Eagle Pharmaceuticals Takes Equity Stake in, with Option to Acquire, Enalare Therapeutics to Advance Global Development of ENA-001, a Novel Agnostic Respiratory Stimulant

August 9, 2022

-- ENA-001 is currently in development for: post-operative respiratory depression, community drug overdose, and Apnea of Prematurity --

-- Approval for post-operative respiratory depression expected in 2026 and community drug overdose thereafter --

-- ENA-001 works peripherally by inhibiting Big Potassium (BK) ion channels in the carotid bodies, which are located in the neck. By inhibiting these channels, ENA-001 utilizes the body's own ventilation control system to stimulate breathing and it does so across multiple causes (etiologies) of respiratory depression. This, and the ability of ENA-001 to address respiratory depression associated with multiple agents (e.g. opioids, benzodiazepines, propofol), differentiates it from other available options --

Key Highlights

- Transaction broadens Eagle's acute care portfolio with ENA-001, a new chemical entity ("NCE") with a unique mechanism of action being developed as an agnostic respiratory stimulant for potential use in multiple patient populations experiencing acute respiratory depression.
- The initial targeted indications include:
  - **Post-operative Respiratory Depression.** Respiratory depression is common in patients recovering from surgery and anesthesia. Up to 36% of patients[1] are at high risk of post-operative respiratory depression which is associated with increased risk of in-hospital mortality, increased length of stay and higher cost. ENA-001 has the potential to treat respiratory depression without interfering with analgesia (pain suppression) or sedation.
  - **Community Drug Overdose.** Drug overdose deaths are at a record high[2] and polysubstance abuse is increasingly common[3]. Current therapeutic options are limited in that they only address a single substance of abuse, typically opioids, and are associated with inducing a withdrawal syndrome. Naloxone is an opioid receptor antagonist indicated only for known or suspected opioid induced depression and may precipitate acute withdrawal. ENA-001 has the potential to treat respiratory depression associated with polysubstance abuse without inciting the withdrawal effect experienced with opioid antagonists, a potential safety consideration.
  - **Apnea of Prematurity (AoP).** The incidence of AoP increases with decreasing birthweight and gestational age. 25% of neonates weighing less than 2,500 g at birth suffer from AoP. 75% of infants born at 28-29 weeks will have AoP and the incidence remains as high as 14% for infants born at 32-33 weeks[4]. Pharmacologic treatment for these neonates is limited to caffeine (methylxanthines), the most widely used first-line treatment option. ENA-001 would be used potentially as monotherapy or in conjunction with current standard of care, caffeine.
- Represents strong strategic fit with Eagle's specialized sales and marketing organization and current and expanding portfolio of hospital and anesthesia products.
- Eagle will make a $25 million investment in Enalare Therapeutics ("Enalare"), $12.5 million which will be paid now and another $12.5 million in six months, followed by two additional potential equity investments of $15 million each contingent upon the achievement of development milestones for ENA-001. In connection with the equity investment, the two companies also entered into an agreement providing Eagle the option to acquire the remaining outstanding shares.
- ENA-001 is expected to enter a Phase 2 study with the first patient by early 2023. The trial is expected to recruit about 200 subjects over one year. The Company anticipates a 2026 launch for post-operative respiratory depression, and community drug overdose thereafter.

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[1] Khanna, Ashish K., Bergese, Sergio D., et al; PRODIGY Group Collaborators. Prediction of Opioid-Induced Respiratory Depression on Inpatient Wards Using Continuous Capnography and Oximetry: An International Prospective, Observational Trial. *Anesthesia & Analgesia.* Volume 113, Issue 4, October 2020.

[2] National Institute on Drug Abuse (2022)

https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

[3] Centers for Disease Control and Prevention (2021)

https://www.cdc.gov/drugoverdose/deaths/other-drugs.html

[4] Bohin, S., Field, D.J., *The Epidemiology of Neonatal Respiratory Disease, Early Human Development*, Volume 37, Issue 2, May 1994

WOODCLIFF LAKE, N.J. and PRINCETON, N.J., Aug. 09, 2022 (GLOBE NEWSWIRE) -- Eagle Pharmaceuticals, Inc. (Nasdaq: EGRX) ("Eagle" or

the “Company”), and Enalare Therapeutics Inc (“Enalare”) today announced an agreement for Eagle to make an equity investment of $25 million in Enalare, a clinical-stage privately held biopharmaceutical company dedicated to developing novel therapies for patients suffering from life-threatening acute respiratory and critical care conditions. The investment also includes an exclusive option for Eagle to acquire all remaining issued and outstanding Enalare stock upon the achievement of development milestones as set forth in the agreement.

As part of the transaction, Eagle will invest up to approximately $55 million, which is expected to occur over the next two years subject to the achievement by Enalare of certain milestones on an agreed upon timeline. The investment consists of an upfront investment of $25 million, $12.5 million now and $12.5 to be paid in six months, and two potential follow-on equity investments of $15 million each contingent upon (i) the commencement of the ENA-001 Phase 2 clinical trial, and (ii) the ENA-001 Phase 2 clinical trial reaching 50% enrollment. Eagle and Enalare have also entered into an agreement providing Eagle the option to acquire the all remaining Enalare shares for an aggregate purchase price ranging from $100-$175 million plus royalty rights ranging from 9%-12% on all future global net sales of any Enalare product, paid to the ex-Eagle holders of Enalare shares at the time of acquisition.

The transaction is expected to provide Eagle with products protected by intellectual property rights, including composition of matter patents, which potentially provide patent term into the mid-2030s to the early 2040s. The Company believes these products have the potential to address significant unmet medical needs for millions of patients worldwide suffering from acute respiratory depression, including those in the hospital post-operative care setting, those experiencing community drug overdose, and preterm infants suffering a common condition known as Apnea of Prematurity.

- Enalare’s lead compound, ENA-001, is an investigational, one-of-a-kind NCE designed as an agnostic respiratory stimulant.
    - It has been shown to be well tolerated in restoring breathing drive and responsiveness in five Phase 1 human studies.
    - Recent topline results of Enalare’s Phase 1 Study 108 indicate that ENA-001 successfully achieved the study’s primary endpoint. It was shown to be safe and well-tolerated and was able to reverse propofol-induced dampening of ventilatory responsiveness in the population studied.
    - Enalare is planning to initiate a Phase 2 clinical study for use in this patient population in the near term.
    - Approval for post-operative respiratory depression expected in 2026, and community drug overdose thereafter.
- ENA-001 is also being developed in an Intramuscular (“IM”) Formulation in partnership with the Biomedical Advanced Research and Development Authority (“BARDA”) (contract number 75A50121C00044) for the potential use in patients experiencing drug overdose in a community setting and as a potential medical countermeasure for mass casualty events. This effort is also supported via a grant from the National Institute on Drug Abuse (NIDA: award number R44DA057133), a division of the National Institutes of Health. Enalare is planning to complete the required preclinical activities with the IM formulation in the near term and to begin human clinical studies in the first half of next year.
- In addition, Enalare is developing ENA-001 for the treatment of Apnea of Prematurity (“AoP”), a condition commonly affecting infants born preterm in which they experience shallow or intermittent stoppage of breathing. Persistent AoP can cause near- and long- term neurological development risks to the infant. ENA-001 has received Rare Pediatric Disease designation from the U.S. Food and Drug Administration (“FDA”) in the treatment of AoP, which potentially provides for a priority review voucher if the product is approved for this indication. Enalare is currently executing an animal proof-of-concept study with ENA-001 in the treatment of AoP and expects to further pursue orphan drug designation and initiate human clinical trials.

“By adding Enalare’s highly differentiated and complementary NCE to our portfolio, we immediately expand Eagle’s long-term growth possibilities. We believe ENA-001 has enormous potential to address important unmet medical needs. It is an agnostic respiratory stimulant with what we view as compelling clinical and health economic value propositions. It is also an ideal fit within our current hospital critical care portfolio, comprised of four approved and two investigational products. BARHEMSYS®, the only proven antiemetic for the treatment of post-operative nausea and vomiting (“PONV”), BYFAVO ®[5], the first new drug approved for procedural sedation in decades, RYANODEX®, and vasopressin are all in market. If approved, landiolol, an ultra-short acting cardio-selective IV beta-blocker, and CAL02, a first-in-class anti-infective agent to treat severe bacterial pneumonia will join our currently approved products to create a formidable hospital/anesthesia product portfolio,” stated Scott Tarriff, President and Chief Executive Officer of Eagle Pharmaceuticals.

“We plan to leverage our strong balance sheet and usher ENA-001 toward a potential 2026 launch. This is a great opportunity for Eagle and one that furthers our transformation into a diversified, branded pharmaceutical company with long-duration assets in acute care,” concluded Tarriff.

“This partnership is an exciting step forward in the development of ENA-001 and for the millions of patients worldwide that can benefit from such a novel agnostic respiratory stimulant,” stated Herm Cukier, President and CEO of Enalare Therapeutics. “Our partnership with Eagle provides us access to capital and a robust infrastructure and commercial platform to develop and potentially launch our product. Without added headcount or expense, Eagle will be able to rely on our experienced and highly regarded team as we move onto Phase 2 and 3 trials, which we believe will successfully demonstrate ENA-001's ability to improve patient respiratory capacity. We look forward to a close and productive working relationship and supporting Eagle in the successful development of Enalare’s products,” concluded Cukier.

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[5] https://bynder.acaciapharma.com/m/403e8c343b2922de/original/Byfavo-PI.pdf

Transaction Rationale

- Enalare's intellectual property with potential patent duration through the mid 2030s to early 2040s offers Eagle access to complementary and diversified revenue streams;
- Eagle believes there is a compelling commercial opportunity for Enalare's lead drug candidate, ENA-001:
  - Agnostic respiratory stimulant with first-in-class mechanism of action;
  - Studied in more than 100 human subjects to date;
  - Differentiated product that significantly expands long-term sales potential and durability of Eagle's hospital business;
  - Synergistic fit with Eagle's current and expanding portfolio of hospital products, with overlap of customer channel and decision makers;
  - Timing of launch, if approved, aligns with anticipated Eagle commercial capacity;
  - Provides the opportunity for strategic expansion into adjacent therapeutic and customer channels.

About ENA-001

ENA-001 is an investigational new chemical entity ("NCE") being developed by Enalare for multiple potential indications, including the prevention and treatment of post-operative respiratory depression. With its novel mechanism-of-action and based on findings to date, it could potentially improve the lives of those impacted by several life-threatening conditions including community drug overdose, post-operative respiratory depression, and apnea of prematurity. If approved, ENA-001 would offer new treatment options for physicians, emergency responders, and caregivers addressing acute respiratory depression across multiple patient populations in multiple settings.

About Enalare Therapeutics Inc

Enalare Therapeutics Inc is a clinical-stage biopharmaceutical company dedicated to developing novel therapies for patients suffering from life-threatening acute respiratory and critical care conditions, including community drug overdose, post-operative respiratory depression, and apnea of prematurity.

About Eagle Pharmaceuticals, Inc.

Eagle is a fully integrated pharmaceutical company with research and development, clinical, manufacturing and commercial expertise. Eagle is committed to developing innovative medicines that result in meaningful improvements in patients' lives. Eagle's commercialized products include vasopressin, PEMFEXY®, RYANODEX®, BENDEKA®, BELRAPZO®, TREAKISYM® (Japan), and BYFAVO® and BARHEMSYS® through its wholly-owned subsidiary Acacia Pharma Inc. Eagle's oncology and CNS/metabolic critical care pipeline includes product candidates with the potential to address underserved therapeutic areas across multiple disease states. Additional information is available on Eagle's website at www.eagleus.com.

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, and other securities law. Forward-looking statements are statements that are not historical facts. Words and phrases such as "anticipated," "forward," "will," "would," "could," "should," "may," "remain," "potential," "prepare," "expected," "believe," "plan," "near future," "belief," "guidance," "estimate," and similar expressions are intended to identify forward-looking statements. These statements include, but are not limited to, statements regarding future events such as statements regarding: any further investments in Enalare and Enalare's development programs; expectations with respect to synergies; expectations that the transaction with Enalare will help improve the care of patients undergoing medical treatments, solidify the Eagle's leadership position in the hospital and anesthesia space and bring long-term value to Eagle's shareholders; expectations with respect to the achievement of development milestones and any further investments by Eagle in Enalare; estimated addressable market size and estimated sales figures; Eagle's marketing, product development, partnering and growth strategy, including relating to the commercialization of BARHEMSYS and BYFAVO and other products and product candidates and Eagle's ability to expand the application of ENA-001, BARHEMSYS and BYFAVO; anticipated timelines of development programs, including with respect to ENA-001; the timing, scope or likelihood and timing of regulatory filings and approvals for Eagle's and Enalare's product candidates, including ENA-001 and landiolol; the ability of ENA-001, BARHEMSYS, BYFAVO, landiolol and other products and product candidates to address unmet clinical needs; the potential market opportunity for products or product candidates, including for BARHEMSYS, BYFAVO, landiolol and ENA-001; expectations regarding expansion of the Company's product portfolio, including with respect to the intellectual property of Enalare and any potential future transactions; the ability of Eagle's executive team to execute on Eagle's strategy and build stockholder value; the ability of Eagle's sales force to commercialize products; expectations regarding Eagle's future growth and the expansion of Eagle's growth possibilities as a result of the Enalare transaction; and the ability of the Company's product candidates to deliver value to stockholders. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the Company's control, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. Such risks and uncertainties include, but are not limited to: the risk that the anticipated benefits of Eagle's recently completed transaction with Acacia Pharma and the transaction with Enalare are not realized; the impacts of the COVID-19 pandemic and geopolitical events such as the conflict in Ukraine, including disruption or impact in the sales of Eagle's marketed products, interruptions or other adverse effects to clinical trials, delays in regulatory review, manufacturing and supply chain interruptions, adverse effects on healthcare systems, disruption in the operations of the Company's third party partners and disruption of the global economy, and the overall impact of the COVID-19 pandemic or other events on Eagle's business, financial condition and results of operations; macroeconomic conditions, such as rising inflation and uncertain credit and financial markets; whether Eagle will incur unforeseen expenses or liabilities or other market factors; whether Eagle will successfully implement its development plan for its product candidates; delay in or failure to obtain regulatory approval of Eagle's or its partners' product candidates, including landiolol and ENA-001; whether Eagle can successfully market and commercialize its products or product candidates; the success of Eagle's relationships with its partners; the availability and pricing of third party sourced products and materials; the outcome of litigation involving any of its products or that may have an impact

on any of Eagle's products; successful compliance with the FDA and other governmental regulations applicable to product approvals, manufacturing facilities, products and/or businesses; general economic conditions, including the potential adverse effects of public health issues, including the COVID-19 pandemic and geopolitical events, on economic activity and the performance of the financial markets generally; the strength and enforceability of Eagle's intellectual property rights or the rights of third parties; competition from other pharmaceutical and biotechnology companies and the potential for competition from generic entrants into the market; the risks inherent in the early stages of drug development and in conducting clinical trials; and factors in addition to the foregoing that may impact Eagle's financial projects and guidance, including among other things, any potential business development transactions, acquisitions, restructurings or legal settlements, in addition to any unanticipated factors, that may cause Eagles actual results and outcomes to materially differ from its projections and guidance; and those risks and uncertainties identified in the "Risk Factors" sections of the Company's Annual Report on Form 10-K for the year ended December 31, 2021, filed with the Securities and Exchange Commission (the "SEC") on March 8, 2022, Eagle's Quarterly Report on Form 10-Q for the quarter ended March 31, 2022, filed with the SEC on May 9, 2022, and its other subsequent filings with the SEC, including Eagle's Quarterly Report on Form 10-Q for the quarter ended June 30, 2022, which Eagle expects to file with the SEC on August 9, 2022. Readers are cautioned not to place undue reliance on these forward-looking statements. All forward-looking statements contained in this press release speak only as of the date on which they were made. Except to the extent required by law, the Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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Important Safety Information **for BYFAVO™ (remimazolam) Injection**

Indications

BYFAVO is a benzodiazepine indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.

Important Safety Information

WARNING: PERSONNEL AND EQUIPMENT FOR MONITORING AND RESUSCITATION AND RISKS FROM CONCOMITANT USE WITH OPIOID ANALGESICS

Personnel and Equipment for Monitoring and Resuscitation

- **Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO.**
- **Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation.**
- **BYFAVO has been associated with hypoxia, bradycardia, and hypotension. Continuously monitor vital signs during sedation and during the recovery period.**
- **Resuscitative drugs, and age- and size-appropriate equipment for bag-valve-mask–assisted ventilation must be immediately available during administration of BYFAVO.**

Risks From Concomitant Use With Opioid Analgesics and Other Sedative-Hypnotics

Concomitant use of benzodiazepines, including BYFAVO, and opioid analgesics may result in profound sedation, respiratory depression, coma, and death. The sedative effect of intravenous BYFAVO can be accentuated by concomitantly administered CNS depressant medications, including other benzodiazepines and propofol. Continuously monitor patients for respiratory depression and depth of sedation.

Contraindication

BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40.

Personnel and Equipment for Monitoring and Resuscitation

Clinically notable hypoxia, bradycardia, and hypotension were observed in Phase 3 studies of BYFAVO. Continuously monitor vital signs during sedation and through the recovery period. Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer BYFAVO. Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation. Resuscitative drugs, and age- and size-appropriate equipment for bag-valve-mask–assisted ventilation must be immediately available during administration of BYFAVO. Consider the potential for worsened cardiorespiratory depression prior to using BYFAVO concomitantly with other drugs that have the same potential (e.g., opioid analgesics or other sedative-hypnotics). Administer supplemental oxygen to sedated patients through the recovery period. A benzodiazepine reversal agent (flumazenil) should be immediately available during administration of BYFAVO.

Risks From Concomitant Use With Opioid Analgesics and Other Sedative-Hypnotics

Concomitant use of BYFAVO and opioid analgesics may result in profound sedation, respiratory depression, coma, and death. The sedative effect of IV BYFAVO can be accentuated when administered with other CNS depressant medications (eg, other benzodiazepines and propofol). Titrate the

dose of BYFAVO when administered with opioid analgesics and sedative-hypnotics to the desired clinical response. Continuously monitor sedated patients for hypotension, airway obstruction, hypoventilation, apnea, and oxygen desaturation. These cardiorespiratory effects may be more likely to occur in patients with obstructive sleep apnea, the elderly, and ASA-PS class III or IV patients.

Hypersensitivity Reactions

BYFAVO contains dextran 40, which can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis. BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40.

Neonatal Sedation

Use of benzodiazepines during the later stages of pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) in the neonate. Observe newborns for signs of sedation and manage accordingly.

Pediatric Neurotoxicity

Published animal studies demonstrate that anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. The clinical significance of this is not clear. However, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life but may extend out to approximately 3 years of age in humans.

Anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Adverse Reactions

The most common adverse reactions reported in >10% of patients (N=630) receiving BYFAVO 5-30 mg (total dose) and undergoing colonoscopy (two studies) or bronchoscopy (one study) were: hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia, and diastolic hypotension.

Use in Specific Populations

Pregnancy

There are no data on the specific effects of BYFAVO on pregnancy. Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to benzodiazepines during pregnancy and labor for signs of sedation and respiratory depression.

Lactation

Monitor infants exposed to BYFAVO through breast milk for sedation, respiratory depression, and feeding problems. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 5 hours after BYFAVO administration.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. BYFAVO should not be used in patients less than 18 years of age.

Geriatric Use

No overall differences in safety or effectiveness were observed between these subjects and younger subjects. However, there is a potential for greater sensitivity (eg, faster onset, oversedation, confusion) in some older individuals. Administer supplemental doses of BYFAVO slowly to achieve the level of sedation required and monitor all patients closely for cardiorespiratory complications.

Hepatic Impairment

In patients with severe hepatic impairment, the dose of BYFAVO should be carefully titrated to effect. Depending on the overall status of the patient, lower frequency of supplemental doses may be needed to achieve the level of sedation required for the procedure. All patients should be monitored for sedation-related cardiorespiratory complications.

Abuse and Dependence

BYFAVO is a federally controlled substance (CIV) because it contains remimazolam which has the potential for abuse and physical dependence.