MIST A great Long Play on The Way

Matteo G. Doye

contact@doyechalmelfreres.com

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Executive summary

With an estimated $5.21 price per share excluding current cash, if Milestone Pharmaceuticals gets their product Etripamil accepted by the FDA this March 27, 2025, with the probability of this acceptance being around 80% according to my assessments.

Milestone Pharmaceuticals (MIST) is a Canadian clinical-stage biopharmaceutical company that is involved in the development of Etripamil, under the brand name CARDAMYST – MIST's sole product candidate. Etripamil is a nasal spray (NS) that is aimed to be fast-acting and self-administered to treat episodes of paroxysmal supraventricular tachycardia (PSVT). It is a calcium channel antagonist, the agonist effect whether directly or indirectly has proven to be efficient to treat PSVT episode as it is the standard of care (AHAIASA Journals). Etripamil acts as an L-type calcium channel blocker that is quickly absorbed by the nasal mucosa. The dose per spray is at 70 mg and can be administered at 10 minutes of interval if the episode persists. Etripamil has a favorable safety profile with no serious adverse events (SAEs) and only mild adverse events (AEs) in the RAPID study (NCT03464019). The results of the RAPID study, a Phase III trial that was split in three distinct parts. It is a multi-center, randomized, double-blind and placebo-controlled study, that provides clear and credible data through this strong study design. The results of this study were positive with a conversion of 64% compared to 31% for placebo (Hazard Ratio (HR) 2.62; $p < 0.0001$), and with a median time to conversion of 17.2 minutes for Etripamil against 53.5 minutes for placebo. The odds ratio (95% Confidence Interval (CI)) are also favorable for Etripamil, especially in the first 30

minutes. Those results were confirmed in open-label study, with the NODE-303 study (NCT04072835) which reflected similar results – note that this study is an open-label.

With its unique type of action and self-administration, it is hard to believe that the FDA will reject Etripamil, as it is an efficient and safe product. The current treatments are not fast-acting and thereby leaves an open door for the FDA to accept a new fast-acting product for PSVT episodes to be quickly terminated. Current treatments include calcium channel blockers that must be administered via intravenous (IV) administration, meaning that patients have to get to the emergency room (ER) in case of PSVT episode. The oral medications are no better, as their taking must be supervised and monitor due to the risks of hypotension and bradycardia. Overall, it is easy to see why a fast-acting self-administered product such as Etripamil is needed to treat PSVT episodes. In addition, the insurance companies would be in favor of Etripamil, as it prevents the patients to do an expensive trip to the ER or being monitored when taking an oral agent in comparison to a self-administered fast-acting nasal spray.

MIST financials

The current price of MIST is at $2 which makes this opportunity a prime opportunity in regard to the risk/rewards ratio. As MIST still has a Phase III trial for the development of Etripamil for Atrial fibrillation, which is a much bigger market than PSVT. With the strong Phase II results one can expect that the stock's value will remain over its cash level even if Etripamil receives a Complete Response Letter (CRL) from the FDA – a CRL from the FDA means the rejection of the product. This makes MIST a great opportunity for investors that are not afraid of binary events.

MIST cash in the third quarter of 2024 was at $76.4 million with their market cap (MC) being at $111.9 million. MIST entered into an agreement on March 27, 2023, with Royalty Purchase Agreement (RTW). RWT agreed to pay MIST $75 million when Etripamil gets FDA approved, in exchange for 7% of annual net sales up to $500 million (Initial Tier Royalty),

4% of annual net sales between $500 million and $800 million, and 1% of annual net sales greater than $800 million (license agreement). In addition to a $5 million equity investments upon the FDA approval from RWT (license agreement).

On May 21, 2021, MIST and Ji Xing Pharmaceuticals came into an agreement where MIST granted Ji Xing Pharmaceuticals an exclusive license to develop and commercialize Etripamil in patients with PSVT in Greater China – upon the FDA approval of Etripamil. MIST will still be eligible to receive up to $107.5 million in milestone payments and royalties on future sales of Etripamil in Greater China from Ji Xing Pharmaceuticals (license agreement).

Here are my financial predictions for MIST according to my Risk-Adjusted Net Present Value (rNPV) model for Etripamil. As it falls under the cardiology therapeutic area, that it is currently at the NDA filling stage, and that we can wait until 2026 for it to be on the market, commercialized. The total market is estimated to be around $500 to $600 million, estimating that they take 30% of the market (conservative view), considering the interest of the insurances and physicians to promote Etripamil. Since it is a cheap, self-administered, fast-acting treatment options when considering the alternatives. The peak annual revenue being at $150 million with the current market size. With a time to reach peak sales at 5 years and a discount rate of 10%.

The rNPV: $345.2 million.

The rNPV per share: $5.21.

These values are excluding the current cash level of $76.4 million that MIST has. If Etripamil gets a CRL (refused) by the FDA, I expect them to trade at their cash-level. In addition, when considering that their Phase III that starts in H1 2025, focusing on atrial fibrillation, which is a bigger market, one could even say that a few weeks, or months after the CRL the stock price could return to its current state of $2 a share. Making it a great opportunity.

Current treatment options

The current treatment for PSVT include Adenosine. It is a potent atrioventricular (AV) nodal blocking agent that is administered via IV and has a 90% success rate in terminating AV-nodal dependent PSVT. The issue with Adenosine is that the patients must go to the ER, which costs money and discomfort since they can not directly relief themselves of the pain.

There is also the Verapamil and Diltiazem, which are both calcium channel blockers with a shared MOA and effects. They are both available in the oral and IV formulation. Nonetheless, the oral formulation when taken by a patient must be taken under supervision of a medical personnel. This is due to the side effects, with a risk of hypotension and bradycardia. Their efficiency ranges from 70% to 90% for the IV formulation, as for the oral formulation, it has a delayed activation and is less effective than the IV formulation for acute episodes.

The other options can be overlooked as they have a moderate efficacy and have a delayed onset. Meaning that Etripamil has a great opportunity to foster a strong place in the PSVT market as it is the only fast-acting efficient treatment solution that can be self-administered.

Clinical Results

The Phase III study was divided into three parts, the first being NODE-301 and the second and third being the RAPID study. The primary endpoint of the first part was the conversion to sinus rhythm within 5 hours. Which was proven to be not significantly higher with Etripamil (HR 1.086; $p = 0.12$). The questions remain with did management selected the primary endpoint, knowing that Etripamil has a short half-life and is aimed to be effective in the short term. Still, this failure in my opinion is not major, although one might raise some questions, for me the most important results are the one's that focus on the results that show if Etripamil is effective in the short term – the agenda of the product and not the 5 hours efficacy.

Assessing the results at 30 minutes of the part 1 of this Phase III, it is clear that the fast-acting properties of Etripamil are there. With 53.7% for Etripamil against 34.7% for placebo (HR 1.87, p = 0.02). The median time to conversion was at 25 minutes for Etripamil against 50 minutes for placebo. The AEs were mild and primarily related to the nasal administration, with 19.6% being discomfort and 8% being congestion. With no serious AEs.

As for the primary endpoint of the RAPID study, it was defined to evaluate the time to conversion of PSVT to sinus rhythm within 30 minutes of Etripamil administration. The results were statistically and clinically significant with a 64% for Etripamil against 31% for placebo (HR 2.62; p < 0.0001), and the median time to conversion was 17.2 minutes for Etripamil against 53.5 minutes for placebo. In addition, the odds ratio (OR) and p-value for the conversion of PSVT to sinus rhythm at predefined time points after treatment with Etripamil versus placebo are shown in the figure 2 below. The OR quantifies the likelihood of conversion to sinus rhythm with Etripamil compared to placebo. If the OR is <1 it means that Etripamil is not effective compared to placebo. A p-value of <0.05 is good, statistically significant. This table shows the strong effectiveness of Etripamil from 3 minutes to 30 minutes, with the range from 3 minutes to 10 minutes being the most effective.

Time to convesrion to sinus rhythm, minutes	Odds ratio (95% CI)	P value
3	4,132 (0,90 - 38,29)	0,049
5	4,198 (1,16 - 22,83)	0,017
10	2,795 (1,09 - 8,09)	0,021
15	2,062 (0,90 - 4,97)	0,065
20	2,238 (1 - 5,24)	0,034
30	2,067 (0,97 - 4,46)	0,04
60	1,312 (0,62 - 2,75)	0,437

Figure 1. Odds ratio (OR) and p-value for the conversion of PSVT to sinus rhythm at predefined time points after treatment with Etripamil versus placebo table (AHA Journals).

Assessing the AEs for the RAPID study, it is clear that most of them were nasal discomfort (23%), congestion (13%), and rhinorrhea (9%). The AEs were more frequent in the Etripamil group (50%) than placebo (11%). Proving a strong safety profile. With no serious AEs.

The open-label studies are not worth looking at according to my views since they are operated in a highly uncontrolled environment, meaning that their results are not scientific or relevant to me and anyone that takes science seriously. Nonetheless I will note the results from the NODE-303 study that is an open-label study, the reasons why I believe that it can still be somewhat relevant is because this study aimed to validate the results from the RAPID study in a highly uncontrolled environment with a much higher patient population in the trial with 1,116 participants. The patient level is not too different from the complete NODE-301 trial, including the three parts, but what makes it interesting is that the control over who was and was not selected for the trial was much less rigorous. This provides a view that one can consider when assessing the actual results of Etripamil.

With an AV nodal dependent supraventricular tachycardia (SVT) conversion at 60% by 30 min and 70% by 60 min, and a median time to conversion of 17 min. The NODE-303 trial results are similar to the ones from the RAPID trial. In this open-label trial, self-administered Etripamil with no direct supervision, demonstrated a high efficacy and a strong safety to terminate SVT. No serious AEs occurred, all the AEs were local to the administration site and remained mild to moderate.

Figure. Plot of Kaplan-Meier estimates of conversion of supraventricular tachycardia to sinus rhythr with etripamil nasal spray (NODE-303, all episodes), and comparison plot from previously reported RAPID trial (randomized, placebo-control double-blind treatment of one episode, etripamil arm)

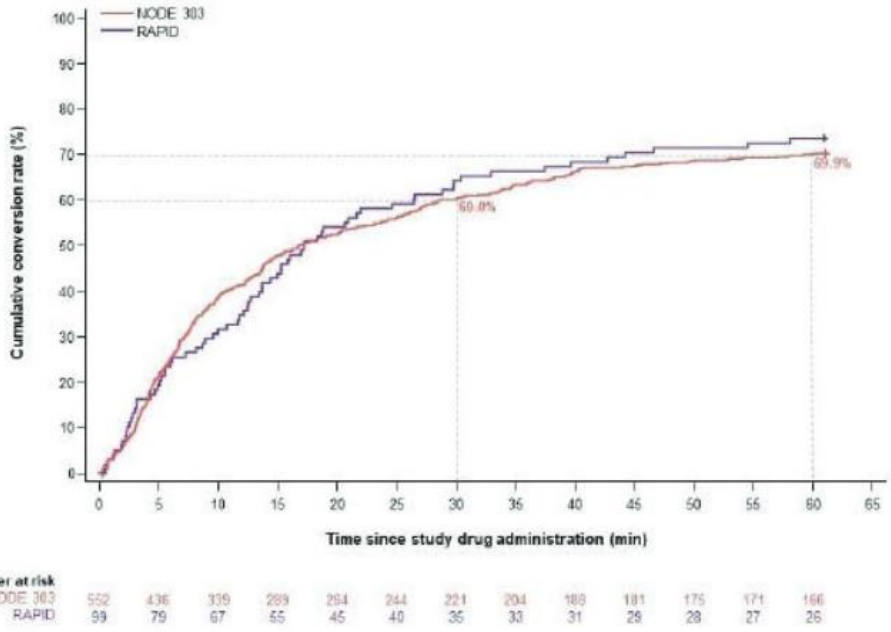

Figure 2. Time to conversion evaluation between NODE-303 study and RAPID study (JACC Journals).

Estimations

Since Etripamil is the only product of its kind for this condition, it is hard to see valuable reasons why the FDA would reject it. As Etripamil is effective in the short term, which it is aimed to be, and it has proven to be a safe option.

In October 2023, MILS submitted their New Drug Application (NDA) to the FDA for Etripamil. In December 2023, the FDA provided MILS with a Refusal to File Letter. The cause for this letter was straightforward, the FDA requested specific clarification about the time of data recorded for the adverse events in the Phase III trials. One important thing to note is that their concerns were not related to the nature or severity of these AEs.

The PDUFA date is set at March 27, 2025. It is at this date that the FDA will either reject Etripamil with a Complete Response Letter (CRL) or accept it. Upon this news the price of the stock will be affected by this binary event.

The probability of acceptance, considering the efficacy, safety, and novel approach that is highly interesting and relevant for the patients. I believe that the FDA will accept Etripamil with an 80% probability – based on the previously cited criteria.

Conclusion

To conclude, I will say that MIST is a great opportunity for any investor that is not afraid of binary events. The risk to reward ratio is highly favorable and one could say that such rates are quite unique in the biotech sector. The results of Etripamil are strong and safe and its application is unique and could significantly help the patients. In addition, I believe that the insurance companies will have a strong incentive to push Etripamil, since its lower cost and easier administration. Overall, I estimated the probability for the FDA to accept Etripamil to be at 80%. As for the price range, for a success it would be around $5.21 per share, excluding their current cash. As for the price level in case of a rejection, it should be around the cash level.

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