Company: Iterum Therapeutics (ITRM)
Catalyst: Read out of Phase 3 Clinical Trial
Investment: Long Common Equity
Current Price: $3.50

Iterum (NASDAQ: ITRM) is a clinical stage pharmaceutical company developing anti-infectives to combat multi-drug resistant pathogens.

Opportunity

Iterum acquired an exclusive worldwide license to sulopenem and its oral prodrug sulopenem etzadroxil from Pfizer. Pfizer has done multiple Phase 1 & 2 trials on the drug in over 1,450 patients which has established a clear safety and pk/dosing profile, the 3 Phase III trials in 2H '19 will establish efficacy.

This has the potential to be the first oral penem which would add significant value to both clinicians and payors. Iterum's stock has fallen due to 1) very little coverage 2) post IPO sell-off & 3) no news. We view this as a very attractive entry price with limited downside risk. We are not going to go into detail on the commercial/ financial model as we believe that even under the most conservative scenario, a successful read out will merit a price over $10/share. That is currently ~2.5-3.0x the current price.

Catalyst

Three Phase III readouts in Q4 2019/ Q1 2020– indications for uUTI, cUTI, & cIAI.

Two Questions to Determine Success

1. Will the oral dosing of sulopenem display sufficient efficacy?

A little background on the science. Antibiotics efficacy is typically measured using a parameter called MIC (minimum inhibitory concentration). MIC is the lowest concentration of a drug that prevents visible growth of a bacteria. Antibiotics can be divided into three different pharmacokinetic/ pharmacodynamic classes: Type I, Type II, & Type III. Penem (e.g. sulopenem) antibiotics are considered Type 2 antibiotics. The PK/PD parameter to maximize efficacy for Type II antibiotics is T>MIC – ie. the ideal dosing regimen for the penem class of antibiotics maximizes the duration of exposure. IV sulopenem has demonstrated that T of ~ 5 hours is sufficient for efficacy. Since a single dose of oral sulopenem + probenecid showed a T>MIC of 3.6 hours, a BID dose (2x a day), seems very plausible to show comparable (if not better) efficacy than the IV sulopenem.

Exhibit 1:

			Sulopenem Parameter (Day 1)			
Treatment	N	Descriptive Statistic	C_{max} (ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	T>MIC (0.5 µg/mL) [hr]	T>MIC (0.5 µg/mL) [%]
500 mg Sulopenem etzadroxil	10	Mean	1928	3871	2.8	23.3
500 mg Sulopenem etzadroxil + 500 mg probenecid	11	Mean	1929	4964	3.6	30.2

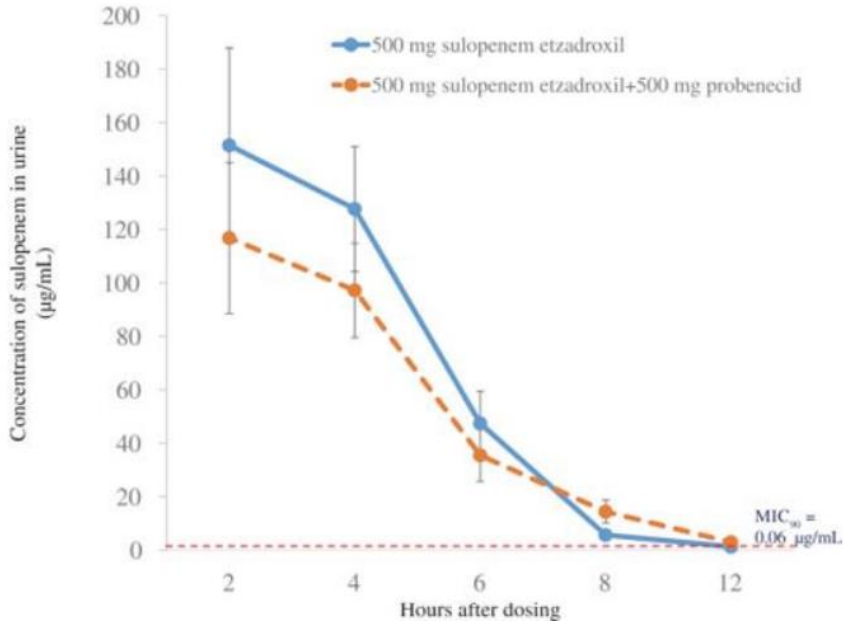
N = number of subjects; C_{max} = maximum plasma concentration; $AUC_{0-\infty}$ = area under the curve from the initiation of dosing extrapolated through infinite time

Source: 2018 10k

Key Takeaway: Note the study in figure 1 shows that probenecid increases the AUC of sulopenem by 28.2% and extends the mean time over MIC, also 28.6%.

Exhibit 2:

Mean total sulopenem exposure in urine after single 500 mg dose of sulopenem etzadroxil with or without probenecid



Source: 2018 10k

Key Takeaway: Peak urine concentrations are almost 2,000-fold higher than the MIC_{90}, and a single dose will exceed the MIC_{90} for the entire BID dosing interval.

2. Does sulopenem target the proper pathogen?

While sulopenem did perform worse than some others in the penem class, it shows clear in-vitro efficacy. Note sulopenem MIC_{90} against major organisms associated with the indications Iterum is going after is less than 1 ug/mL (Less than 4 uG/mL tends to be the standard for efficacy).

Exhibit 3:

A comparison of the *in vitro* activity of sulopenem relative to other carbapenems, as well as to currently prescribed oral agents for UTI, is provided below. The activity of sulopenem at slightly higher doses was very similar to that of ertapenem and meropenem, which are currently commercially available. In addition, sulopenem is noted to have potent *in vitro* activity against relevant organisms that are resistant to fluoroquinolones and trimethoprim-sulfamethoxazole and are ESBL positive. The prevalence of resistance for the existing generic antibiotics, now exceeding 20% for many pathogens, underscores the challenge of treating patients with uUTI in an outpatient setting or releasing patients from the hospital with a cUTI or cIAI on a reliable stepdown oral therapy.

	E. coli N=189		*K. pneumoniae* N=65		*P. mirabilis* N=19	
Penem Class:	**MIC90 (µg/mL)**	**% S**	**MIC90 (µg/mL)**	**% S**	**MIC90 (µg/mL)**	**% S**
Sulopenem	**0.06**	*	**0.12**	*	**0.25**	*
Ertapenem	0.015	100	0.12	97	0.03	100
Meropenem	0.03	100	0.06	97	0.12	100
Oral Agents Currently on Market:						
Nitrofurantoin	16	97	≥64	23	≥64	0
Fosfomycin	8	98	128	86	64	95
Ciprofloxacin	≥2	77	1	91	≥2	74
Trimethoprim-Sulfamethoxazole	≥32	74	≥32	86	≥32	58
Amoxicillin-Clavulanate	16	76	≥16	80	≥16	74

N = bacterial samples; each product candidate was tested using the same sample size
% S = percentage susceptible, meaning the proportion of the number of isolates tested that had a MIC below the FDA defined susceptibility breakpoint; boxed values signify a percentage susceptible below 80%, which is the threshold for concern for use of an antibiotic before a culture is available
* Susceptibility breakpoints are established by the FDA and documented in product labeling based on the antibacterial agent treatment efficacy in Phase 3 clinical trials associated with a specific MIC. As such, susceptibility breakpoints have not yet been determined for sulopenem.

Key Takeaway: While sulopenem did perform worse than some others in the penem class, it shows clear in-vitro efficacy. In other words, while not the best, it is clearly good enough. Further note, MIC_{90} against major organisms associate with the indications Iterum is going after is less than 1 ug/mL (Less than 4 uG/mL tends to be the standard for efficacy).

Safety Profile

Exhibit 3:

Safety Profile of Oral Sulopenem and Sulopenem

Sulopenem is a thiopenem and a member of the class of ß-lactam antibiotics, a class from which numerous safe and well tolerated antibiotics have been available for over thirty years. Adverse event data collected as part of the Japanese Phase 2 development program with the IV formulation conducted by Pfizer provided preliminary insights into the safety profile for sulopenem, which will continue to be assessed with additional clinical trials. We view the clinical safety profile of sulopenem established by the Japanese data as also relevant and supportive of oral sulopenem because it metabolizes to the active metabolite, sulopenem, in plasma. A summary of the adverse event data from the Japanese program is provided below:

	Sulopenem				
	250 mg BID (N = 296)	500 mg BID (N = 867)	Miscellaneous* (N = 247)	Comparators (N = 64)	Total (N = 1474)
No. of patients who experienced at least one:					
Adverse Event	14 (4.7)	35 (4.0)	1 (0.4)	3 (4.7)	53 (3.6)
Drug-Related Adverse Event	9 (3.0)	22 (2.5)	1 (0.4)	3 (4.7)	35 (2.4)
Serious Adverse Event	2 (0.7)	1 (0.1)	—	1 (1.6)	4 (0.3)
Drug-Related Serious Adverse Event	1 (0.3)	—	—	1 (1.6)	2 (0.1)
SAE Leading to Death	2 (0.7)	1 (0.1)	—	1 (1.6)	4 (0.3)
AE Leading to Premature Discontinuation of Study Drug	8 (2.7)	16 (1.8)	—	2 (3.1)	26 (1.8)
SAE Leading to Premature Discontinuation of Study Drug	1 (0.3)	—	—	—	1 (0.1)

* Miscellaneous doses include patients receiving a total daily dose of 250 mg, 750 mg, 1500 mg or 2000 mg, including patients receiving a single dose of sulopenem in the population PK sub-study.

Key Takeaway: We don't believe there are any safety or toxicity issues with either the IV or oral dosing of sulopenem.

Market

The leading indication is for Urinary Tract Infections (UTI) – will make up majority of the sales. Iterum's differentiator is that they are developing an oral formulation for a step down from the IV – the market outside the hospital is an attractive commercial opportunity. For instance, Alan Carr at Needham thinks it is a $500M - $1B opportunity. It will compete in the market of the ~260k penem scripts per year – oral formulation provides a clear differentiator.

Other Points of Note

- Strong global rights & exclusivity (composition patent through 2034 (2029 + 5 yr extension)
- Iterum has 3 studies under SPA with the FDA. They are all Non-inferiority (it's not worse than the comparator), however, superiority will help commercial success, especially for uUTI

Risks:

- All three, or any 3, of the Phase III trials due to read out in Q4 could fail to meet their endpoint.
- Changing dosing from 500mg 2x a day to 1g 1x per day
- Licensing Agreement with Pfizer/ Will need to issue shares

Valuation:

Our analysis shows that the value of the company is at least $100M if any single indication gains approval. Realistically, we think this company has a value between $300-$500M if they pass these Phas III trials.

Conclusion:

We believe this is an opportunity that can return multiples in the short term and could be 5x-10x in the 18-24 month range. We think the probability of success in either uUTI or cUTI is ~70%. If all three trials fail, we expect the value to be ~$25M – as determined by cash on hand – which represents a 50% decline.