers in Chemistry* review we surveyed. Most of these are not in active clinical testing and thus are not overly relevant to our ATE valuation, but they collectively give us confidence that the medical benefits of *in vivo* hydrogen sulfide release are well-documented and well-established. A few examples of other hydrogen sulfide-releasing drug candidates on which data were published include the following.

SDSS: A dithiolethione-derivatized form of the hydroxypropionic acid drug Danshensu, this agent was described as recently as last year in the journal *Frontiers in Pharmacology*, with that paper from researchers in China and Singapore showing protection of osteoblasts (bone-forming cells) from oxidative stress-induced programmed cell death (apoptosis), and researchers were careful to show that hydrogen sulfide was indeed released from SDSS and that its non-derivatized parent drug Danshensu did not have the cyto-protective activity that SDSS did.

S-diclofenac: A dithiol-thione derivative of the long-ago approved NSAID diclofenac (Novartis' Voltaren, and the active drug in Nuvo Research's Pennsaid 2% marketed in the US by Horizon Pharma) was actually one of the earlier hydrogen sulfide-releasing NSAIDs to be characterized in the medical literature, dating back in our analysis to 2007 in a paper published by National University of Singapore researchers in *Free Radical Biology & Medicine*. Baseline characteristics of S-diclofenac were certainly positive, with S-diclofenac showing all of the anti-inflammatory activity that diclofenac itself confers (the actual studies showing this used bacterial endotoxin/lipopolysaccharide to induce endotoxic shock in test animals) with fewer gastric lesions apparent in S-diclofenac-treated animals.

Several S-diclofenac studies have been published since by various groups, including a 2012 *British Journal of Pharmacology* paper from European researchers reporting in breast cancer cell assays that the drug slowed down biochemical pathways that would otherwise drive bone breakdown by osteoclasts. And another relatively recent study we surveyed published in 2011 in the journal *PLoS ONE* by China-based researchers focused on how S-diclofenac mitigated cardiotoxicity caused by anthracycline drugs like doxorubicin in animal models (the proposed mechanism was that it slowed the down-regulation of gap junction proteins in the heart). But as with SDSS, we have not seen any clinical trials emerge from these academic findings. Regardless, our point here is to emphasize that hydrogen sulfide's medical utility has been well-recognized through many drug development efforts designed to exploit its properties, which initially gave us confidence that ATB-346 could reveal superior side effect profile to its parent drug naproxen, and that prediction has been borne out by new positive Phase II ulceration rate data.

Zopranol: An already approved anti-hypertensive angiotensin-converting enzyme (ACE) inhibitor drug sold in Europe by Menarini Group (Private) called zofenopril (branded either as Zopranol or in combination with hydrochlorothiazide as Zoprazide) is actually a prodrug of an active agent called zofenoprilat, and many studies have shown that as part of zofenoprilat's pharmacologic activity, it also releases hydrogen sulfide as one of the mechanisms by which it confers cardio-protective activity. The drug has two sulfur atoms in its structure, one of which is a thioester of benzoic acid that is cleaved in the body to release hydrogen sulfide. We will not expand on zofenopril any further other than to say that it is frequently featured in review articles in the medical literature as evidence of the pharmacologic benefits of *in vivo* hydrogen sulfide release and we thus see zofenopril's underlying chemistry as being supportive of Antibe's pipeline potential.

Peer Analysis: Osteoarthritis Treatments

Current experimental therapies targeting osteoarthritis range in diverse modalities and treatment approaches. We provide a number of highlights below.

Regeneron

Regeneron and partner Teva's fasinumab is an anti-nerve growth factor (NGF) mAb that aims to modulate pain in patients with osteoarthritis. On the mechanism of action, Chang and colleagues note in the *Journal of Pain Research* (2016) that inhibition of NGF prevents binding to a tyrosine kinase receptor known as tropomyosin-related kinase A (trkA) and decreases the sensitivity to pain. NGF levels are notably elevated in multiple chronic pain conditions and a review of clinical data indicates fasinumab is presently under clinical hold.

Purdue/Shionogi

Purdue (Private) and Shionogi (4507-JP, NR) have partnered to develop an analgesic agent V-120083/S-120083 aimed at the treatment of moderate-to-severe chronic pain in patients with knee osteoarthritis. Most recently, the asset completed a 276-patient Phase II trial, although additional details on the asset or its future clinical status have yet to be disclosed.

Bone Therapeutics

Belgium-based Bone Therapeutics (BOTHE-EU, NR) focuses on the treatment of osteoarthritis through the firm's injectable visco-antalgic product JTA-004. The therapy aims to mimic the effect of synovial fluid, and thereby restore function by lubricating the knees, as well as reducing local inflammation. This form of therapy is known as viscosupplementation, where lubricating substances (generally hyaluronic acid) are locally injected into the knee. It is

hypothesized that such substances can reduce the impact of joint friction, thereby improving function and ultimately reducing the pain experienced with knee osteoarthritis. Treatment via viscosupplementation remains controversial, with mixed support given the disparity in treatment efficacy observed by physicians.

Presently, JTA-004 is being evaluated in a four-arm 164-patient Phase II/III trial, with topline data expected by Sep/18. The primary endpoint of the trial will evaluate the change in pain score (as measured by the WOMAC VA3.1 pain subscale score) at month 6, against an undisclosed reference product (likely Sanofi's [SAN-EU, NR] hyaluronan-derivative hylan-based injection Synvisc or Fidia Pharma's [Private] hyaluronic acid injection Hylagan).

Taiwan Liposome Company

Taiwanese firm Taiwan Liposome Company (4152-TW, NR) is a lipid nanoparticle firm whose BioSeizer platform deploys multi-layer lipid membranes encapsulated around therapeutically active molecules, and are designed to release the active ingredient/drug over a sustained period. In osteoarthritis, the firm's TLC599 is a lipid encapsulated formulation of dexamethasone sodium phosphate, and is designed to provide pain management in the disease over three months or more. The therapy is delivered locally through a microneedle that penetrates small joints. TLC599 is a Phase II stage asset, and currently in a 77-patient three-arm (12mg and 18mg formulations, respectively, while placebo is normal saline) Phase II trial with data expected by Aug/18. The primary endpoint will evaluate for changes in the WOMAC pain sub-scale score at week 12 from baseline.

Previously results from a 40-patient Phase I/II trial were reported in Jan/17. Results indicated that the patients treated with the 12mg dose were able to demonstrate a decrease from baseline regarding the Visual Analogue Scale (VAS) by a -3.14 point mean change at each study evaluation period (weeks 1, 4, 8 and 12). As well, a reduction in VAS was observed in the 6mg arm, although mean change was -1.95 points. On the WOMAC scale, the 12mg/6mg arms reported a mean change of -3.57/-1.5 points, respectively.

Ampio Pharmaceuticals

Taking more of a biologic approach as it relates to the treatment of pain due to knee osteoarthritis, Ampio Pharmaceuticals' (AMPE-NYSE, NR) Ampion is an intra-articular injection of low molecular weight fraction of human serum albumin. The therapy last completed pivotal Phase III testing back in Dec/17, with results reported in that period as well. Specifically, the therapy was able to realize the primary endpoint of meeting the OMERACT-OARSI responder criteria at 71% of Ampion treated patients (versus the threshold of 30% as a consideration of meaningful treatment). The firm recently disclosed plans in Apr/18 to submit a BLA for the therapy, with discussions with the FDA currently under way prior to submission.

On other scales, the therapy was able to demonstrate a 53% decrease in pain along the WOMAC A scale, and 50% improvement on the WOMAC C scale, as well as a 45% improvement in quality of life as measured by the Patient Global Assessment (PGA). On secondary endpoints, the therapy was able to demonstrate significance in a composite endpoint of pain and function at 12 weeks from baseline. A fuller and more detailed analysis of the trial is expected in the near term as well, at an undisclosed scientific meeting.

Exhibit 15 – Derivation of ATB-346 Peak Market Potential Just in Osteoarthritis Alone

	2016A	2017A	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
Current Population, United States (M)	323.1	325.4	327.6	329.9	332.2	334.6	336.9	339.3	341.6	344.0	346.4
Proportion, Doctor-diagnosed arthritis (M)	73.3	73.9	74.4	74.9	75.4	75.9	76.5	77.0	77.6	78.1	78.6
Proportion, with Osteoarthritis (M)	43.0	43.3	43.6	43.9	44.2	44.6	44.9	45.2	45.5	45.8	46.1
Proportion, risk of failing NSAID regimen (M)	36.6	36.8	37.1	37.3	37.6	37.9	38.1	38.4	38.7	38.9	39.2
Target patient population, United States (M)	**36.6**	**36.8**	**37.1**	**37.3**	**37.6**	**37.9**	**38.1**	**38.4**	**38.7**	**38.9**	**39.2**
Pricing: Assume Annual Celebrex WAC (US$)	US$1,656	US$1,656	US$1,656	US$1,656	US$1,656	US$1,656	US$1,656	US$1,656	US$1,656	US$1,656	US$1,656
Est. Value of Target Medical Market (US$B)	**US$60.6**	**US$61.0**	**US$61.4**	**US$61.8**	**US$62.3**	**US$62.7**	**US$63.2**	**US$63.6**	**US$64.0**	**US$64.5**	**US$64.9**

Source: World Bank, United States Census Bureau, Hootman et al (2016), Cisternas et al (2016), Courtney et al (2002)

Sizing Up the Medical Market

According to Hootman and colleagues in *Arthritis & Rheumatology* (2016), 22.7% of the US population or 52.5M adults had doctor-diagnosed arthritis. It is estimated that this figure could increase by 49% to 78.4M by 2040. Osteoarthritis, which falls under the umbrella definition of arthritis, is the most common form of arthritis in the US, and is estimated to affect ~13.4% of US adults or 30.8M individuals, as estimated by Cisternas and colleagues in *Arthritis Care & Research* (2016). Obesity, age (over 65), and gender (female) tended to increase the risk of developing osteoarthritis. Our back-of-the-envelope calculations indicate that osteoarthritis cases contribute to ~58.7% of all arthritis cases diagnosed.

The OA Research Society International (OARSI) guidelines (2014) generally recommend that patients start off on a low-level analgesic (acetaminophen) first before considering NSAIDs. As pointed out by Courtney and colleagues in *Annals of the Rheumatic Diseases*, the availability of acetaminophen may mean that patients would have likely engaged in self-treatment before consulting a doctor. That said, NSAID discontinuation was found to be disconcertingly high, with only 10-15% of patients still on a NSAID regimen after 12 months.

Applying the abovementioned metrics as a means of gauging the size of the market, we found a potential pool of osteoarthritis patients at 39.2M by 2026. On pricing, we would consider pricing metrics to mirror closely to that of Pfizer's Celebrex. The drug has since experienced loss-of-exclusivity as well as the entry of generic competitors since 2014. Our focus thus will rely on the economics prior to generic entry. According to a presentation by Pharmacy Healthcare Solutions in which the 100mg formulation of Celebrex was discussed as a case, it was noted that Celebrex's wholesale acquisition cost (WAC) was $4.28/capsule (for interested readers, generic competition resulted in the decline in unit price to $1.30/capsule two months after generic entry). This was roughly consistent when compared to a separate Consumer Reports article sourcing Symphony data for Celebrex; a 30-day supply was ~US$138 (US$4.60/day) for the brand retail price. By applying Celebrex's pricing of US$138/month as an assumption for branded ATB-346, we value the market to grow to US$64.9B by 2026. A 1% market share capture in 2026 is the equivalent of US$649M in value.

Exhibit 16 – Comparable Companies for Antibe

Company	Curr	Sym	Shares out (M)	Share price 18-Apr	Mkt cap ($M) (curr)	Mkt cap ($M) (C$)	Ent val ($M) (curr)	Ent val ($M) (C$)	Status of lead program
Nitric Oxide peers									
Nicox S.A.	EUR	CXRX	29.6	€ 7.04	€ 208	$326	€ 243	$380	NCX 470 is a nitric oxide-donating bimatoprost analog aimed at the treatment of patients with open-angle glaucoma or ocular hypertension; IND submission in H118; previously the firm had a nitric oxide derivative of aspirin (NCX 4016) for the treatment of cancer pain but was later discontinued
Novan, Inc.	USD	NOVN	26.0	$3.17	$83	$104	$88	$111	SB206 is a topical nitric oxide releasing gel that is advanced in a 108-pt Phase II trial for the treatment of genital warts; the firm's other lead asset SB204 is pending an additional pivotal trial in acne vulgaris in Q118
Large-cap peers involved in osteoarthritis therapies									
Ono Pharmaceutical Co., Ltd.	JPY	4528	514.2	¥2,537.50	¥1,304,742	$15,370	$1,258,344	$14,823	ONO-4474 is a tropomyosin receptor kinase inhibitor currently in a 280-pt Phase II trial that was completed in early H118
Pfizer Inc.	USD	PFE	5,948.6	$36.49	$217,064	$274,284	$241,006	$304,537	Eli Lilly-partnered tanezumab is a nerve growth factor mAb aimed at the reduction of pain associated in patients with osteoarthritis of the knee; currently in a 810-pt Phase III trial with data expected in
Regeneron Pharmaceuticals, Inc.	USD	REGN	107.6	$321.39	$34,580	$43,696	$33,874	$42,803	Mitsubishi Tanabe/Teva-partnered Fasinumab/MT-5547 is an anti-Nerve Growth Factor fully human mAb aimed at the reduction of pain related to osteoarthritis, currently in parallel Phase III trials (3640-pt FACT OA1 and 2,700-FACTO OA2) with data expected in
Shionogi & Co., Ltd.	JPY	4507	314.4	¥5,550.00	¥1,744,677	$20,552	$1,564,180	$18,426	V120083 is a Purdue-partnered analgesic that completed a 276-pt Phase II moderate-to-severe chronic knee osteoarthritis pain trial (Jan/18); compared against naproxen and placebo
Vertex Pharmaceuticals Incorporated	USD	VRTX	254.9	$163.36	$41,637	$52,613	$40,169	$50,757	VX-150 is a Nav 1.8 sodium channel blocker; completed a 124-patient Phase II knee osteoarthritis trial in Jan/17, saw decrease of 0.8 units on WOMAC pain subscale
Average						**$58,135**		**$61,691**	
Antibe Therapeutics Inc.	**CAD**	**ATE**	**199.3**	**$0.48**	**$96**	**$96**	**$92**	**$92**	**ATB-346 is a hydrogen sulfide derivative of naproxen, currently in Phase II trials for the reduction of pain associated with osteoarthritis**

Source: Consensus data - CapitalIQ, descriptions and chart created by Echelon Wealth Partners

Exhibit 17 – Comparable Companies for Antibe

Company	Curr	Sym	Shares out (M)	Share price 18-Apr	Mkt cap ($M) (curr)	Mkt cap ($M) (C$)	Ent val ($M) (curr)	Ent val ($M) (C$)	Status of lead program
Osteoarthritis Pain/Chronic Pain									
Ampio Pharmaceuticals, Inc.	USD	AMPE	84.8	$3.03	$257	$325	$249	$314	AP-003-C/Ampion is an intra-articular injection, low molecular weight fraction of human serum albumin with the active in treatment of osteoarthritis pai; completed 125-pt Phase III trial in Dec/18
Anika Therapeutics, Inc.	USD	ANIK	14.7	$45.91	$677	$855	$520	$657	CINGAL is cross-linked viscoelastic hyaluronic acid, approved in Canada; US-based 576-pt Phase III trial comparing to Monovisc and Triamcinolone Hexacetonide is ongoing; data expected by Jun/18
Axsome Therapeutics, Inc.	USD	AXSM	25.5	$2.60	$66	$84	$42	$53	Disodium zoledronate tetrahydrate formulation AXS-02, an osteoclast inhibitor targeting knee osteoarthritis associated with bone marrow lesions; 346-pt Phase III trial completed in Sep/17
Bone Therapeutics SA	EUR	BOTHE	7.5	€ 7.64	€ 57	$89	€ 71	$111	JTA-004 is an injectable visco-antalgic product currently in a 164-pt Phase II/III trial in patients with symptomatic knee osteoarthritis, and compared against Ostenil Plus (a reference visco-supplement); data expected in
Camurus AB (publ)	SEK	CAMX	37.3	SEK 115	SEK 4,280	$645	SEK 3,965	$597	CAM2038 is a long-acting subcutaneous buprenorphine for the treatment of chronic pain
Collegium Pharmaceutical, Inc.	USD	COLL	33.0	$24.89	$822	$1,039	$705	$891	Abuse-deterring extended-release oxycodone Xtampza, based on DETERx wax-based microsphere tchnology, was FDA-approved in Q216; acquires rights to transmucosal fentanyl form Onsolis from BioDelivery Sciences also
Depomed, Inc.	USD	DEPO	63.5	$7.02	$446	$563	$945	$1,194	Commercial-stage drug delivery pain/CNS-focused; sells diclofenac form CAMBIA & extended-release tapentadol NYCYNTA ER; neuropathic pain drug cebranopadol in clinical testing
DURECT Corporation	USD	DRRX	153.3	$2.47	$379	$479	$362	$457	Diversified portfolio, not pain-focused, but oxycodone formulation RemoxyER based on Oradur platform; NDA resubmission in Q118. Post-operative pain drug SABER-bupivacaine failed in Phase III
Egalet Corporation	USD	EGLT	52.9	$0.67	$35	$45	$47	$59	Extended-release abuse-deterring morphine Arymo ER, oxycodone tablet Oxaydo & ketorolac tromethamine spray Sprix all FDA-approved; Guardian-formulated oxycodone Egalet-002 in Phase III lower back pain testing
Elite Pharmaceuticals, Inc.	USD	ELTP	791.5	$0.10	$76	$96	$86	$109	Extended-release abuse-deterring bead-based naloxone-containing opioid forms based on ART platform; ANDA for extended-release oxycodone filed in Q317; FQ318 sales were US$2.5M
Endo International plc	USD	ENDP	223.3	$5.74	$1,282	$1,620	$8,608	$10,877	Diversified pain portfolio that includes Lidoderm (lidocaine patch), Opana ER (oxymorphone), Percodan (oxycodone-aspirin), Percocet (oxycodone-acetaminophen), Voltaren Gel (diclofenac)
Flexion Therapeutics, Inc.	USD	FLXN	37.6	$26.36	$992	$1,253	$759	$959	Flexion's Zilretta received FDA approval in Oct/16 (non-opioid intra-articular triamcinolone acetonide formulation Zilretta) for knee osteoarthritis pain; pricing was estimated to be US$570/dose
Horizon Pharma Public Limited Company	USD	HZNP	165.0	$13.99	$2,308	$2,916	$3,458	$4,370	Sells Nuvo's topical DMSO-based diclofenac formulation Pennsaid 2% in US; also naproxen-esomeprazole form Vimovo & ibuprofen-famotidine form Duexis; 2017 net product sales US$1.06B
Mallinckrodt Public Limited Company	USD	MNK	86.4	$13.99	$1,209	$1,527	$6,682	$8,444	Diversified pharma firm with pain franchise, generic formulations of fentanyl, morphine, oxycodone, oxymorphone, hydromorphone; clinical pipeline iron-ically has few pain therapies in Phase I-III testing
Nektar Therapeutics	USD	NKTR	160.9	$92.54	$14,892	$18,817	$14,841	$18,753	NKTR-181 is mu-opioid agonist analgesic, completed Phase III SUMMIT trials (638 patients, either opioid-naïve and opioid experienced) for treating chronic low back pain or chronic non-cancer pain
Omeros Corporation	USD	OMER	48.3	$15.15	$732	$924	$732	$925	Diversified portfolio, but GPCR-targeted pipeline has pain candidates (MRGE); FDA-approved Omidria (phenylephrine-ketorolac intraocular solution) targets post-ocular surgery (cataract removal) pain
Orexo AB (publ)	SEK	ORX	34.7	SEK 38	SEK 1,331	$200	SEK 1,322	$199	Markets Abstral (sublingual fentanyl) for breakthrough cancer pain; acute pain drug OX51 and opioid dependence/pain drug OX382 in Phase I/II
Pacira Pharmaceuticals,	USD	PCRX	40.7	$35.70	$1,453	$1,837	$1,419	$1,793	DepoFoam liposome platform; lead drug is FDA-approved local anesthetic Exparel (injectible bupivacaine)
Taiwan Liposome Company, Ltd.	TWD	4152	56.2	TWD 110	TWD 6,182	$266	TWD 5,398	$233	TLC599 is a lipsome encapsulated steroid currently in a 72-pt Phase II trial aimed at the treatment of patients with osteoarthritis of the knee; data expected in Jul/18
Tetra Bio-Pharma Inc.	CAD	TBP	153.0	$0.73	$112	$112	$109	$109	Dronabinol XL/PPP002 is an Intelgenx-partnered buccally-absorbed THC formulation targeting chronic pain; Phase II trial initiated in Q118
Zogenix, Inc.	USD	ZGNX	35.0	$40.85	$1,429	$1,805	$1,135	$1,434	Lead is ZX008 (fenfluramine) in Dravet's disease & Lennox Gastaut Syndrome; legacy pain franchise (FDA-approved hydrocodone Zohydro ER) sold to Pernix in Q115 for US$100M plus US$283.5M milestones
Average						**$1,690**		**$2,502**	
Antibe Therapeutics Inc.	**CAD**	**ATE**	**199.3**	**$0.48**	**$96**	**$96**	**$92**	**$92**	**ATB-346 is a hydrogen sulfide derivative of naproxen, currently in Phase II trials for the reduction of pain associated with osteoarthritis**

Source: Consensus data – CapitalIQ, descriptions and chart created by Echelon Wealth Partners

Citagenix: Revenue-Generating Subsidiary Augments Near-Term Cash Flow

Antibe formally acquired Citagenix as a subsidiary in Oct/15 beginning first with an 85% stake in the company (and separately acquiring 100% of all preferred shares of Citagenix), and formally completing the transaction through the acquisition of the remaining 15% stake as of Feb/16.

At present, Citagenix is currently the sole revenue-generating division for the firm. Citagenix specialized in dental regenerative medicine through the sale of medical therapies and instruments. Within Citagenix's commercial portfolio, the firm mainly sells within three main product categories: bone graft substitutes, dental barrier membranes (to support and bone tissue regeneration), and surgical instruments. Publicly available research on Citagenix's slate on regenerative medicine products were generally sparse, but we did identify reviews in which Citagenix products were involved alongside its other peers.

Exhibit 18 – Commercially Available Resorbable Collagen Membranes

Commercial Product	Manufacturer	Ticker	Collagen Type	Collagen Source	Resorption Rate
Non-cross-linked collagen membrane					
CollaTape/CollaPlug/ CollaCote	Integra LifeSciences Corp	NasdaqGS:IART	Type I	Bovine tendon	10-14 days
Periogen	Collagen Corporation	Private; acq. by Inamed then by Allergan (AGN-NY,NR)	Type I & III	Bovine dermis	4-8 weeks
Bio-Guide	Geistlich	Private	Type I & III	Porcine skin	2-4 weeks
Tutodent	Tutogen Medical GmbH	NasdaqGS:RTIX (merged with Regeneration Biologics in 2008)	Type I	Bovine pericardium	8-16 weeks
Cross-linked collagen membrane					
OsseoGuard	Zimmer Biomet, Inc.	NYSE:ZBH	Type I	Bovine tendon	6-9 months
OsseoGuard Flex	Zimmer Biomet, Inc.	NYSE:ZBH	Type I & III	Bovine dermis	6-9 months
Ossix Plus	Datum Dental Ltd.	Private	Type I	Porcine tendon	4-6 months
BioMend	Zimmer Biomet, Inc.	NYSE:ZBH	Type I	Bovine tendon	8 weeks
BioMendExtend	Zimmer Biomet, Inc.	NYSE:ZBH	Type I	Bovine tendon	18 weeks
RCM6	ACE Surgical Supply Co. Inc.	Private	Type I	Bovine tendon	26-38 weeks
Mem-Lok	BioHorizons IPH, Inc.	NasdaqGS:HSIC (acq. by Henry Schein in 2013)	Type I	Bovine tendon	26-38 weeks
Neomem	**Citagenix Inc.**	**TSX:ATE (acq. by Antibe)**	**Type I**	**Bovine tendon**	**26-38 weeks**
OssGuide	Bioland	KOSDAQ:A052260	Type I	Porcine pericardium	6 months

Source: Modified from Wang et al, "Biodegradable Polymer Membranes Applied in Guided Bone/Tissue Regeneration: A Review", Polymers (2016 March)

- In one Dutch review by Stok and colleagues in *Bone & Joint Research* (2017 Jul), researchers compared Citagenix's Orthoblast against Grafton's demineralised bone matrix (DBM) for use as a bone graft extender across a number of different types of fractures (tibia, fibula, femur, humerus, forearm, and acetabulum). Fracture healing occurred in all Orthoblast-treated patients (100%) compared to 69% of Grafton-treated patients.
- A Chinese review by Wang and colleagues in *Polymers* (2016 March) notes that collagen-based membranes of which Citagenix's Neomem was included, had several properties that would encourage its use in guided tissue regeneration (GTR) and guided bone regeneration (GBR) applications. Among such properties include tissue integration, fast vascularization, and biodegradation without foreign-body reaction. While excellent in use for the aforementioned applications, there also remain other risks associated with use, including that of developing disease transmission from animal-derived collagen (Neomem is derived from bovine tendon) and the risks that usage could lead to greater susceptibility of infection as well. Aside from regenerative medicines, the firm does sell medical instruments that are not just focused on dental surgery, but also for applications in plastic surgery, general surgery, and veterinary surgery.

Exhibit 19 – Product Offerings by Citagenix

Product	Type	Application
Bone Graft Substitute		
C-Graft Putty C-Blast Putty DynaGraft-D DynaBlast PentOS OI Putty PentOS OI Flex PentOS OI Fill PentOS OI Sponge	Demineralized Bone Matrices ("DBMs")	• Periodontal defects • Implant site development • Coronal defects around • Immediate implants • Extraction site repair • Implant dehiscence defects • Sinus lift procedures • Moderate localized ridge defects • Sockets Preservation
Raptos Allograft	Irradiated bone particulates (cancellous, cortical and corticocancellous)	• Mineralized component in a composite graft • As a graft extender • Osseous defects
Eclipse Synthetic Granules	Synthetic resorbable bone substitute	• Ridge preservation • Extraction site repair • Sinus lifts • Ridge augmentation • Osseous defects • Periodontal defects
Barrier Membranes		
Neomem Neomem FlexPlus NeoGuarde	Resorbable collagen membrane (bovine derived) Resorbable collagen membrane (porcine derived)	• Guided tissue regeneration ("GTR") • Guided bone regeneration ("GBR")
NeoDerm	Accellular human dermis	• Replacement of inadequate tissue for the repair, reinforcement or supplemental support of soft tissue defects
DynaMatrix Plus	Extracellular matrix (porcine derived)	• Soft tissue remodeling & grafting • Soft tissue augmentation/bulking • Gingival recession
BioXclude	Alllograft amnion and chorion tissue	• Site preservation • Bony defects around teeth and implants • Ridge augmentation • Over block grafts and ridge splits • Covering the lateral window in sinus elevations • Mild gingival recession
Cytoplast Ti-250	Titanium-reinforced high-density PTFE membrane	• On-lay grafting in ridge augmentation procedures • GTR • Structural support when grafting 3 or 4-walled extraction sites
Other Products		
Neoplug / Neocote / Neotape	Collagen dental wound dressings (bovine derived)	• Collagen matrices engineered from highly purified Type 1 collagen • Thickness and pore structure allow fluid and blood absorption at the defect site
Cytoplast PTFE Suture	Soft monofiliant suture	• Ideal for dental bone grafting and implant procedures • Mono lament construction doesn't allow bacterial wicking into the surgical site
PeriAcryl	Cyanoacrylate tissue adhesive	• Fast drying butyl cyanoacrylate tissue adhesive with low viscosity • Displays hemostatic properties and a bacteriostatic action

Source: Historical Company Information – Antibe

Financial Summary

While the firm's main focus is the advancement of ATB-346 in the forefront, Antibe still relies on tangible revenue contribution from its Citagenix subsidiary. Citagenix began formally contributing revenues of $4.4M as at year-end F2016 (Mar/16). Gross margin was $2.4M/46.3%. As Citagenix previously operated as a private firm, we have little basis for comparison on past historic trends. We digress — a year forward, F2017 revenue was $9.1M representing double the growth in F2016, and with gross margin contribution of $3.9M/43.4% implying stability in gross margins. At the most recent quarterly financials, T9M Citagenix revenue reported in FQ318 (CQ417) was $6.3M and appears likely to be on track to meet or exceed F2017 revenue of that magnitude.

Exhibit 20 – Revenue Forecasts for Antibe

Year-end March 31 (C$, except per share data)	2017A	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
ATB-346, US												
Current Population, United States (M)	325.4	327.6	329.9	332.2	334.6	336.9	339.3	341.6	344.0	346.4	348.9	351.3
Proportion, Doctor-diagnosed arthritis (M)	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*
Proportion, with Osteoarthritis (M)	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*
Proportion, high risk of failing on NSAID regimen (M)	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*
Target patient population, United States (M)	**36.8**	**37.1**	**37.3**	**37.6**	**37.9**	**38.1**	**38.4**	**38.7**	**38.9**	**39.2**	**39.5**	**39.8**
Price per treatment, annually (US$)	$1,656	$1,656	$1,656	$1,656	$1,656	$1,656	$1,656	$1,656	$1,656	$1,656	$1,656	$1,656
Est. value of target medical market (US$M)	$60,991	$61,418	$61,847	$62,280	$62,716	$63,155	$63,597	$64,043	$64,491	$64,942	$65,397	$65,855
% Market Share	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.7%	1.0%	1.2%	1.4%
Gross revenue, ATB-346 (US$M)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	192.1	451.4	649.4	784.8	922.0
Gross revenue, ATB-346 (C$M)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$236.3	$555.3	$798.8	$965.3	$1,134.0
Royalty rate on gross sales (%)	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
ATB-346, royalty revenue, US (C$M)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$70.9**	**$166.6**	**$239.6**	**$289.6**	**$340.2**
ATB-346, Select EU/Middle Eastern Countries (EME)												
Current population, blended (M)	101.4	102.4	103.4	104.5	105.5	106.6	107.6	108.7	109.8	110.9	112.0	113.1
Proportion, Doctor-diagnosed arthritis (M)	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*	*23%*
Proportion, with Osteoarthritis (M)	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*
Proportion, high risk of failing on NSAID regimen (M)	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*
Target patient population, select EME countries (M)	**11.5**	**11.6**	**11.7**	**11.8**	**11.9**	**12.1**	**12.2**	**12.3**	**12.4**	**12.6**	**12.7**	**12.8**
Price per treatment, annually (€)	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325	€ 1,325
Est. value of target medical markets (€, M)	€ 15,207	€ 15,359	€ 15,512	€ 15,667	€ 15,824	€ 15,982	€ 16,142	€ 16,304	€ 16,467	€ 16,631	€ 16,798	€ 16,966
% Market Share	0%	0%	0%	0%	0%	0.0%	0.0%	0.0%	0.5%	0.8%	1.1%	1.2%
Gross revenue, ATB-346 (€, M)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	82.3	133.1	184.8	203.6
Gross revenue, ATB-346 (C$M)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$126.0	$203.6	$282.7	$311.5
Royalty rate from Laboratoires Acbel on gross sales (%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
ATB-346, royalty revenue, select EME (C$M)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$6.3**	**$10.2**	**$14.1**	**$15.6**
ATB-346 royalty revenue (C$M)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$70.9**	**$172.9**	**$249.8**	**$303.7**	**$355.8**

Source: Forecasts/estimates – Echelon Wealth Partners

Financial Forecasts

Revenues

Our revenue forecasts are split between growth for the Citagenix franchise and Antibe's ATB-346.

- On Citagenix, we currently forecast that annual revenue growth of 5% can be sustained throughout our forecast period, achieving annual sales of $13.7M by F2028 at 55% gross margin.
- On Antibe's ATB-346, beginning with the US, our forecasts were guided by the abovementioned market size metrics, and uses the same pricing and population metrics as noted above. We do expect that by time of approval (which we conservatively assume could transpire by FH124, with launch in FH224 by future partners) Antibe would have identified suitable distribution partners and so derive royalty revenue from ATB-346 at a rate of 30%, an aggressive but achievable royalty rate, in our view, if cash-contributing partners are identified during Phase III testing. In the first year of approval, F2024, we project ATB-346 to achieve royalty revenue of $70.9M, then increasing to $166.6M in F2024, and up to $239.6M in F2026; F2025 is the reference year in our EBITDA/EPS-based valuation methods, as we will describe below.

- Separately we contemplate the impact from the firm's regional partnership with Laboratoires Acbel (Private) as it relates to select geographies in Europe and the Middle East (specifically Greece, Romania, Serbia, Bulgaria, Albania, Algeria, and Jordan). The partnership entails a 5% royalty on net sales of the therapy over a period of 30 years. In our model, we apply similar metrics in deriving our target medical population while deploying the use of Celebrex pricing metrics denominated in Euros instead. We project ATB-346 to achieve relevant regulatory approval in F2025 and derive royalty revenue of $6.3M in the first year, increasing to $10.2M in F2026 and achieving peak annual royalties of $15.6M by F2028.
- There certainly remains upside to forecasts on advancement of Antibe's other pipeline initiatives, but given the relatively early stage of development (assets are predominantly in preclinical development), we will omit these assets from our forecasts, at least until further clinical progress is made with the other assets.

Exhibit 21 – Income Statement & Financial Forecast Data for Antibe

Year-end March 31 (C$, except per share data)	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
Revenue											
Product Sales, Citagenix	8,402,275	8,822,388	9,263,508	9,726,683	10,213,017	10,723,668	11,259,852	11,822,844	12,413,986	13,034,686	13,686,420
Royalty revenue, ATB-346	0	0	0	0	0	0	70,895,206	172,878,582	249,815,719	303,712,979	355,780,049
Total revenue	**$8,402,275**	**$8,822,388**	**$9,263,508**	**$9,726,683**	**$10,213,017**	**$10,723,668**	**$82,155,058**	**$184,701,426**	**$262,229,705**	**$316,747,664**	**$369,466,469**
Y/Y revenue growth(%)	*-7.2%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*666.1%*	*124.8%*	*42.0%*	*20.8%*	*16.6%*
Operating Expenses											
Cost of Sales, Citagenix	5,050,412	4,852,314	5,094,929	5,155,142	4,595,858	4,825,651	5,066,933	5,320,280	5,586,294	5,865,609	6,158,889
Gross margin, Citagenix	$3,351,863	$3,970,075	$4,168,579	$4,571,541	$5,617,160	$5,898,018	$6,192,918	$6,502,564	$6,827,693	$7,169,077	$7,527,531
Gross margin, Citagenix (%)	*39.9%*	*45.0%*	*45.0%*	*47.0%*	*55.0%*	*55.0%*	*55.0%*	*55.0%*	*55.0%*	*55.0%*	*55.0%*
Total gross margin, inc ATB-346 royalties	**3,351,863**	**3,970,075**	**4,168,579**	**4,571,541**	**5,617,160**	**5,898,018**	**77,088,125**	**179,381,146**	**256,643,411**	**310,882,056**	**363,307,580**
G&A expense	3,160,469	3,528,955	3,705,403	3,890,673	4,085,207	4,289,467	4,503,941	4,729,138	4,965,595	5,213,874	5,474,568
Selling and marketing expense	3,293,359	3,087,836	3,242,228	3,404,339	3,574,556	3,753,284	7,131,232	11,053,139	13,088,445	13,673,529	13,684,748
R&D Expense	2,146,275	3,000,000	5,500,000	10,000,000	10,000,000	7,500,000	6,500,000	5,500,000	5,000,000	5,000,000	5,000,000
Milestones from future partners	0	0	0	(7,500,000)	(7,500,000)	(7,500,000)	(7,500,000)	(7,500,000)	(7,500,000)	(7,500,000)	(7,500,000)
EBITDA	**($5,248,240)**	**($5,646,717)**	**($8,279,052)**	**($5,223,471)**	**($4,542,603)**	**($2,144,734)**	**$66,452,952**	**$165,598,870**	**$241,089,371**	**$294,494,652**	**$346,648,264**
EBITDA margin (%)	(62.5%)	(64.0%)	(89.4%)	(53.7%)	(44.5%)	(20.0%)	80.9%	89.7%	91.9%	93.0%	93.8%
EBT	**($7,100,927)**	**($7,193,557)**	**($9,825,893)**	**($6,770,312)**	**($6,089,444)**	**($3,691,575)**	**$64,906,111**	**$164,052,029**	**$239,542,531**	**$292,947,811**	**$345,101,423**
Tax expense	0	0	0	0	0	0	19,471,833	49,215,609	71,862,759	87,884,343	103,530,427
Effective tax rate (%)	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*
Net income, fully-taxed	**($7,100,927)**	**($7,193,557)**	**($9,825,893)**	**($6,770,312)**	**($6,089,444)**	**($3,691,575)**	**$45,434,278**	**$114,836,420**	**$167,679,771**	**$205,063,468**	**$241,570,996**
EPS (basic, fully-taxed)	($0.04)	($0.04)	($0.05)	($0.03)	($0.03)	($0.02)	$0.21	$0.52	$0.77	$0.94	$1.10
Adjusted EPS (fd, fully-taxed)	**($0.03)**	**($0.03)**	**($0.04)**	**($0.02)**	**($0.02)**	**($0.01)**	**$0.16**	**$0.41**	**$0.60**	**$0.73**	**$0.86**
Shares out (basic)	162,967,313	198,967,313	208,967,313	218,967,313	218,967,313	218,967,313	218,967,313	218,967,313	218,967,313	218,967,313	218,967,313
Shares out (fd)	243,294,115	259,467,313	269,467,313	279,467,313	279,467,313	279,467,313	279,467,313	279,467,313	279,467,313	279,467,313	279,467,313

Source: Historicals – Antibe Therapeutics, Forecasts/estimates – Echelon Wealth Partners

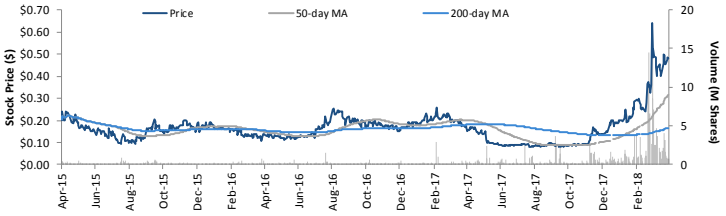
Summary and Valuation

Initiating coverage on ATE with a Speculative BUY rating and $1.40 price target. We are initiating coverage on Antibe Therapeutics with a **Speculative BUY rating and one-year PT of $1.40**. Our PT as always is derived through the average of three methodologies including NPV, and multiples of our F2025 EBITDA/EPS. In our F2025 reference year, we believe that Antibe's ATB-346 franchise will be ostensibly approved and significant traction gained in relevant target geographies. Across all methods, we incorporate a discount rate of 40%, which we believe is actually conservative based on Phase I/II data already generated, and which we expect to revisit as ATB-346 clinical testing advances through imminent dose-ranging testing this year. Our model assumes that pivotal Phase III knee osteoarthritis testing in two placebo-controlled studies, probably using the conventional WOMAC scale as the pain intensity measure, could commence by FH120 as stated earlier, and conclude efficacy testing (probably over a three-month timeframe, although six-month data could be necessary) by FH222, with NDA filing by FH123 leading in our analysis to FDA approval by FH124 and US launch by future partners in FH224. Our model assumes, as shown in Exhibit 20, that Antibe will receive a 30% royalty on sales by future partners and a royalty at this level, while aggressive, seems reasonable to us if the firm partners ATB-346 on Phase III terms. We expect the drug to be in pivotal Phase III testing in F2020 as stated. We again emphasize that we do see value in the firm's ketoprofen-based ATB-352 (probably targeting acute pain markets currently targeted by ketoprofen itself) and acetylsalicylic acid-based

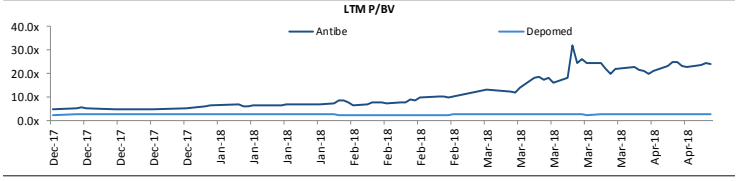
ATB-340, which could be highly attractive as a cardiovascular risk-mitigation pharmaceutical at low doses, just as acetylsalicylic acid itself is in some patients, but with upside potential to acetylsalicylic acid if gastro-protective activity can be demonstrated in future Phase I/II studies. Our model does not currently ascribe market value to ATB-352/ATB-340, but we believe we will have abundant justification for doing so once either or both assets advance into formal clinical testing.

As we conventionally do for clinical-stage drug developers, we ascribe a 20x multiple to fully-diluted, fully-taxed EPS forecasts as a separate valuation method, in this case as ascribed to our F2025 fd fully-taxed EPS forecast of $0.41; we separately ascribe a 12.5x EV/EBITDA multiple to our adjusted F2025 EBITDA forecast of $165.6M (predominantly from ATB-346 economics but also with some baseline gross margin contribution from Citagenix), with our EV calculation incorporating pro forma cash of $5.0M and LT residual debt post-convertible debt conversion of $1.3M, as reported in FQ318 financial data. We again emphasize that we are conservatively deriving revenue/EBITDA forecasts solely from Citagenix and from ATB-346, just because it seems clear to us that this asset will remain a core focus of the firm at least until it advances into Phase III, and so there is substantial upside to be realized as ketoprofen-based ATB-352 and acetylsalicylic acid-based ATB-340 advance into formal human testing. Taking the average of our NPV and EBITDA/EPS-based valuation methods, as shown in Exhibit 3, we derive a one-year PT for ATE of $1.36, which we round to $1.40. With the stock currently trading at a substantial discount to our PT, unjustifiably in our view based on GI ulceration rate data quality, we **ascribe a Speculative BUY rating to ATE**. At current levels, our PT corresponds to a one-year return of 192%.

TEARSHEET - Antibe Therapeutics (ATE-V, $0.48, SPEC BUY, PT: $1.40)



Historical Valuations



Financial Summary/Key Metrics	2018E	2019E	2020E	2021E	2022E	2023E	2024E
C$000s except per share data							
Product sales, Citagenix	8,402	8,822	9,264	9,727	10,213	10,724	11,260
Royalty revenue, ATB-346	0	0	0	0	0	0	70,895
Total product revenue	8,402	8,822	9,264	9,727	10,213	10,724	82,155
Growth (%)	NA	5.0%	5.0%	5.0%	5.0%	5.0%	666.1%
Cons.	0.0	0.0	0.0	NA	NA	NA	NA
Cons. 3 Mts. Ago	0.0	0.0	0.0	NA	NA	NA	NA
EBITDA	**($5,248)**	**($5,647)**	**($8,279)**	**($5,223)**	**($4,543)**	**($2,145)**	**$66,453**
Margin	NA	NA	NA	NA	NA	NA	80.9%
Cons.	NA	NA	NA	NA	NA	NA	NA
Cons. 3 Mts Ago	NA	NA	NA	NA	NA	NA	NA
Net income, fully-taxed	(7,101)	(7,194)	(9,826)	(6,770)	(6,089)	(3,692)	$45,434
EPS (fully taxed)	**($0.03)**	**($0.03)**	**($0.04)**	**($0.02)**	**($0.02)**	**($0.01)**	**$0.16**
Cons.	($0.04)	($0.04)	($0.04)	NA	NA	NA	NA
Cons. 3 Mts. Ago	($0.05)	($0.04)	($0.04)	NA	NA	NA	NA
P/E	NA	NA	NA	NA	NA	NA	2.3x
EV/EBITDA	NA	NA	NA	NA	NA	NA	1.4x

Valuation			
NPV	30%	40%	50%
Implied value/share[1]	$2.05	$1.18	$0.76
Price/earnings multiple, F2025	15.0x	20.0x	25.0x
Implied value/share[1]	$1.15	$1.53	$1.91
EV/EBITDA multiple, F2025	10.0x	12.5x	15.0x
Implied value/share[1]	$1.10	$1.37	$1.65
One Year Antibe Therapeutics Target Price		**$1.40**	

[1] Based on F2025 fd fully-taxed EPS of $0.41; EBITDA of $165.6M, discounted at 40%, FD S/O of 259.5M, but FD S/O of 279.5M embedded in our model

[2] Pro forma cash after Apr/18 warrant exercise of $5.0M (FQ318 cash $1.95M, $4.0M from warrant exercise, less YTD operating cash loss), FQ318 total debt after convertible debt conversion of $1.29M

Company Description

Antibe is a clinical stage drug developer, whose lead clinical asset is gastro-protective hydrogen sulfide-releasing analog of naproxen called ATB-346, for which positive Phase I/II pain and GI ulceration rate data are already available & future Phase II/III testing is being contemplated, with knee osteoarthritis as the initial focus market.

Consensus		Return
Rating:	No Opinion	
Target:	$1.80	275.0%
Median:	$1.80	275.0%
High:	$1.80	275.0%
Low:	$1.80	275.0%
# Est:	1	
Consensus Distribution		
Sector Outperform/Buy		0
Sector Perform/Hold		0
Sector UnderPerform/Sell		0

Key Statistics	Value	
52-Wk High:	$0.79	164.6%
52-Wk Low:	$0.08	16.7%
Avg Vol (3-Mo)	0.39	
Shares O/S:	199.3	
Market Cap:	95.5	
Adj. Proforma Cash ($M):	5.0	
Ent. Value ($M):	91.8	
Div Yield:	0.0%	
Website:	www.antibethera.com	
FYE:	Mar 31	
Employees:	41	

Top Institutional Ownership	M Shares	% Held
Goodman & Company, Investment Counsel Inc.	4.1667	2.1%
Goodman & Company, Investment Counsel Inc.	4.1667	2.1%
NFQ Ventures	1.6000	0.8%
Next Edge Capital Corp.	NA	NA
NA	NA	NA
NA	NA	NA

Comparables and Peer Analysis									% Return				Consensus Valuations					
													EBITDA			EPS		
	Ticker	Trading CCY	Current Price	Target Price	Dividend Yield	% Return	Market Cap	Ent. Value	1-Week	1-Month	3-Month	1-Year	T12M	2018E	2019E	T12M	2018E	2019E
Antibe Therapeutics Inc.	**ATE**	**CAD**	**$0.48**	**$1.40**	**0.0%**	**191.7%**	**95.5**	**91.8**	**(3.0%)**	**33.3%**	**152.6%**	**174.3%**	**(6.3)**	**0.0**	**0.0**	**($0.05)**	**($0.04)**	**($0.04)**
Anika Therapeutics, Inc.	ANIK	USD	$45.91	$68.33	0.0%	48.8%	676.9	519.7	(1.4%)	(12.4%)	(21.0%)	3.7%	50.0	42.6	44.8	$2.18	$1.42	$1.82
Camurus AB (publ)	CAMX	SEK	SEK 115	SEK 122	0.0%	5.8%	4,279.9	3,965.4	0.2%	2.3%	(19.5%)	(1.9%)	-SEK 240.4	-SEK 234.4	SEK 130.3	-SEK 5.11	-SEK 4.99	SEK 3.47
Collegium Pharmaceutical, Inc.	COLL	USD	$24.89	$31.80	0.0%	27.8%	822.1	704.8	9.9%	(8.1%)	23.2%	155.8%	(73.0)	(30.0)	25.0	($2.47)	($0.70)	$1.31
Depomed, Inc.	DEPO	USD	$7.02	$8.57	0.0%	22.1%	445.9	944.5	5.7%	6.8%	(9.9%)	(41.7%)	93.8	127.8	128.3	($1.63)	$0.77	$0.88
DURECT Corporation	DRRX	USD	$2.47	$3.40	0.0%	37.7%	378.7	361.9	(0.4%)	22.3%	111.1%	178.3%	(14.3)	0.0	0.0	($0.03)	($0.23)	($0.21)
Nicox S.A.	COX	EUR	$8.89	$18.90	0.0%	112.6%	263.0	242.6	(1.2%)	(3.1%)	(13.2%)	(2.3%)	(19.5)	(12.2)	(15.5)	($0.24)	($0.40)	($0.54)
Novan, Inc.	NOVN	USD	$3.17	$11.50	0.0%	262.8%	82.5	88.0	1.9%	(4.2%)	(6.2%)	(43.6%)	(33.2)	(31.0)	0.0	($2.32)	($2.14)	$0.00
Vertex Pharmaceuticals Incorporated	VRTX	USD	$163.36	$189.00	0.0%	15.7%	41,637.0	40,168.5	2.8%	(4.3%)	3.9%	42.5%	614.2	904.5	1,273.2	$1.06	$3.08	$4.52
Ampio Pharmaceuticals, Inc.	AMPE	USD	$3.03	NA	0.0%	NA	257.1	248.9	0.7%	12.2%	4.5%	422.3%	(14.4)	0.0	0.0	($0.79)	$0.00	$0.00
Nektar Therapeutics	NKTR	USD	$92.54	$100.56	0.0%	8.7%	14,891.8	14,840.9	(10.0%)	(11.9%)	31.9%	397.9%	(24.2)	719.3	202.7	($0.62)	($1.53)	($2.13)
Average					0.0%	73.4%			93.5%	25.0%	23.4%	116.8%						

Comparables - Multiples Analysis	FCF Yield			Current - EV/EBITDA			Target - EV/EBITDA			EV/REV			P/E			P/BV		
	T12M	2018E	2019E	T12	2018E	2019E	T12M	2018E	2019E	2018E	2019E	2020E	T12M	2018E	2019E	T12M	2017E	2018E
Antibe Therapeutics Inc.	**0.0%**	**0.0%**	**0.0%**	**-14.5x**	**NA**	**NA**	**NA**	**NA**	**NA**	**11.2x**	**8.3x**	**6.6x**	**-9.7x**	**NA**	**NA**	**23.9x**	**0.0x**	**0.0x**
Anika Therapeutics, Inc.	3.5%	0.0%	0.0%	10.4x	12.2x	11.6x	10.4x	12.5x	NA	4.5x	4.2x	0.0x	21.0x	32.3x	25.2x	NA	2.4x	2.2x
Camurus AB (publ)	(5.4%)	(3.3%)	0.0%	-16.5x	-16.9x	30.4x	NA	NA	NA	59.3x	8.8x	16.1x	NA	NA	33.1x	NA	21.4x	13.0x
Collegium Pharmaceutical, Inc.	(5.6%)	2.0%	7.5%	-9.7x	-23.5x	28.2x	NA	NA	NA	2.4x	2.0x	1.8x	NA	NA	19.0x	NA	0.0x	0.0x
Depomed, Inc.	17.0%	21.2%	19.0%	10.1x	7.4x	7.4x	10.1x	7.4x	NA	3.6x	3.6x	3.4x	NA	9.1x	8.0x	NA	4.4x	7.7x
DURECT Corporation	0.0%	0.0%	0.0%	-25.3x	NA	NA	NA	NA	NA	19.2x	25.4x	20.6x	NA	NA	NA	NA	0.0x	0.0x
Nicox S.A.	(6.6%)	5.3%	0.0%	-12.5x	-19.9x	-15.7x	NA	NA	NA	22.3x	23.9x	7.9x	NA	NA	NA	NA	2.3x	2.8x
Novan, Inc.	0.0%	0.0%	0.0%	-2.7x	NA	NA	NA	NA	NA	0.0x	0.0x	7.3x	NA	NA	NA	NM	0.0x	0.0x
Vertex Pharmaceuticals Incorporated	1.7%	5.0%	7.6%	65.4x	44.4x	31.5x	NA	NA	NA	14.6x	12.0x	9.8x	154.5x	53.0x	36.2x	20.4x	15.1x	11.6x
Ampio Pharmaceuticals, Inc.	0.0%	0.0%	0.0%	-17.3x	NA	NA	NA	NA	NA	0.0x	0.0x	0.0x	NA	NA	NA	NA	0.0x	0.0x
Nektar Therapeutics	0.8%	1.8%	4.9%	-612.8x	FALSE	FALSE	NA	20.9x	NA	44.5x	41.0x	38.9x	NA	NA	NA	NA	12.1x	8.6x
Average				-56.9x	0.6x	15.6x	10.2x	13.6x	NA	16.5x	11.7x	10.2x	NA	NA	NA	22.1x	5.2x	4.2x

[1] Targets, forecasts and valuations reflect consensus estimates derived from Capital IQ

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Company: Antibe Therapeutics | ATE:TSXV
I, Douglas Loe, hereby certify that the views expressed in this report accurately reflect my personal views about the subject securities or issuers. I also certify that I have not, am not, and will not receive, directly or indirectly, compensation in exchange for expressing the specific recommendations or views in this report.

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Is this an issuer related or industry related publication?	Issuer
Does the Analyst or any member of the Analyst's household have a financial interest in the securities of the subject issuer? If Yes: 1) Is it a long or short position? Long Position; and, 2) What type of security is it? Common Shares.	Yes
Does the Analyst or household member serve as a Director or Officer or Advisory Board Member of the issuer?	No
Does Echelon Wealth Partners Inc. or the Analyst have any actual material conflicts of interest with the issuer?	No
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Has the Analyst had an onsite visit with the Issuer within the last 12 months? Toronto, Company Head Quarters, March 22nd 2018	Yes
Has the Analyst or any Partner, Director or Officer been compensated for travel expenses incurred as a result of an onsite visit with the Issuer within the last 12 months?	No
Has the Analyst received any compensation from the subject company in the past 12 months?	No
Is Echelon Wealth Partners Inc. a market maker in the issuer's securities at the date of this report?	No

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Buy	The security represents attractive relative value and is expected to appreciate significantly from the current price over the next 12 month time horizon.
Speculative Buy	The security is considered a BUY but in the analyst's opinion possesses certain operational and/or financial risks that are higher than average.
Hold	The security represents fair value and no material appreciation is expected over the next 12-18 month time horizon.
Sell	The security represents poor value and is expected to depreciate over the next 12 month time horizon.
Under Review	While not a rating, this designates the existing rating and/or forecasts are subject to specific review usually due to a material event or share price move.
Tender	Echelon Wealth Partners recommends that investors tender to an existing public offer for the securities in the absence of a superior competing offer.
-Dropped Coverage	Applies to former coverage names where a current analyst has dropped coverage. Echelon Wealth Partners will provide notice to investors whenever coverage of an issuer is dropped.

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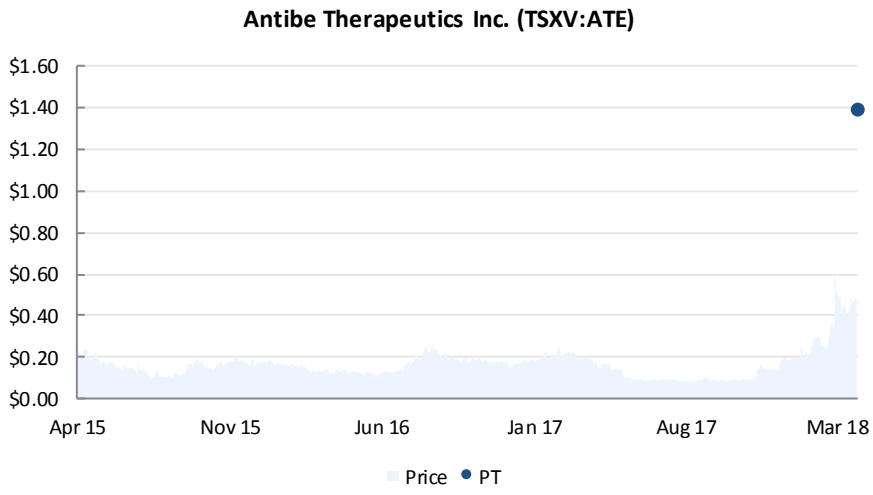
Recommendation Hierarchy	Buy	Speculative Buy	Hold	Sell	Under Review	Restricted	Tender
Number of recommendations	56	53	12	1	4	0	3
% of Total (excluding Restricted)	44%	42%	10%	1%	3%		
Number of investment banking relationships	7	27	1	1	0	0	2
% of Total (excluding Restricted)	19%	75%	3%	3%	0%		

PRICE CHART, RATING & PRICE TARGET HISTORY



Date	Target (C$)	Rating
19 Apr 2018	$1.40	Spec Buy

Coverage Initiated: Apr 19, 2018

Data sourced from: Capital IQ

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