Enalare Therapeutics Inc.

Developing and commercializing novel therapies for life-threatening acute respiratory and critical care conditions

April 2021

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dmotto@enalare.com

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Enalare Therapeutics Introduction

Who We Are

A clinical stage biopharmaceutical company dedicated to developing novel therapies for life-threatening acute respiratory and critical care conditions

Company Profile

- Portfolio of novel compounds with strong IP into 2030s and beyond
- Lead product ENA-001 preparing to initiate pivotal studies for Drug Overdose, commercial launch in ~ 2 years
- Multiple additional indications including blockbuster potential in Peri-op care
- Strong leadership with world class scientists and top tier industry operators

Recent Developments

- Closed successful $10 million seed round to expand operations and advance clinical readiness
- Strong interest from BARDA and NIH for grants and partnership
- Initiating Series A raise to fund development through expected 2022 NDA filing

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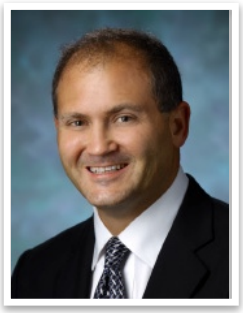
Enalare Senior Management & Board of Directors

Herm Cukier
Chief Executive Officer
& Board Member

- CEO and Board Member of BioDelivery Sciences (NASDAQ: BDSI)
- SVP of Allergan - leading several multi-billion dollar divisions
- Chief Marketing Officer and Member Company Management Team - Organon Biosciences
- Executive positions with top tier companies including Bayer, BMS, and Pfizer
- MBA Columbia Business School
- BSE University of Pennsylvania



Dr. Joseph Pergolizzi
Chief R&D Officer
& Board Member

- Internationally recognized thought leader in areas of perioperative and pain medicines, drug development and regulatory affairs
- Highly published in top tier journals
- Frequent scientific advisor for public and private companies
- Serial entrepreneur, started more than 20 companies
- Johns Hopkins School of Medicine
- Georgetown School of Medicine - residency

Daniel Motto
Chief Operating Officer

- EVP of Hikma Pharmaceuticals leading US Injectable Division
- SVP Allergan (Actavis) - Head of Business Development, Portfolio & Business Intelligence, Global Generic Medicines
- SVP Teva, Global Business Development
- Executive positions with top tier companies including Johnson & Johnson and Novartis
- MBA Johnson College of Business, Cornell University
- MS Engineering, Cornell

Board of Directors

Gino Santini
Former member of Eli Lilly's executive committee leading Corporate Strategy and Business Development. Prior roles over a career spanning nearly three decades included president of US operations, various leadership positions in international regions and president of the women's health franchise. Board member of multiple public companies including Horizon, Collegium and Intercept Pharmaceuticals.

Bob Yedid
30 yrs of experience as a buy-side analyst, portfolio manager, private equity investor and investment banker holding positions at Warburg Pincus and Bear Sterns. Currently focuses on providing CEOs and CFOs with strategic advice on key investor issues at LifeSci Advisors. Former Board member of The Medicines Co. and Vaxart. MBA Stanford School of Busines, BA Yale University.

Joseph Petko
20 yrs experience in corporate finance and investment analysis. Currently co-Chief Investment Officer for public equity investing at Ashford Capital, with a focus on small cap growth companies. Prior experience in financial positions in the pharmaceutical industry at Merck & Co. MBA Lehigh University, BBA Wharton, University of Pennsylvania.

Mark Coleman, MD
President of National Spine and Pain Centers, the nation's largest interventional pain management group. Early advisor in the formation of Axsome Therapeutics and a member of its board of directors since 2014. Diplomat of the American Board of Anesthesiology and highly sought after pharmaceutical and medical device scientific advisor. MD from Johns Hopkins University School of Medicine, BA Wesleyan Univ.

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Strong Scientific Advisory Board and support functions

Scientific Advisory Board

Lead Investigator

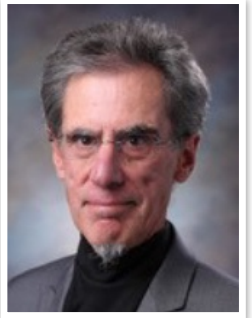
Albert Dahan, MD, PhD

World renowned expert in areas of anesthesia and pain and advisor to top regulatory agencies. Founder and Head of Anesthesia & Pain Research Unit at Leiden University. Member of several editorial boards and has published 100s of articles in peer reviewed journals. Leiden University Medical Center, Professor of Anesthesiology

Lead Investigator

TJ Gan, MD

Distinguished leader in anesthesiology working to define best-practice. Chairman of the Department of Anesthesiology at Stoney Brook Medicine and former faculty at the Duke Clinical Research Institute. Founding President of the American Society for Enhanced Recovery (ASER) and dedicated to improving perioperative care through his role in establishing Enhanced Recovery After Surgery (ERAS) programs.



Robert Raffa, PhD

Internationally renowned scientist and key opinion leader in pain pathways and analgesics. Over 30 years industry, academia and government experience in engineering and pharmacology. Former team co-leader for analgesics drug discovery at Johnson & Johnson. Currently affiliated with University of Arizona College of Pharmacy and Temple University School of Pharmacy

David Battleman, MD

A seasoned healthcare executive with over 20 years of experience, spanning academia, industry and management consulting. Prior to establishing TrueNorth Lifesciences, David served as a senior principal in the consulting practice within IMS Health. MD, Weill Cornell Medical College, MBA Wharton School of Business, M.Sc. Harvard School of Public Health

Alexander Kraus, PhD

Accomplished international executive with over 20 years experience in the pharma industry. Former Head of Pharmaco-kinetics at Grünenthal GmbH and Vice President TRF Business at Grünenthal USA, Inc. Frequent presenter on abuse prevention of prescription drugs. Former Head of Search & Evaluation at Aquestive Therapeutics.

Eugene Vortsman DO

Practicing emergency medicine specialist with experience treating substance abuse and COVID patients at the largest provider of healthcare in NY State, Northwell Health. Serves as the Medicine Lead for both the Opiate Task Force and Sepsis Task Force. Research experience at Northwell Health, Cornell-Presbyterian Hospital, and University of Medicine and Dentistry of New Jersey

Enalare Team

Alfred Schweikert, PhD, RAC - Regulatory Affairs

Over 35 years experience in the pharmaceutical industry, with 25 years devoted to management of regulatory affairs. Extensive global regulatory and development experience with drugs, devices and biologics covering the full life-cycle of development to post marketing. Prior roles with Hoffman La Roche, Schering Plough, Johnson & Johnson, and Baxter.

Frank Diana, PhD - Operations/CMC

More than 30 years experience with CMC (Chemistry, Manufacturing and Controls), Analytical and Pharmaceutical Development for early development through NDA/BLA submission as well as for marketed products. Prior roles with Endo Pharmaceuticals, Johnson & Johnson and DuPont.

NEMA RESEARCH
Clinical Research Organization (CRO)

Lowenstein Sandler
IP Counsel

NDAP
NDA Partners Model Informed Drug Development

Wollmuth Maher & Deutsch LLP
Corporate Counsel

pulsecx
Healthcare Marketing

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Acute Respiratory Depression – A National Health Emergency

Respiratory Depression

Respiratory Depression is a condition characterized by slow and ineffective breathing resulting in:

- low levels of oxygen (hypoxemia) and/or
- high levels of carbon dioxide (hypercapnia)

If left untreated it can cause life-threatening complications, and in some cases, death.

Common Causes:

Medications

- Sedatives
- Narcotics for pain
- Alcohol
- Other substances that depress brain function
- Synergistic effect from drug combinations

Health Conditions

- Obesity and aging
- Viral or bacterial infections (e.g. COVID)
- Neuromuscular diseases
- Sleep apnea
- Chronic lung diseases

Initial Target Markets

Drug overdose

- US deaths reached record high of 86K[1] and rapidly growing
- Polysubstance (multi-drug) abuse a growing issue
- Current treatment option is incomplete – only addresses opioid overdose
- Expedited pathway to market expected

Post-operative care

- Large and growing at-risk populations – aging, obesity, other
- Unmet medical need, 10x in-hospital mortality risk[2]
- 70mil+ surgeries in US performed annually
- Compelling health economic benefits by reducing ICU/overall hospital length of stay
- Significant long-term commercial potential – US and Ex-US

Respiratory infections

- Acute and chronic respiratory complications associated with infections
- COVID-19 pandemic highlighting risks – e.g. silent hypoxemia
- High mortality rate if require ventilator
- Urgent need for new therapies to address on-going incidence and pandemic spikes

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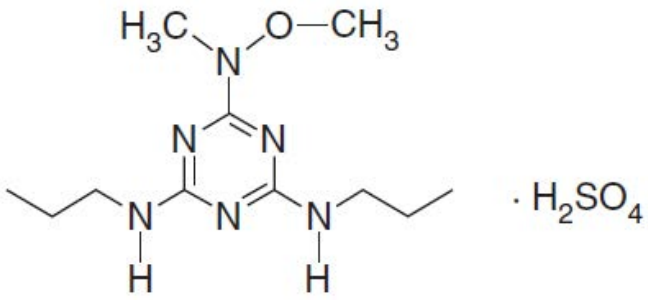
[1] US HHS, Centers for Disease Control and Prevention (CDC), Provisional Drug Overdose Death Counts 12-month ending July 2020, data available as of Feb 7, 2021
[2] Postoperative Respiratory Failure, Thompson, Shaun L.; Lisco, Steven J, International Anesthesiology Clinics. 56(1):147-164, Winter 2018

ENA-001: A first-in-class New Chemical Entity (NCE)

Agnostic Ventilatory Stimulant

- Novel mechanism-of-action (MoA) - inhibits Big Potassium (BK) ion channels
- Utilizes body's chemical ventilation control system to beneficially influence breathing
- Affects ventilation via the peripheral chemoreceptor pathways in the carotid body



ENA-001 hydrogen sulphate salt

2-N,O-dimethylhydroxylamino-4,6-bispropylamino-s-triazine

Product Profile

- Stimulates ventilation in patients with acute respiratory insufficiency, irrespective of the depressive cause
- Addresses hypercapnia (high CO_2) and hypoxemia (low O_2) caused by drug overdose and peri-operative conditions
- Safe and well tolerated
- Does not interfere with pain suppression or sedation
- No combative withdrawal (vs opioid antagonist)
- Duration that mimics that of fentanyl derivatives and other common depressive agents

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ENA-001 development significantly de-risked given abundance of data and clear pathway forward

Advanced Development Status

- Extensive clinical and non-clinical data:
  - Proof-of-concept with multiple depressive agents in animals
  - 12 tox studies across multiple species (incl. 28 day)
  - 4 clinical studies – dosing, safety and proof-of-concept in Humans (incl. 5-day infusion)
- Open IND with FDA
- Over $35mil invested
- 10yrs+ of development
- Issued compound patents and additional IP pending
- New drug product (API) complete, clinical supply underway
- Next-generation formulation development initiated – bolus/Intramuscular
- BARDA partnership and grant funding
- Fast Track designation engagement with FDA

Next Steps (2021)

- Finalize clinical protocol for drug overdose pivotal study (FDA feedback pending)
- Model-Informed Drug Development (MIDD) on dosing
- Clinical trial start 2H 2021
- Intra-muscular (IM) development and next-gen IV formulation
- Development plan for post-operative respiratory depression indication
- File additional patents

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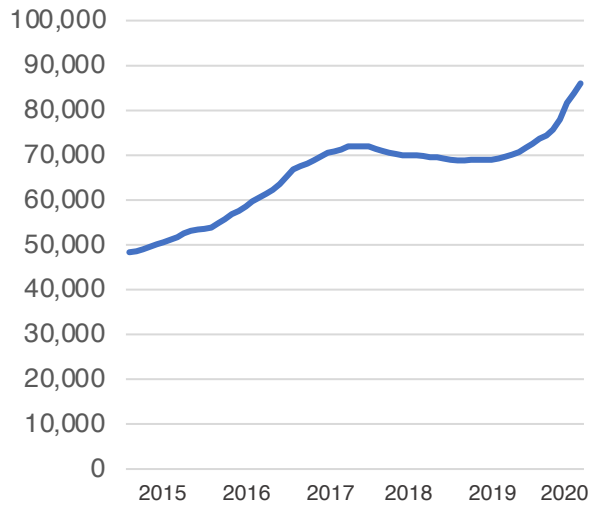
Multiple indications for respiratory depression present a significant $1billion+ market opportunity

Drug Overdose

- Sales potential (yr 5) of $350M to $500M+
- Drug overdose deaths at record high
- Clear unmet medical need for poly-substance overdose and potent, long duration opioids

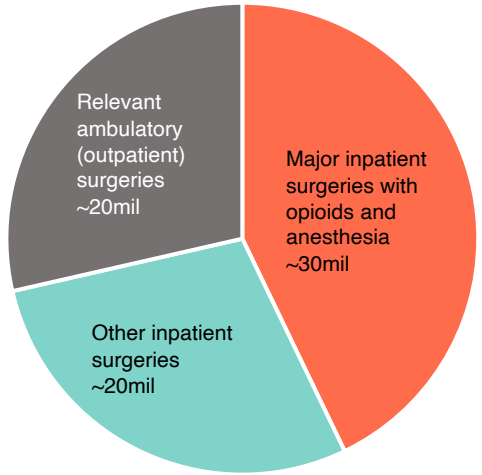
Number of Drug Overdose Deaths US CDC, 12 Months-ending July 2020[1]



Post-Operative

- Sales potential (yr 5) $650M to $1.5B+
- High incidence of respiratory depression episodes (> 40%), significant cost burden
- Limited treatment options available

70+ million procedures performed annually in the US[2,3]



Resp. Infections/COVID

- Sales potential (yr 5) $75M to $250M+
- Increasing trend in ventilator use, even pre-COVID-19 pandemic
- Risk from future pandemic events

Critical need for pharmacological treatment options

- ✓ On-going incidence of ~200K sepsis/ respiratory infections annually
- ✓ COVID-19 lung damage and on-going complications
- ✓ Severe risks associated with silent hypoxemia (low O_2 levels)
- ✓ Challenge of weaning patients off ventilators
- ✓ Enhance CPAP treatment

[1] US HHS, Centers for Disease Control and Prevention (CDC), Provisional Drug Overdose Death Counts 12-month ending July 2020, data available as of Feb 7, 2021
[2] Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic, Anesth Analg. 2017 November ; 125(5): 1733–174
[3] Ambulatory Surgery Data From Hospitals and Ambulatory Surgery Centers: United States, National Health Statistics Reports, Number 102, February 28, 2017

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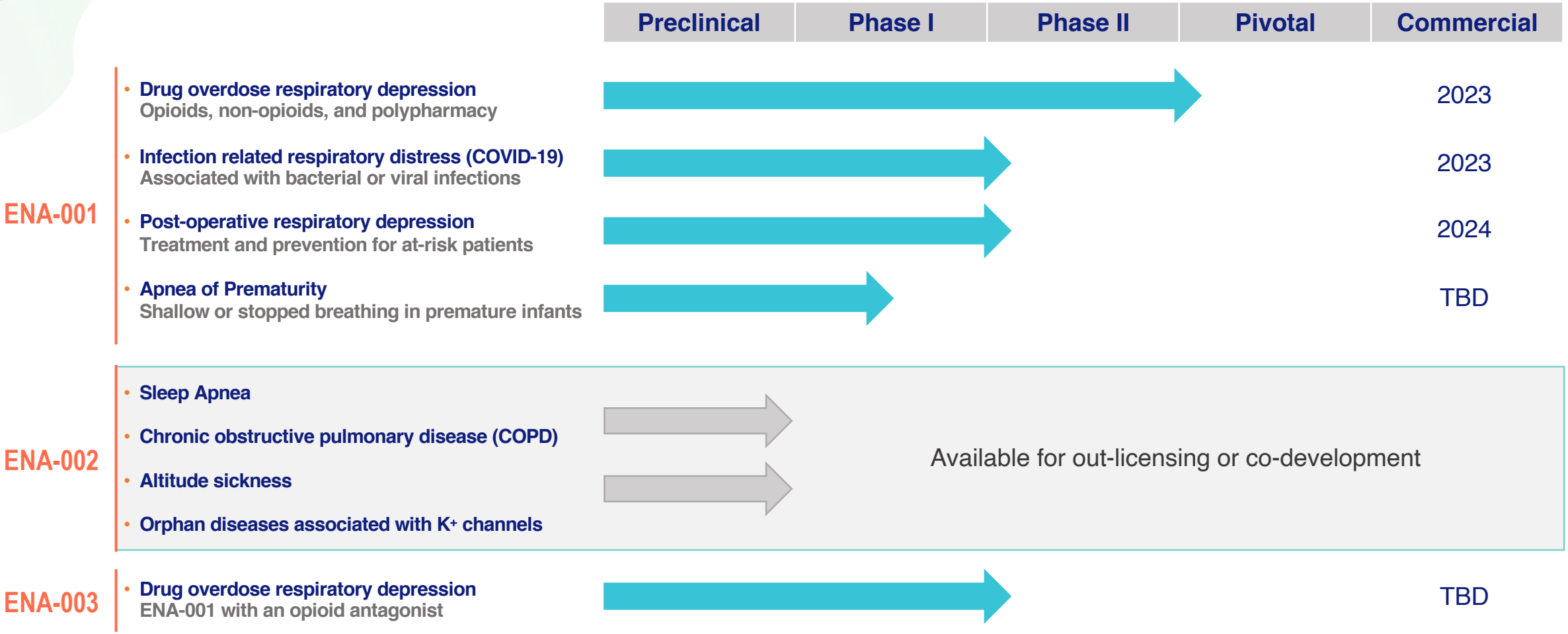
Enalare's pipeline has the potential to dramatically improve medical practice and patient outcomes in multiple settings



ENA-001/ENA-003: Ex-US geographies available for out-licensing

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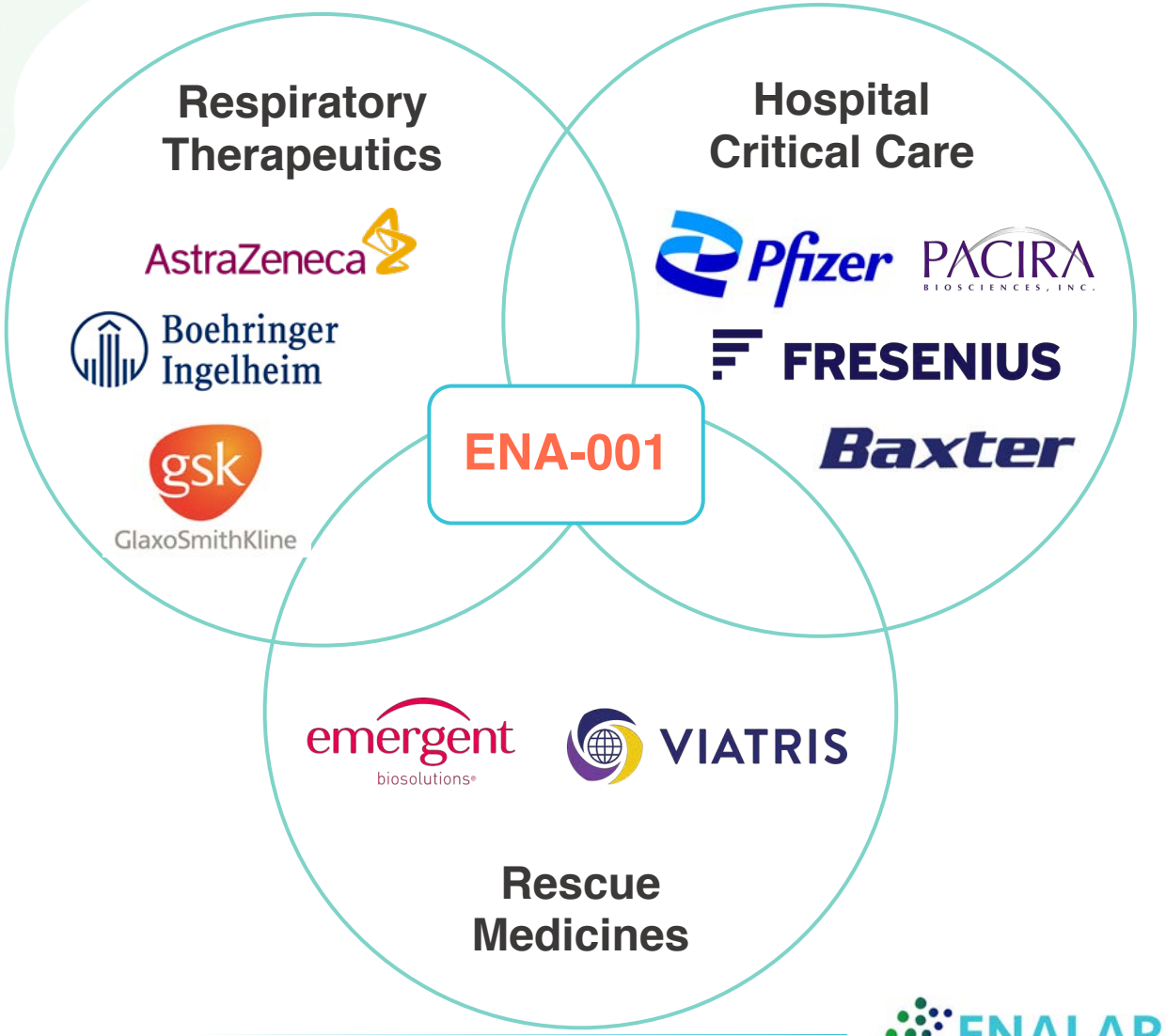
ENA-001's broad applications span several segments of the healthcare market



Healthcare categories:

- Respiratory Therapeutics
- Hospital Critical Care
- Rescue/Emergency medicine

ENA-001 for the treatment of respiratory depression:

to stimulate ventilation in patients with acute respiratory insufficiency, including such conditions as persistent postoperative hypoxemia and drug induced respiratory depression

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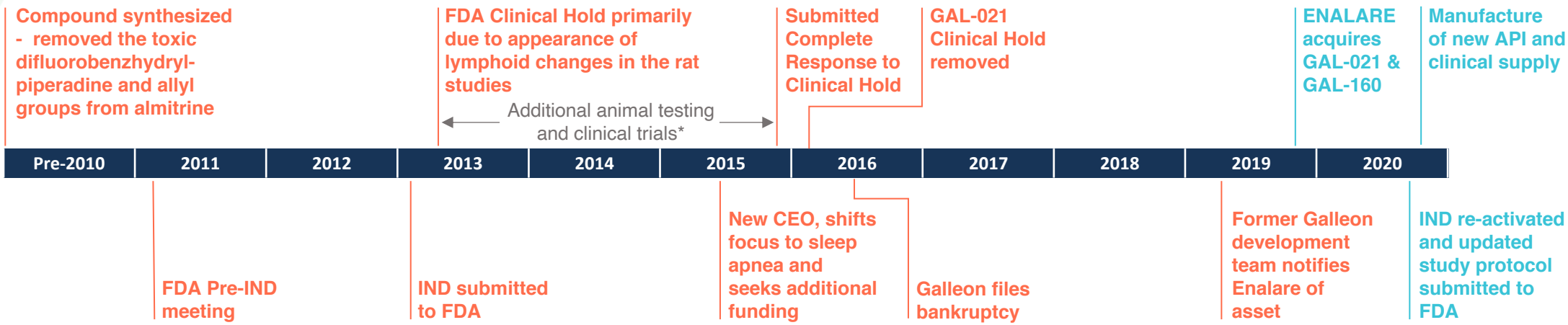
ENA-001 historical development timeline
$35+ million invested to-date

Galleon Pharmaceuticals Development of GAL-021 (now ENA-001)



Market Developments

Growing need for a new respiratory stimulant

- **Obesity and aging population increasing respiratory risks**
- **US substance abuse epidemic accelerates**
- **COVID-19 pandemic highlights risks of infection-related respiratory distress**

*GAL-021-104 & 106 studies in humans approved by the Dutch Early Ethics Committee

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ENA-001's strong intellectual property includes issued composition-of-matter patents

Issued Patents

- **US 9,351,972**

  Compounds as Respiratory Stimulants for Treatment of Breathing Control Disorders or Diseases

  Includes NCE and Pharmaceutical Composition claims

  Expires 11/29/2031 (+ PTE opportunity)

- **US 9,162,992**

  Compounds and Compositions for Treatment of Breathing Control Disorders or Diseases

  Includes NCE, Pharmaceutical Composition and Method of Treatment claims

  Expires 11/29/2031

Patent and Trademark Applications

- Pending International PCT Application directed to combination therapy for the treatment of opioid overdose, stimulant overdose and polypharmacy overdose. Anticipated expiration of 2040
- Pending U.S. Provisional Application directed to composition and methods for the treatment of respiratory depression in infected patients (including COVID-19). Anticipated expiration of 2041
- 'Enalare' and 'Enalare Therapeutics' trademark applications pending and website domain secured (www.enalare.com)

Patent term extension (PTE) opportunity of up to 5 years on issued patent
Filing strategy in place for future patent opportunities including pharmaceutical formulations, pharmacokinetic/pharmacodynamic profiles, new indications and dosing regimens

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ENA-001 shown to be safe and efficacious across four clinical trials totaling ~100 subjects

Study	Description	# of Subjects
GAL-021-101	Single, ascending dose study in healthy subjects.	30
GAL-021-102	Extended the dose range explored during the initial study by a factor of 2 and established the maximum respiratory stimulatory dose in the healthy subjects without concomitant use of opioids or anesthetic agents.	18
GAL-021-104	Assessed the potential therapeutic utility under conditions that simulate the post-operative state. Alfentanil was used to suppress ventilation.	23
GAL-021-106	Designed to evaluate the safety and tolerability in healthy subjects during 5 days of 12-hour continuous infusion of 0.125, 0.25, and 0.5 mg/kg.	28

- ✓ Dosing
- ✓ Proof-of-Concept Efficacy
- ✓ Safety & Tolerability

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Enalare presents a compelling investment opportunity

Poised to fundamentally change clinical practice in the treatment of acute respiratory depression

✓ Significant medical need	• Convergence of health emergencies with commonality of respiratory depression • Critical need for a safe, agnostic ventilatory stimulant in multiple treatment settings
✓ Robust proof-of-concept	• Positive safety and efficacy results across four human trials • Extensive pre-clinical platform, including 12 toxicology studies in multiple animal species
✓ Clear & expedient path to market	• Well defined development program with clear endpoints for reversal of respiratory depression • Initiating registration trials for lead indication – estimate approval in ~ 2 years
✓ Large market opportunities	• Broad medical and health economic benefits driving $1.5B+ sales potential* • Novel mechanism-of-action with patent protection through 2031, additional patents pending
✓ Proven top-tier team	• Demonstrated ability to develop and launch blockbuster products with consistent value creation • Industry leading scientists and advisors

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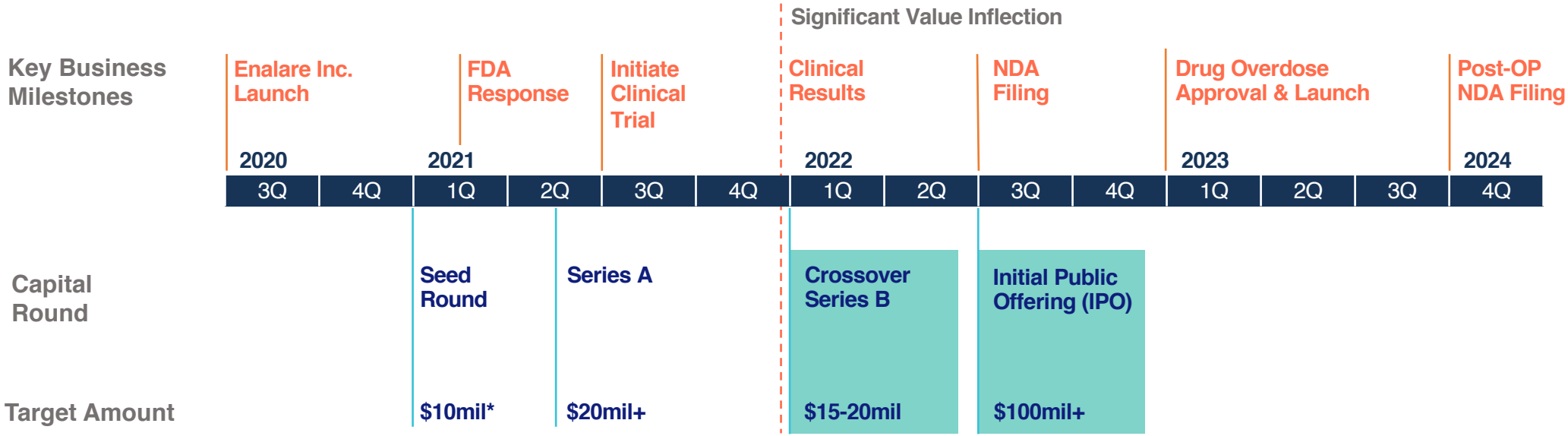
*Enalare internal analysis

Enalare proposed capital plan with key milestones



Key Expenses

• API production • Clinical supply • Drug development modeling	• Clinical trial • IP Development • Next-gen formulation	• 2nd Clinical (drug overdose) • Post-Op Phase II • NDA preparation	• Launch prep • Commercial supply • Staff expansion	• Launch execution • Post-Op Phase III • Pipeline expansion

*Exceeded original target of $3-5mil

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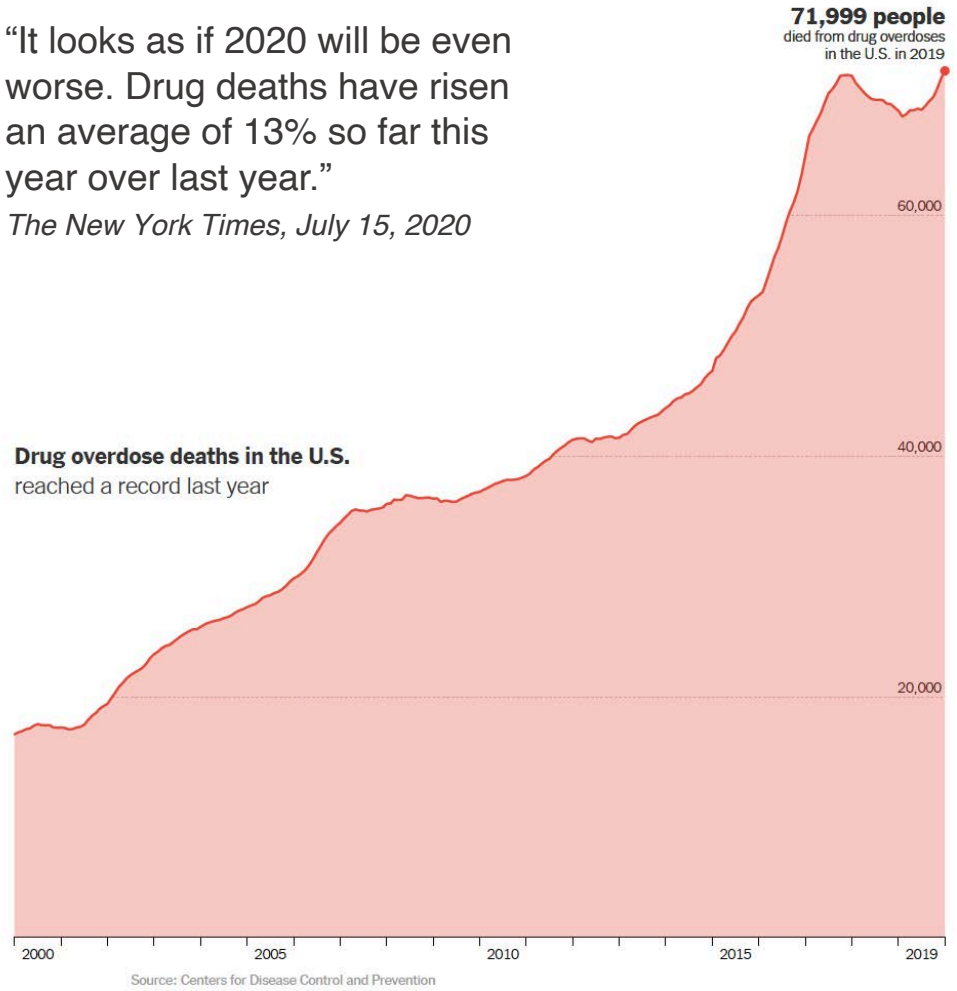
The drug overdose epidemic is escalating and evolving - dire need for an agnostic respiratory stimulant

- Drug deaths in the US rose to record levels in 2020
- COVID-19 has only further accelerated this trend, with 86,001 overdose deaths reported by the CDC[1]
- Poly-pharmacy (multiple drug) abuse is estimated at greater than 40% and rising[2]
- For every drug overdose that results in death, there are many more non-fatal overdoses
  - Approximately 20mil users misuse opioids and other depressant drugs annually[3]
  - Significant burden on healthcare systems, hospital resources and payors[4]
- Naloxone (approved in 1971) is the only marketed reversal agent – problematic and incomplete:
  - Efficacy limited to opioid overdose
  - Agitated patients consume significant ER resources

"It looks as if 2020 will be even worse. Drug deaths have risen an average of 13% so far this year over last year."

The New York Times, July 15, 2020



[1] US HHS CDC, 12-month ending July 2020, data available as of Feb 7, 2021
[2] NIH National Institute on Drug Abuse
[3] Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health, SAMHSA, U.S. Department of Health and Human Services
[4] Opioid Overdoses Costing U.S. Hospitals an Estimated $11 Billion Annually, Premier Inc, January 2019

Current treatments for drug overdose are inadequate and ill suited for many treatment scenarios

Drug overdose assessment - many unknowns

- ? Drugs involved, poly-pharmacy, potency
- ? Medical history, concomitant conditions
- ? Potential for agitation/ combativeness and other withdrawal symptoms

Treatment needs:

- ✓ Effective agnostic ventilatory stimulant for multiple drug classes
- ✓ Fast onset, long duration of action
- ✓ No precipitated withdrawal or reversal of analgesia
- ✓ Favorable safety profile across patient types

"I just need to make sure the patient is breathing and then I can focus on treatment."

Emergency Medicine Physician

Approved products	Indication	Product Issues
Naloxone (Narcan) approved 1971	Opioid overdose	• Opioid withdrawal symptoms • Removes pain relief • Potential agitation • Short duration
Flumazenil (Romazicon) approved 1991	Benzodiazepine overdose	• Contraindications and the possibility of it causing severe adverse effects including seizures, adverse cardiac effects, and death
Doxapram (Dopram) approved 1965	Mild to moderate respiratory and CNS depression due to drug overdosage	• Side effects include high blood pressure, panic attacks, rapid heart rate, tremor, sweating, and vomiting. Convulsions have been reported. • Contraindicated in people with coronary heart disease, epilepsy, and high blood pressure.

Opioids: fentanyl, hydrocodone, oxycodone, morphine, etc.
Benzodiazepines: diazepam (Valium), alprazolam (Xanax), clonazepam (Klonopin), etc.

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Post-operative respiratory distress – Significant risk to patient safety and time delays within surgical theater

Up to 36% of patients are high risk of respiratory depression following surgery[1]

Current treatment options are limited

Post-operative Respiratory Depression

Increasing Severity

1. Check airway for obstructions, verbal & physical stimulation
2. Oxygen supplementation
3. Positive pressure ventilation (e.g. CPAP)
4. Reduce opioid use
5. Administer naloxone and/or flumazenil

Intubation/Ventilator
Risk for patient and significant cost for healthcare system

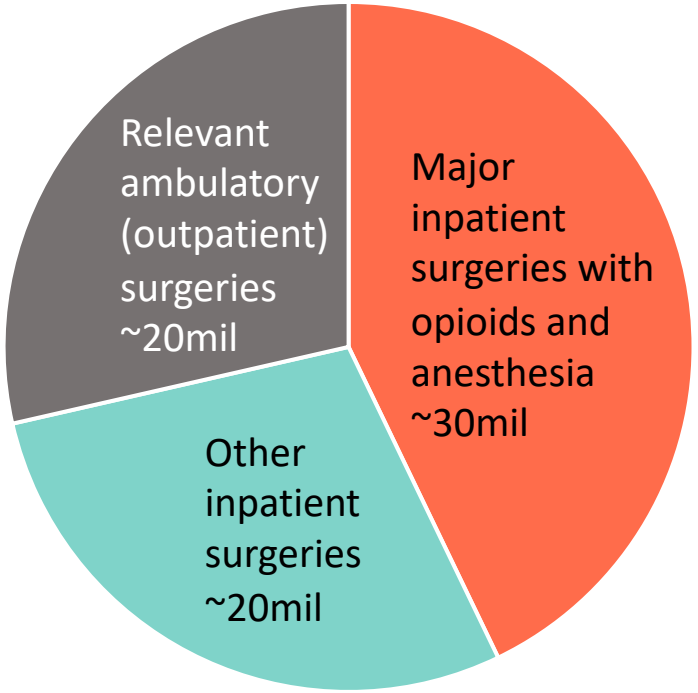
Target properties for a respiratory stimulant therapeutic in the post-operative setting

Desired Properties	ENA-001
Improves respiration	✓
Does not affect analgesia	✓
Works quickly	✓
Works under conditions of hypercapnia (rising CO_2)	✓
Pharmacokinetics that allow for easy adjustment	✓
Enhances the ventilatory response under hypoxic conditions (low O_2)	✓
Works with analgesics and other suppressive classes	✓

[1] Prediction of Opioid-Induced Respiratory Depression on Inpatient Wards, A. Khanna, et al. Anesthesia & Analgesia: October 2020

Large post-operative market opportunity with compelling health economics around treatment of respiratory depression

70+ million procedures performed annually in the US



50 million inpatient procedures[1]

20 million outpatient procedures[2]

Respiratory Distress presents a major cost burden on hospitals[3,4,5,6]

Incremental hospital stay with a respiratory event	• 5-9 days • 2-3X multiple
Incremental costs with a respiratory event	• Avg. $50-60K/ hospitalization • 4X+ multiple
ICU Admissions (unplanned)	• 17-47% have a respiratory indication
Mechanical ventilation costs	• $27 billion annually (1/3 of ICU costs)

[1] Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic, Anesth Analg. 2017 November ; 125(5): 1733–174
[2] Ambulatory Surgery Data From Hospitals and Ambulatory Surgery Centers: United States, National Health Statistics Reports, Number 102, February 28, 2017
[3] Characterisation and monitoring of postoperative respiratory depression: current approaches and future considerations, S. Ayad, *et al.* British Journal of Anaesthesia, 123 (3): 378e391, 2019
[4] Association of Opioids and Sedatives with Increased Risk of In-Hospital Cardiopulmonary Arrest from an Administrative Database, February 25, 2016
[5] Premier Market Research Hospital Database Study, Galleon Pharmaceuticals, 2012
[6] Rao, et al."Postoperative Respiratory Impairment Is a Real Risk for Our Patients: The Intensivist's Perspective," Anesthesiology Research and Practice, vol. 2018

COVID-19 and other viral and bacterial infections leading to lung complications and acute respiratory distress

COVID-19

- The COVID-19 pandemic and others like it will be a concern for the global population in the years ahead
- Over 28 million US infections, deaths now exceed 500,000[1]
- Virus expected to persist even with vaccines and improved treatment
- US Federal programs for accelerated pathways to market for new therapeutics:
  - Emergency Use Authorization (EUA)
  - Coronavirus Treatment Acceleration Program (CTAP)
  - Expanded access

Lung Damage & Respiratory Distress

- COVID-19 can cause respiratory issues such as pneumonia and silent hypoxemia
- Sepsis, and other possible complications of COVID-19, can also cause lasting harm to the lungs
- ~5% of symptomatic COVID-19 patients require admittance to ICU
- Respiratory distress may require CPAP and/or mechanical ventilation for serious cases
- Currently 30-50% mortality rate for patients put on ventilators

Role of ENA-001

- ENA-001 has been called a "pharmacologic ventilator"[2] and it may have role as an add-on therapy for certain cases
  - Delay or prevent mechanical ventilation
  - Enhance CPAP
  - Aid in weaning off ventilator
- A recent study in COVID patients with a similar compound, almitrine, showed potential beneficial effects
- ENA-001 may improve patient outcomes by a reduction in the risk for oxygen deprivation
- Potential management option for acute and chronic symptoms

[1] Johns Hopkins University, as of Feb. 26, 2021
[2] Joseph F. Cotten, MD, PhD, Editorial, *Anesthesiology*

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ENA-001 formats will address the administration requirements of multiple treatment settings

Format		Treatment setting: Operating Room (OR) Intensive Care Unit (ICU) Post Anesthesia Care Unit (PACU)	Treatment setting: Emergency Room (ER)	Treatment setting: Field-based administration (emergency responder)
Vial - bolus or continuous infusion Intravenous (IV)		X	X	
Pre-filled Syringe Intramuscular (IM)		X	X	X
Autoinjector Intramuscular (IM)				X

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ENA-001 is well positioned for success in today's healthcare environment

Key characteristics critical for a successful launch

Commercialization/ market coverage

Focused commercial targets – hospitals, clinics, emergency responders

- Ability to achieve 80%+ market coverage with 60-80 field-based personnel
- Enalare's leadership team has decades of experience building and managing pharmaceutical commercial teams and supporting infrastructure

Health economics/ value proposition

Strong Health Economics and Outcomes Research (HEOR) support

- Reduced length of hospital stay
- Reduced admittance to ICU
- Reduced need for re-intubation or ventilation
- Reduced mortality

Access

Clear decision makers and 1st-in-class status

- Hospital Pharmacy and Therapeutics (P&T) committees: evaluate the clinical use of medications and develop policies for managing access to them
- ENA-001 is a 1st-in-class, unique drug – no comparators or need to show improvement over an existing therapy

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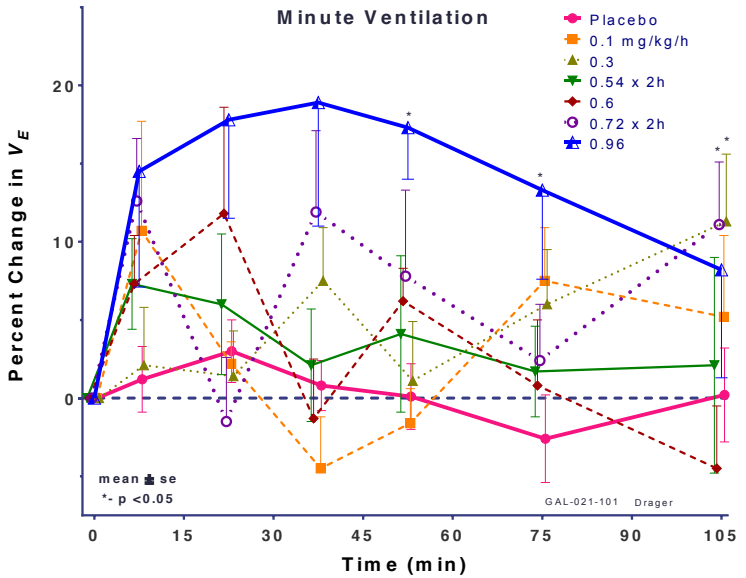
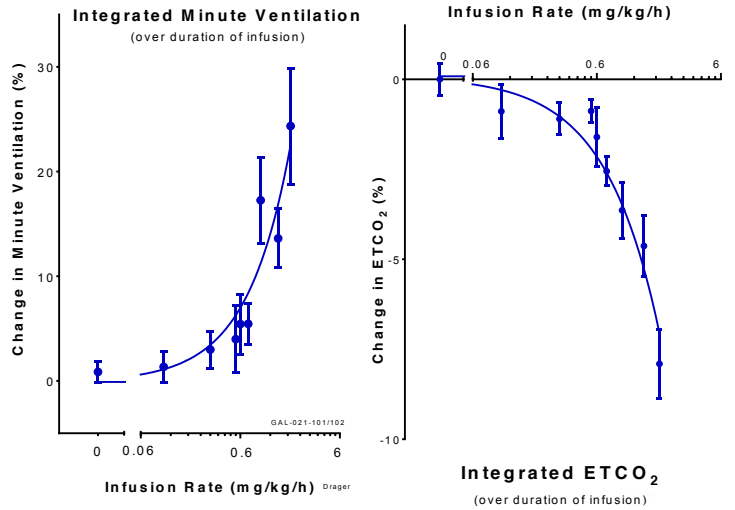
Clinical study 101/102: two rising single dose studies

- Repeated single-dose designs in healthy volunteers
  - Dose range: 0.1 to 1.92 mg/kg/h
- Safety - clean to ~1.1 mg/kg/h
  - Hyperventilation and hypocapnia in 2 subjects at 1.92 mg/kg/min
  - $ETCO_2$ -↓to 22 and 29 torr
  - IV site burning sensation (partially pH - related)
  - GI (N/V) – 4 subjects (top 2 doses)
  - Clinical chemistries – no change
- Pharmacodynamic (PD)
  - Increasing Minute Ventilation and decreasing $ETCO_2$
- Pharmacokinetic (PK)
  - Rapid rise and decline with infusion – Terminal half life (t1/2) of 5.6 hours





Minute Ventilation is defined as the total volume of gas entering (or leaving) the lung per minute and is calculated as the product of tidal volume and respiratory rate

$ETCO_2$: End Tidal CO_2. Maximal concentration of carbon dioxide (CO_2) at the end of an exhaled breath

Clinical study 104 proof-of-concept study design with alfentanil

Goal: Test ENA-001 IV under challenging conditions that simulate post-surgical care

- High carbon dioxide (also desensitizes ventilatory control arc to drugs)
- Opioid doses that cause moderate to severe respiratory depression
- Concomitant anti-emetics (required by opioid use)
- No interference with opioid analgesia

Period	Part 1	Part 2 (+ analgesia testing)
1	Baseline (n=12)	Baseline (n=8)
2	CO_2 increased and clamped	Ambient air
3	Alfentanil (titrated) and continued	Same drug doses
4	ENA-001 at 0.4 mg/kg/hr	Same drug doses
5	ENA-001 at 1.1 mg/kg/hr	Same drug doses
6	Alfentanil increase X 2	Same drug doses
7	Continue CO_2 clamp & stop drugs	Ambient air
Respiratory parameters measured on last 10 min of each 30+ minute period		

Design: Double-blind, placebo-controlled, 2-part, 4-period crossover study in 23 healthy subjects

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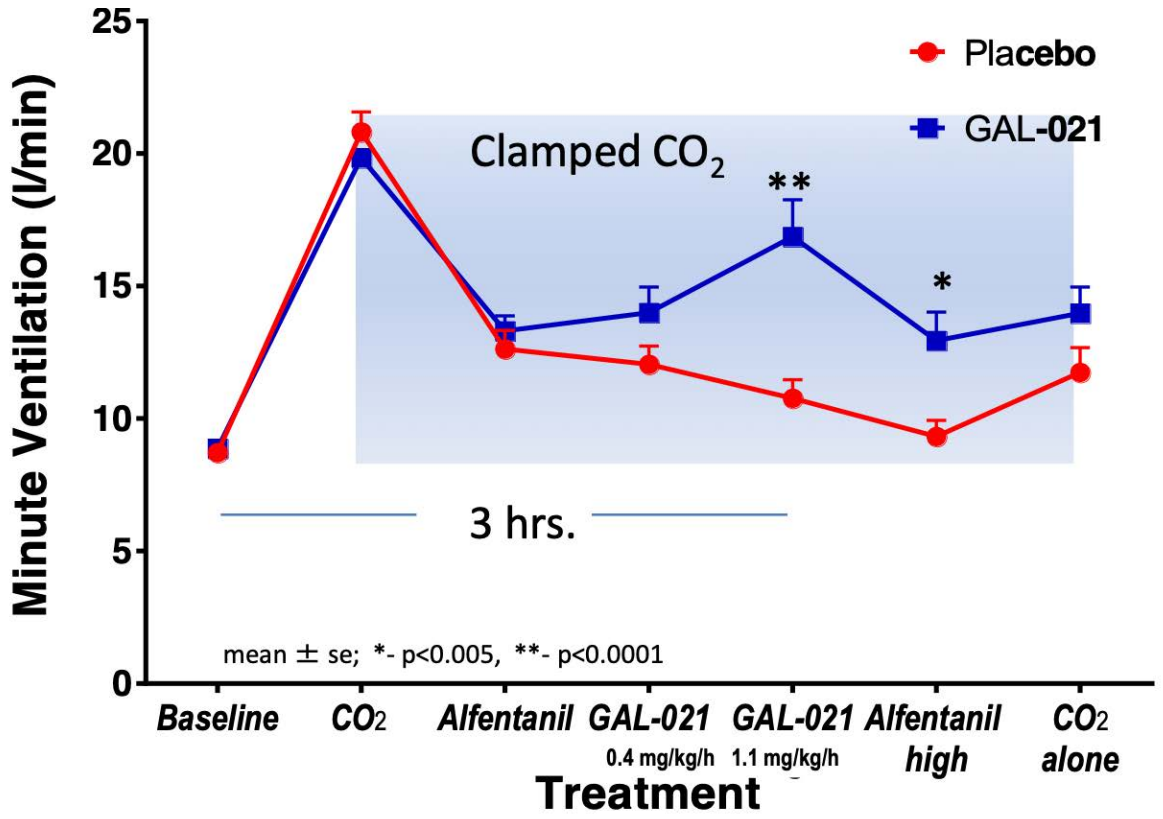
Clinical study 104: part 1 - respiratory stimulatory effects in subjects with impaired respiratory drive

1. Starting baseline
2. Minute ventilation increased rapidly with CO_2 administration to ≈ 20 l/min
3. Alfentanil administration decreased CO_2 - stimulated minute ventilation by 64% which further declined during the subsequent segments with placebo treatment
4. Low dose ENA-001 (0.4 mg/kg/h) tended to increase minute ventilation (9.8% vs. placebo, p ≈ 0.07)
5. High dose ENA-001 (1.1 mg/kg/h) further increasing minute ventilation (21.4%, p < 0.0001)
6. Alfentanil and infusion rate increase, minute ventilation declined for both GAL-021 and placebo while statistically significant separations continued
7. Stop Alfentanil and ENA-001 administration



GAL-021 = ENA-001

Minute Ventilation is defined as the total volume of gas entering (or leaving) the lung per minute and is calculated as the product of tidal volume and respiratory rate

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Study 106: rising multiple dose 5-day study of ENA-001

Objectives: Safety, Tolerability, Pharmacokinetics (PK)

- Standard Double Blinded, Placebo Controlled Study
- Infusions: 12 hours x 5 days
- Three Dose Levels (0.125, 0.25, 0.5 mg/kg/h)
- n= 28 subjects

Study 106 Results	
Safety & Tolerability	• Well tolerated except for infusion site burning sensation and local phlebitis after several days of the infusions • CV parameters similar (corrected for baseline) – Blood pressure transient post-infusion increase – Cardiac intervals unchanged • Endocrine-metabolic parameters similar to placebo
Pharmacokinetics (PK)	• Similar Days 1 and 5 • "well-behaved" PK

Pivotal clinical trials will be conducted by a leading world expert on acute respiratory depression

Dr. Albert Dahan

Professor Anesthesiology,
Leiden University Medical Center
The Netherlands

- FDA Advisor/subject matter expert
- Focus on the physiology and pathophysiology of respiratory regulation
- Chairman of the LUMC Institutional Review Board
- Founder and Head of the Anesthesia & Pain Research Unit
- Published over 300 papers in peer-review journals
- MD, VuMC Amsterdam
- PhD, Leiden University

Collaboration with Enalare

- Member of Enalare Scientific Advisory Board
- Developing ENA-001 study designs and will conduct registrational clinical studies
- Enalare sponsoring postdoctoral fellowship under Dr. Dahan

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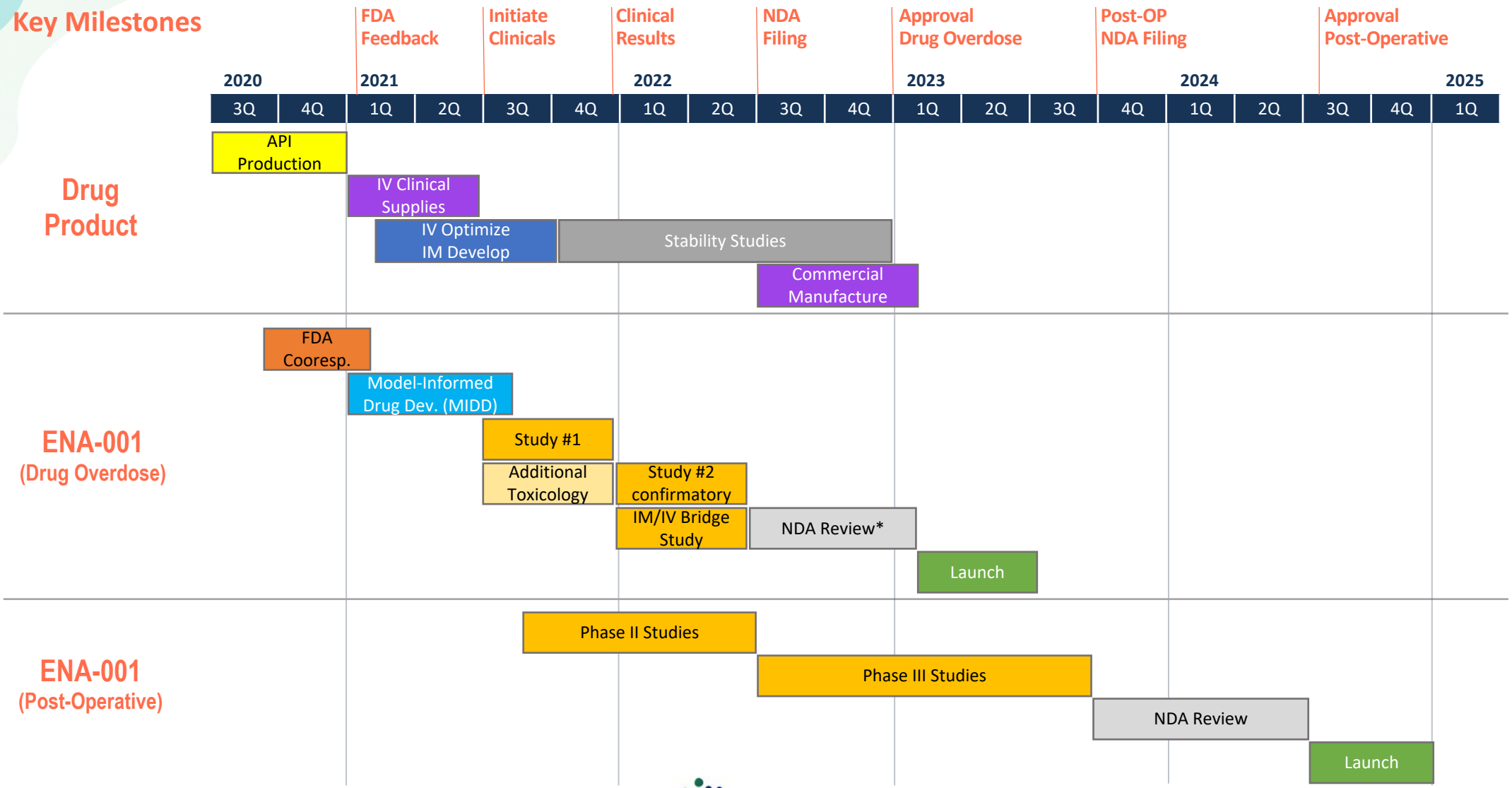
For more information:

www.enalare.com

Enalare's compounds qualify for multiple non-dilutive funding opportunities

US Agency	Biomedical Advanced Research and Development Authority (BARDA)	National Institutes of Health (NIH)	Department of Defense (DoD)	NIH/FDA/CDC SBIR
Division	Chemical Medical Countermeasures (CMC)	National Institute on Drug Abuse (NIDA)	Army Medical and Materiel Command (USAMRMC)	Small Business Innovation Research Grants (SBIR)
Mission	Enhancing the Nation's public health security and emergency preparedness	Advance science on the causes and consequences of drug use and addiction	Provide solutions to medical problems of importance to the American Service	Advance promising technologies and products that align with the mission to improve health and save lives.
Status	Progressed to Stage II evaluation	Application underway	Under evaluation	Under evaluation

ENA-001 clear and rapid path to market



* Fast Track designation requested, opportunity for Breakthrough Therapy

BACK-UP

The complex human ventilatory control system provides multiple pathways for affecting respiration

The chemical ventilation control system relies on a set of chemosensors:

- Brainstem (central chemoreceptors)
- Carotid bodies (peripheral chemoreceptors)

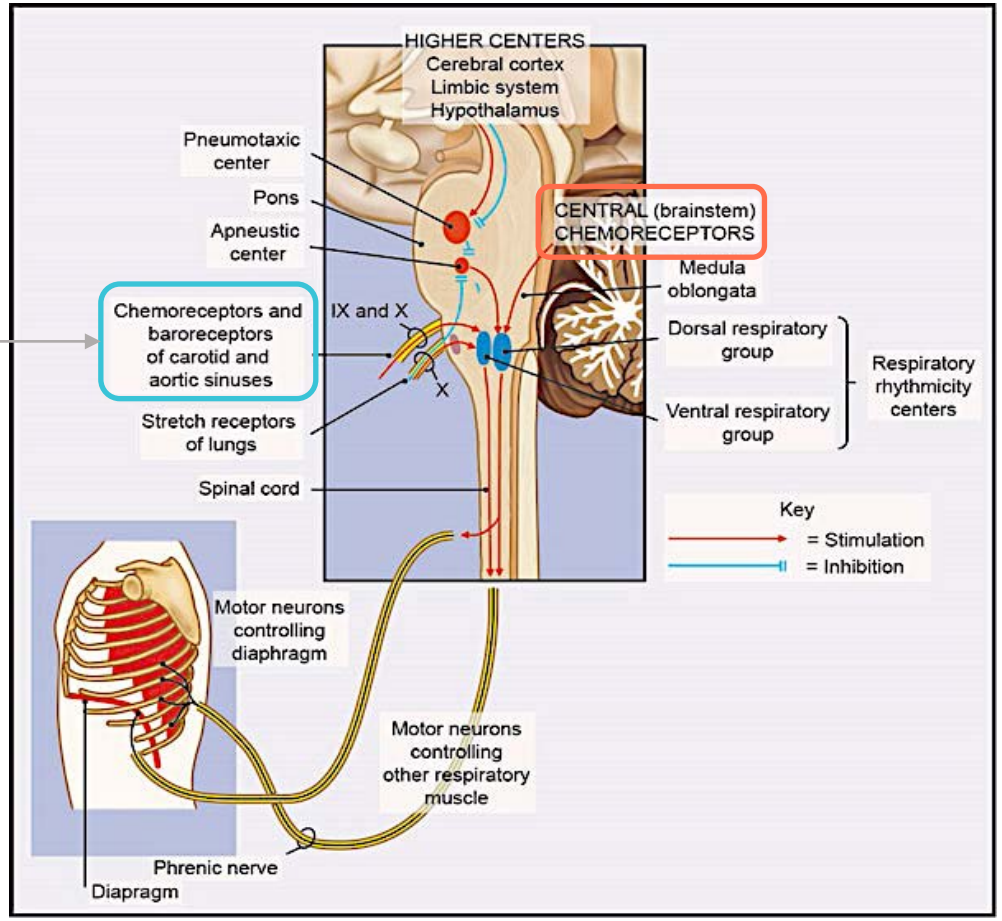
Deviations from chemical cellular homeostasis will typically result in adaptations in breathing frequency and tidal volume.

A variety of different receptors are expressed on respiratory neurons, and their activation or inhibition will directly affect breathing.

Depending on the circumstances, this may be:

- Advantageous (specific receptor agonists/antagonist may beneficially influence breathing); or
- Disadvantageous (specific drugs may depress ventilation, causing potentially fatal conditions)

ENA-001 affects ventilation via the peripheral chemoreceptor pathways
Safely activating peripheral signals to stimulate breathing



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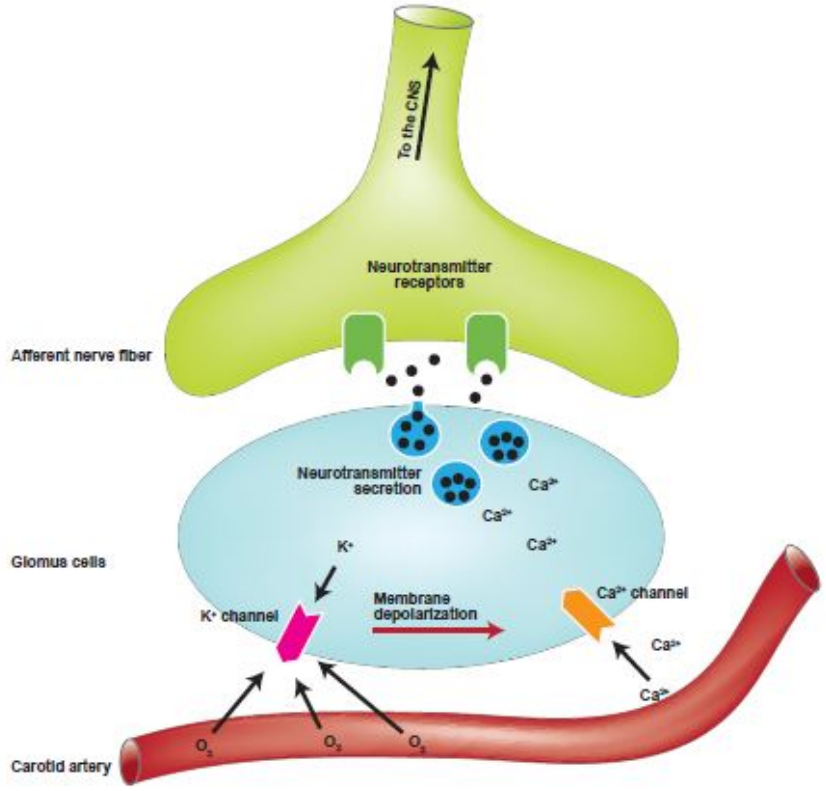
BACK-UP

ENA-001's unique Mechanism of Action (MoA) safely stimulates the peripheral breathing components

- ENA-001 acts through large-conductance Ca^{2+} and voltage-activated K^+ channels in the carotid body to stimulate respiration and increase minute ventilation
- The primary molecular mechanism underlying the ventilatory stimulant effects of ENA-001 appears to be functional inhibition of big potassium (BK) channels.*
- The beneficial effects on respiration are assumed to derive by mimicking the hypoxic (low O_2) inhibition of BK channels: this promotes depolarization of carotid body type I cells and precipitates voltage-gated Ca^{2+} influx where the resultant increase in intracellular Ca^{2+} ($[Ca^{2+}]_i$) elicits neurotransmitter release to activate sensory afferent discharge to the brainstem (via the carotid sinus nerve) and ultimately to corrective changes in breathing.



Schematic Model of Oxygen Sensing in the Carotid Body

*Exploring secondary MoA

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BACK-UP