UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **December 6, 2022**

Eagle Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-36306**	**20-8179278**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

50 Tice Boulevard, Suite 315 **Woodcliff Lake, NJ** (Address of principal executive offices)	**07677** (Zip Code)

Registrant's telephone number, including area code: **(201) 326-5300**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligations of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol**	**Name of each exchange on which registered**
Common Stock (par value $0.001 per share)	EGRX	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On December 6, 2022, Eagle Pharmaceuticals, Inc., or the Company, released an investor presentation relating to the Company's hospital-based products and product candidates, including BARHEMSYS, BYFAVO, Landiolol, and CAL02 and Enalare Therapeutics Inc.'s ENA-001. The Company will refer to the presentation during its previously announced Investor Day taking place on December 6, 2022, at 8:00am ET.

A copy of the above-referenced presentation is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference. The information furnished pursuant to Item 7.01 of this current report, including Exhibit 99.1, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities of that section, and shall not be deemed incorporated by reference into any of the Company's filings under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, regardless of any general incorporation language in such filing, except as shall be expressly set forth by specific reference in such filing. The furnishing of the information in this Current Report on Form 8-K is not intended to, and does not, constitute a determination or admission by the Company that the information in this Current Report on Form 8-K is material or complete, or that investors should consider this information before making an investment decision with respect to any security of the Company.

Item 9.01 Financial Statements and Exhibits.

Exhibit No.	Description
99.1	Presentation of the Company, dated December 6, 2022.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: December 6, 2022

EAGLE PHARMACEUTICALS, INC.

By: /s/ Scott Tarriff
Scott Tarriff
Chief Executive Officer

EAGLE PHARMACEUTICALS

Investor Day

December 6, 2022

EAGLE PHARMACEUTICALS

Forward-Looking Statements

This presentation 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 with respect to: the Company's development programs, products and pipeline; any further investments in Enalare and Enalare's development programs; the potential exercise of the Company's option to acqu of Enalare's outstanding shares; the ability of the Company's products to address challenges faced by healthcare providers and hospitals today; the Company's ability to achieve revenue growth; the potential for the Company to transition into a diversified pharmaceutical company with a portfolio of branded, first-in-class assets; the Company's and Enalare's ability to obtain and maintain regulatory approval of its products and product candidates; the Company's clinical development plan for its product candidates, including the number and timing of development initiatives or new indications for the Company's product candidates; the ability of the Company's and Enalare's products and product candidates; the development of, potential benefits of and expected regulatory activities and matters with respect to the product candidates of the Company and Enalare; the potential therapeutic and economic benefits of the Company's and Enalare's products and product candidates; potential commercial opportunities, addressable market patient populations and settings for the Company's and Enalare's products and product candidates; the achievement of milestones and deliverables; the potential use of ENA-001 to help preterm infants with respiratory conditions; the ability of ENA-001 and other products and product candidates to address unmet clinical needs, including for patients with post-operative respiratory depression and in combatting community drug overdose; CAL02's ability to neutralize virulence factors produced by bacteria that are common associated severe pneumonia; the potential of CAL02 to be a medical breakthrough and offer unique therapeutic benefits to seriously ill patients, potentially improving the treatment regimen for patients with severe community-acquired pneumonia, shortening the duration of illness and improving patient outcomes; the Company's expectations for the design and timing of the planned CAL02 Phase 2 study, including with respect to enrollment and site selection and the timing thereof; potential regulatory exclusivity, CAL02's potential eligibility for fast track and breakthrough therapy designations and the potential for a CAL02 new drug application for the treatment of SCABP to qualify for priority review; the ability of hospital environmental trends to bolster the value proposition of the Company's acute care portfolio, including of Barhemsys and Byfavo; the ability of Barhemsys to reduce overall hospital stays; the strategic fit of Barhemsys and Byfavo with the Company's specialized hospital-based salesforce; the Company's marketing, product development, partnering and growth strategy, including relating to the commercialization of Barhemsys and Byfavo, and the ability of Acacia's technology and know-how to help the Company achieve its strategy; the ability of Barhemsys, Byfavo and Landiolol to address unmet clinical needs; the ability of Barhemsys to offer significant economic savings to hospitals and ambulatory centers; the ability of Byfavo to offer potential health economic benefits and enable shorter procedure times and greater patient throughput; t potential market opportunity for the Company's products or product candidates, including for Barhemsys, Byfavo or Landiolol; expected patient volumes; the progress and success of the Company's launch of any products; the period of marketing exclusivity for products or product candidates, including CAL02; the timing, scope or likelihood and timing of regulatory filings and approvals from the FDA for the Company's product candidates and the Company's ability to maintain regulatory approval of its products and prod candidates; the Company's clinical development plan for the product candidates; the implementation of certain healthcare reform measures; the ability of the Company to obtain and maintain coverage and adequate reimbursement for its products; the success of Company's collaborations with its strategic partners and the timing and results of these partners' preclinical studies and clinical trials, and the Company's potential earnings potential through such collaborations; the Company's plans and ability to advance the pro candidate in its pipeline; potential opportunities for, and the Company's ability to complete, business development transactions, in a timely manner, on favorable terms to the Company, or at all; the sufficiency of the Company's cash flows and capital resources a expectations with respect to deployment of cash resources; and the Company's ability to achieve expected future financial performance and results. 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 th the anticipated benefits of the Company's recently completed transaction with Acacia are not realized; the ability of Enalare to achieve milestones and deliverables under the BARDA agreement and otherwise accelerate and achieve successful results in the development of ENA-001; the impacts of the COVID-19 pandemic and geopolitical events such as the conflict in Ukraine, including disruption or impact in the sales of the Company's marketed products, interruptions or other adverse effects to clinical trials, delay 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 o other events on the Company's business, financial condition and results of operations; macroeconomic conditions, including rising inflation and uncertain credit and financial markets; whether the Company will incur unforeseen expenses or liabilities or other mark factors; whether the Company will successfully implement its development plan for its product candidates; delay in or failure to obtain regulatory approval of the Company's or its partners' product candidates; whether the Company can successfully market and commercialize its product candidates; the success of the Company'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 our 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 issu including the COVID-19 pandemic and geopolitical events, on economic activity and the performance of the financial markets generally; the strength and enforceability of the Company's intellectual property rights or the rights of third parties; competition from othe 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; factors in addition to the foregoing that may impact th Company'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 the Company's actual results an 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 Exchan Commission (the "SEC") on March 8, 2022, the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 2022, filed with the SEC on May 9, 2022, the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2022, filed with SEC on August 9, 2022, the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2022, filed with the SEC on November 9, 2022 and its other subsequent filings with the SEC. Readers are cautioned not to place undue reliance on the 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 ever that occur or circumstances that exist after the date on which they were made.

This presentation includes statistical and other industry and market data that the Company obtained from industry publications and research, surveys and studies conducted by third parties or us. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. All of the market data used in this presentation involves a number of assumptions limitations, and you are cautioned not to give undue weight to such estimates. While the Company believes these industry publications and third-party research, surveys and studies are reliable, the Company has not independently verified such data. The industr which the Company operates is subject to a high degree of uncertainty, change and risk due to a variety of factors, which could cause results to differ materially from those expressed in the estimates made by the independent parties and by the Company.

This presentation includes statements and commentary of independent third parties, including key opinion leaders and Enalare, which are strictly the views, opinions and expectations of such third parties and are not the responsibility of the Company.

EAGLE PHARMACEUTICALS

Eagle Investor Day Agenda

7:30 AM	**Registration and Breakfast**
8:00 AM	**Overview of the Day** Scott Tarriff
8:10AM	**Introduction of the Speakers** Dr. Mike Greenberg
8:20AM	**ENA-001** Herm Cukier Dr. Joe Pergolizzi & Dr. TJ Gan – Postoperative Respiratory Depression Dr. Eugene Vortsman – Community Overdose Dr. Prem Fort – Apnea of Prematurity
9:15AM	**CAL02** Dr. Andre Kalil – Disease State Overview – Therapeutic Potential Dr. Valentin Curt – CAL02 Overview and Development Plan
9:50AM	**Midmorning Break** (15 minutes)
10:05AM	**Barhemsys® and Byfavo®** Deb Hussain – Hospital Landscape Dr. TJ Gan – Barhemsys Dr. Rick Dutton – Byfavo
10:55AM	**Landiolol** Dr. Mike Greenberg
11:05AM	**Q&A/Panel Discussion**
11:50 AM	**Lunch**

EAGLE PHARMACEUTICALS

Eagle Hospital Business Overview

Acute Care Hospital

Commercially Available

RYANODEX®

For treatment of malignant hyperthermia

Vasopressin

Approved to increase blood pressure in adults with vasodilatory shock

Barhemsys

Byfavo

Pipeline & Potential Pipeline

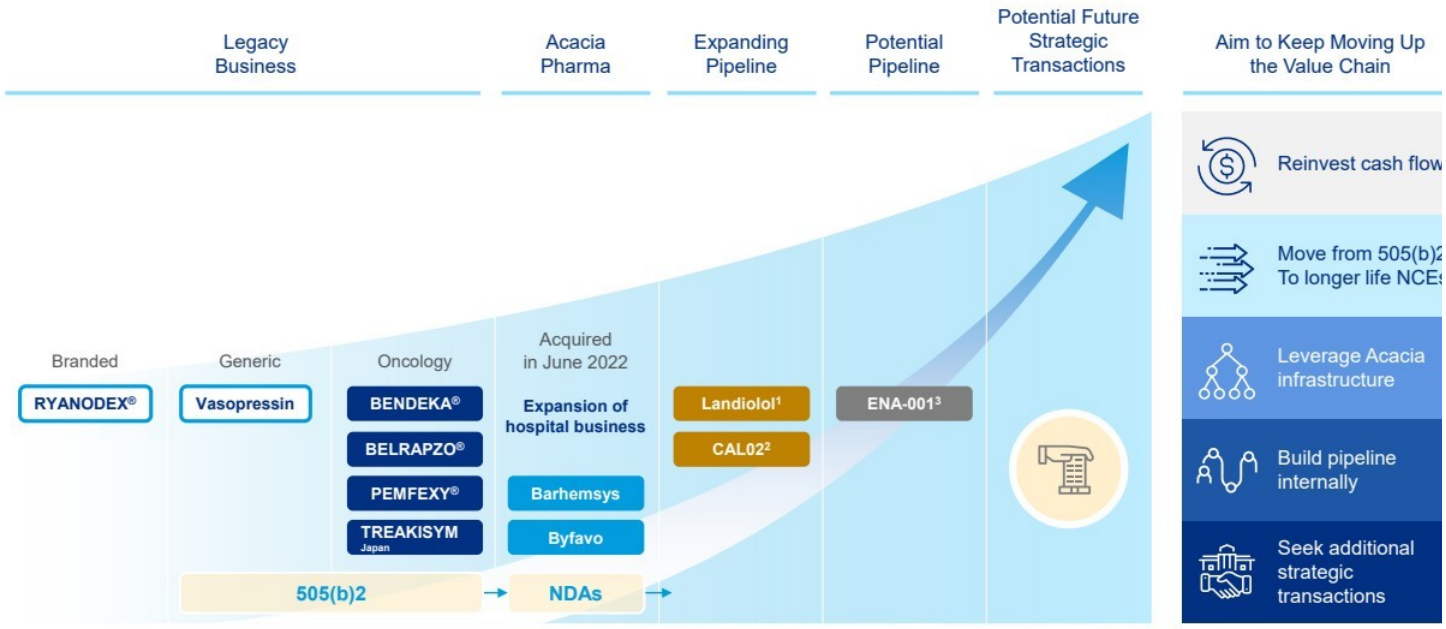
Landiolol[1]	CAL02[2]	ENA-001[3]
NDA Filing Stage	Phase II Study Stage	Phase II Study Stage

Hospital business currently being commercialized by 50 field resources

EAGLE PHARMACEUTICALS

1Eagle Pharmaceuticals. Press Release, January 31, 2022. https://investor.eagleus.com/press-releases/news-details/2022/Eagle-Pharmaceutic on-Track-to-Support-Submission-of-New-Drug-Application-in-Second-Quarter-2022-for-Landiolol-a-Beta-1-Adrenergic-Blocker/default.aspx. 2Ea Pharmaceuticals. Press Release, November 14, 2021. https://investor.eagleus.com/news-releases/news-release-details/eagle-pharmaceuticals-announces-fda-acceptance-investigational. 3 On 8/9/22 Eagle took an equity stake in, with option to acquire, Enalare

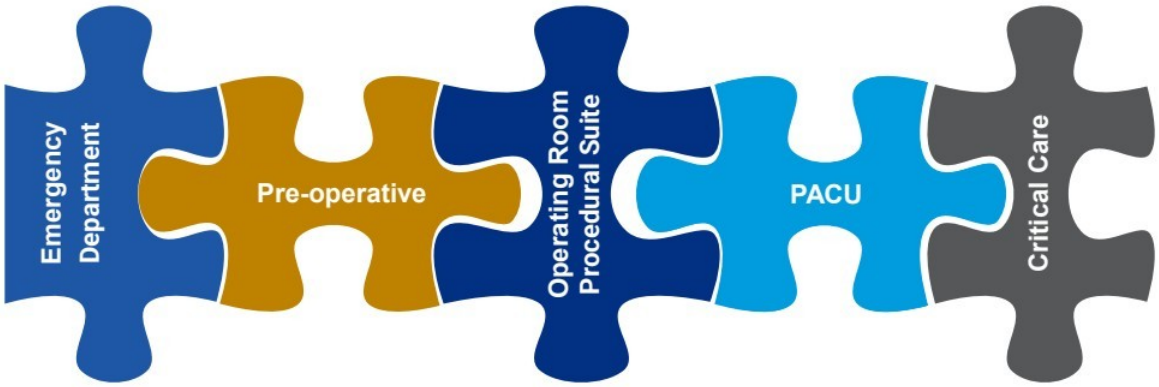
The Evolution of Eagle Pharmaceuticals



EAGLE PHARMACEUTICALS

1Eagle Pharmaceuticals. Press Release, January 31, 2022. https://investor.eagleus.com/press-releases/news-details/2022/Eagle-Pharmaceutic on-Track-to-Support-Submission-of-New-Drug-Application-in-Second-Quarter-2022-for-Landiolol-a-Beta-1-Adrenergic-Blocker/default.aspx. 2Ea Pharmaceuticals. Press Release, November 14, 2021. https://investor.eagleus.com/news-releases/news-release-details/eagle-pharmaceuticals- announces-fda-acceptance-investigational. 3 On 8/9/22 Eagle took an equity stake in, with option to acquire, Enalare

Introduction of the Speakers



Emergency Department	Pre-operative	Operating Room Procedural Suite	PACU	Critical Care
Byfavo	Byfavo	Barhemsys	Barhemsys	Byfavo
Ryanodex	Vasopressin	Byfavo	Ryanodex	Vasopressin
Landiolol	ENA-001	Ryanodex	Vasopressin	Landiolol
ENA-001		Vasopressin	Landiolol	ENA-001
CAL02		Landiolol	ENA-001	CAL02
		ENA-001		

EAGLE PHARMACEUTICALS

Eagle Speakers

Scott Tarriff

- Founder, Chief Executive Officer, President, Director of Eagle Pharmaceuticals
- Held executive-level positions at Par Pharmaceutical Companies, Inc. and Bristol-Myers Squibb
- Received prestigious Ernst and Young Entrepreneur Of The Year® Award in the Specialty Pharmaceutical category, NJ

Valentin Curt, MD

- Interim Chief Medical Officer, SVP Clinical Drug Development, at Eagle Pharmaceuticals, Inc.
- 25+ years of experience in clinical drug development and managing global clinical development plans
- Prior executive positions held at Imbrium Therapeutics, Purdue Pharma, Daiichi Sankyo, and Novartis

Michael Greenberg, MD

- Vice President of Medical Affairs at Eagle Pharmaceuticals
- Emergency medicine physician with expertise in medical affairs
- Prior experience consulting with the FDA Center for Drug Evaluation and Research (CDER)

Deb Hussain

- Senior Vice President, Head of Commercial, at Eagle Pharmaceuticals
- 25 years of pharmaceutical industry experience leading commercial launches in the hospital and critical care space
- Joined Eagle from Acacia Pharma, with prior experience at Eli Lilly and Company

KOL Biographies

Herm Cukier

- Executive Chairman, President, and CEO of Enalare Therapeutics
- Successful executive with commercial and operational expertise across several global, blockbuster products
- 30+ years industry experience in senior leadership roles with preeminent organizations, including Bayer, Bristol Myers Squibb, and Pfizer

Dr. Richard Dutton

- Chief Quality Officer for US Anesthesia Partners (USAP)
- Responsible for data analysis and performance measurement using the collective data and evaluations of all USAP practices to improve patient safety and clinical outcomes
- Served in clinical leadership positions with the American Society of Anesthesiologists, including Chief Quality Officer and Medical Director of the Anesthesia Quality Institute

Dr. Prem Fort

- Attending Neonatologist, Johns Hopkins All Children's Maternal, Fetal & Neonatal Institute
- Co-chair of the MFN research council
- Research focus includes respiratory management of premature infants, control of breathing, and apnea of premature, specifically as it relates to its management with caffeine

Dr. TJ Gan

- Professor and Head, Division of Anesthesiology, Critical Care and Pain Medicine, UT Texas MD Anderson Cancer Center, Houston, Texas
- Perioperative Medicine Executive Section Editor of Anesthesia and Analgesia and on the Editorial Board of Perioperative Medicine
- Over 300 manuscripts in peer-reviewed journals and numerous books and book chapters

KOL Biographies

Dr. Andre Kalil

- Professor of Medicine at the University of Nebraska Medical Center Division of Infectious Diseases
- Named the 2021 Scientist Laureate, the highest honor UNMC bestows upon researchers
- Practicing physician and clinical researcher working on many challenging infections, including transplant-related infections, pneumonia, sepsis, Ebola and COVID-19

Dr. Joseph Pergolizzi

- Chief Research and Development Officer, Board Member and Co-founder of Enalare Therapeutics
- Internationally recognized thought leader in areas of perioperative and pain medicines, drug development, and regulatory affairs
- Highly published in top-tier journals and a frequent scientific advisor for public and private companies. He is a serial entrepreneur who has started more than 20 companies

Dr. Eugene Vortsman

- Emergency Medicine Attending Physician and Clinical Director of Addiction Medicine and Disease Management for the Emergency Department at Long Island Jewish Medical
- Chair of Pain Committee of Long Island Jewish Medical Center
- Co-chair of the Northwell System Substance Abuse and Pain Advisory Committee
- Associate Professor of Emergency Medicine for Hofstra Medical School

ENA-001

ENA-001 - Potential to Improve Clinical Outcomes for Patients

Significant Medical Need
Respiratory Depression Affects Millions of Patients

- Post-operative
- Community Drug Overdose
- Apnea of Prematurity

Potential Novel Solution

- Agnostic Respiratory Stimulant
- Rapid Acting
- Multiple Formulations
- Novel Molecule

Data Confidence
Strong Foundation of Data

- Five Phase 1 Human Studies
- No SAEs
- More than 100 animal studies

External Support
Support and Partnership with Major Government Entities

- BARDA Partnership
- NIH Funding

Commercial Opportunity
Could Lead to Significant Value Creation

- Strong IP
- Global Rights
- Blockbuster Analogs

Pathway to Approval

- Fast-Track Status
- Orphan Drug Designation
- Rare Pediatric Disease Designation
- HHS ASPR BARDA support

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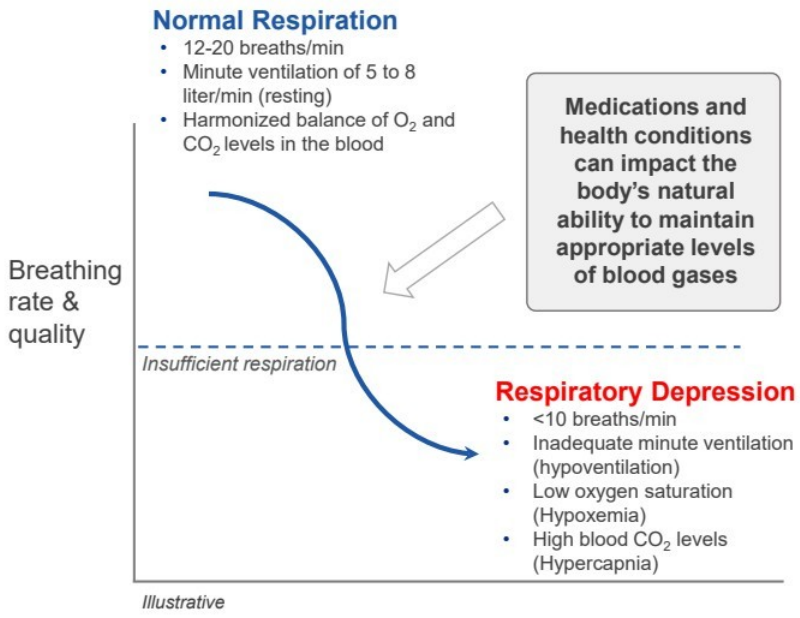
Respiratory Depression: A Global Health Emergency



Common Causes of Respiratory Depression

Medications

- Sedatives and anesthetics
- Narcotics (Opioids)
- Alcohol
- Other substances that depress brain function
- Synergistic effect from drug combinations

Health Conditions

- Obesity and aging
- Viral or bacterial infections
- Neuromuscular diseases
- Sleep apnea
- Chronic lung diseases
- Under-developed respiratory control system

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Partnership with BARDA on Development of ENA-001 as a Rescue Medicine for Drug-induced Respiratory Depression

Enalare/BARDA ENA-001 Partnership

- Supports development of an intramuscular (IM) formulation of ENA-001 for use as a threat-agnostic therapeutic agent in the community setting
- Partnership includes funding, scientific guidance, and active engagement with FDA interactions
- Contract for up to $50 million over six years – supports development program through an NDA filing

ENA-001 - Multiple Product Candidates Under Development with Potential to Benefit Patients Across the Hospital and Community Settings

	Post-operative respiratory depression Treatment and prevention for at-risk surgical patients	**Community drug overdose & MCM*** Opioids, non-opioids, and polypharmacy overdoses	**Apnea of prematurity** Shallow or stopped breathing in premature infants
Setting of Use	Hospital & Ambulatory (outpatient) clinics	Community, First Responders, ER	Hospital Neonatal Intensive Care Units
Addressable Market	300+ million annual global surgical procedures	Worsening drug overdose epidemic, >100K US deaths annually	10% of infants born premature globally
Profile	Strong health economics, Global blockbuster opportunity	Government support via partnerships with NIH & BARDA	FDA Orphan Drug & Rare Pediatric Disease Designations

* MCM = Medical Countermeasure

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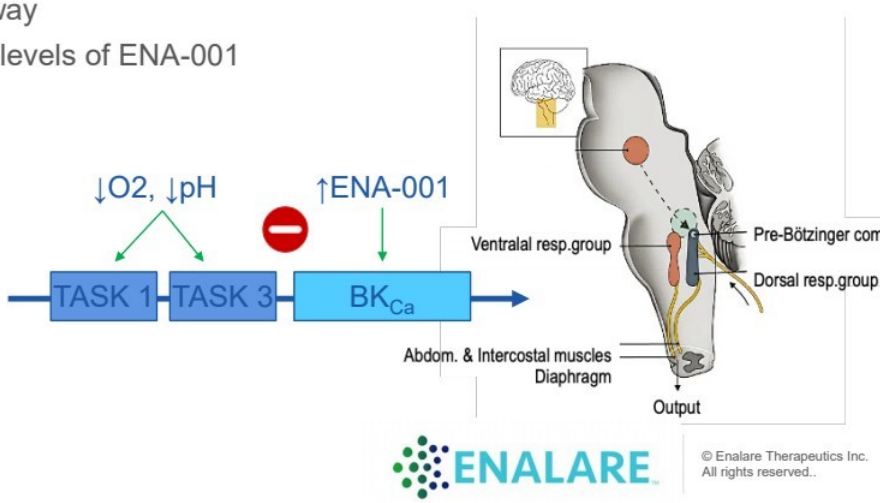
ENA-001 = A One-of-a-Kind Molecule with a Novel Mechanism of Actio

- Depolarization of carotid body glomus cells drives breathing
- Channel agonists decrease potassium conductance
  - Low oxygen, pH (and doxapram) act on TASK channels
  - ENA-001 acts on BK channels
- BK channels = greater inherent conductance vs TASK
  - ✓ More sensitive transduction pathway
- Action occurs at relatively low plasma levels of ENA-001
  - ✓ Low risk of untoward effects



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ENA-001 = A Unique Product Profile with Potentially Broad Applications to Stimulate Breathing

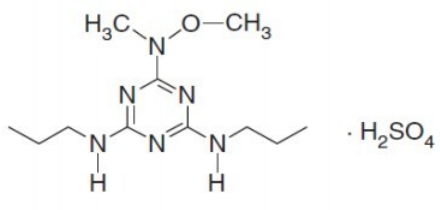
Agnostic: Potential to stimulate breathing irrespective of the cause of respiratory depression; potential to be used across multiple patient populations

Natural: Utilizes the body's ventilation control system to beneficially influence breathing

Peripheral: 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



- ✓ May rapidly stimulate ventilation in patients with acute respiratory insufficiency
- ✓ Intended not to interfere with pain suppression or sedation
- ✓ May avoid the withdrawal effect experienced with opioid antagonists

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ENA-001 = Well Tolerated Across Five Clinical Studies Totaling >110 Subjects

Study	Description	# of Subjects
GAL-021-101	Single, ascending dose study in healthy subjects.	30
GAL-021-102	Extended the dose range - 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
ENA-001-108	Assessed the potential therapeutic utility under conditions that simulate the post-operative state. Propofol was used to suppress ventilation.	12

The Emergence of an Exciting Product Profile

- ✓ Well Tolerated
- ✓ Agnostic Efficacy
- ✓ Therapeutic Dose
- ✓ Consistent Results

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Clinical Study 104: Respiratory Stimulatory Effects in Subjects with Impaired Respiratory Drive due to an Opioid

Study Design:

- Healthy volunteers
- Administered low and high levels of alfentanil, a potent opioid, to induce moderate to severe respiratory depression

Observations:

- Well tolerated
- Clinical trial data indicated:
  - Improvements across multiple respiratory metrics
  - No impact on pain analgesia

Conclusion: ENA-001 continuous infusion IV produced respiratory stimulatory effects during opioid-induced respiratory depression

-Study was a Phase 1b trial in healthy volunteers targeted at a post operative respiratory depression indication
-Conducted at Center for Human Drug Research, (CHDR), Zernikedreef 8, 2333 CL Leiden, The Netherlands
-Registered with the EnduraCT database, No: 2012-004363-50

Clinical Study 106: Rising Multiple Dose 5-day Study of ENA-00

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)

	Study 106 Results
Safety Profile & 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

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Clinical Study 108: Respiratory Stimulatory Effects in Subjects with Impaired Respiratory Drive due to an Anesthetic

Objective: To determine the safety, tolerability, and ventilatory response of low and high doses of ENA-001 under both hypoxic and hypercapnic conditions in conjunction with low and high doses of propofol

- Primary Safety Endpoint: treatment emergent adverse events
- Primary Ventilatory Endpoint: Hypoxic Sensitivity (Δ ventilation/Δ SaO2)

Model: Healthy volunteers with ventilatory depression (desensitization) via propofol administration in the presence of no, low, or high doses of ENA-001

- Hypoxic sensitivity determined by hypoxic challenge, with and without hypercapnic challenge

Results: Well tolerated with no serious adverse events (SAEs)

- Hypoxic sensitivity increased with high dose of ENA-001 ($p<0.0001$) under all conditions of no, low, and high dose of propofol
- Hypoxic sensitivity restored to above baseline levels during high dose propofol exposure

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ENA-001 Timeline*

- Post-op (Fast-track)
  - Start fentanyl tox study ~ in early 2023
  - Expect to start Phase 2 enrollment ~ as early as 3Q23
  - Potential for Phase 2 topline data ~ in 2Q24

- Community Drug Overdose (BARDA and NIH funding)
  - Currently executing toxicology studies with intramuscular formulation (IM)
  - Expect to start Phase 1 enrollment as soon as mid-year 2023

- Apnea of Prematurity (Rare Pediatric Disease and Orphan Drug designations)
  - Recently completed animal proof of concept
  - Designing next set of animal studies and clinical pathway

*Expected for planning purposes

Real World Experience – Respiratory Depression

Dr. TJ Gan	Division Head of Anesthesiology, Critical Care and Pain Medicine MD Anderson	Post-operative respiratory depression
Dr. Eugene Vortsman	Emergency Medicine Physician Clinical Director of Addiction Medicine and Disease Management Northwell Health	Community drug overdose
Dr. Prem Fort	Neonatologist Johns Hopkins All Children's Maternal, Fetal & Neonatal Institute	Apnea of prematurity

ENALARE

The Burden of Respiratory Depression

T. J. Gan, M.D., M.B.A., F.R.C.A., M.H.S.
Professor and Division Head
Anesthesiology, Critical Cre and Pain Medicine
UT Texas MD Anderson Cancer Center
Founding President, American Society for Enhanced Recovery (ASER) aserhq.org | enhancedrecovery.org
President, Perioperative Quality Initiative (POQI.org)

Postoperative Pulmonary Complications (PPC)

- PPC is any event that occurs in the postoperative period that produces physiologic dysfunction or clinical disease
- Incidence 2 - 40%
- 2.7–3.4% of patients undergoing non-cardiac surgery (NSQIP database)
- 9.6% in elective abdominal surgeries in VA patients

Lawrence VA et al. J Gen Intern Med 1995;10(12):671-678
Dimick JB et al. J Am Coll Surg 2004;199(4):531-537

Prediction and Monitoring for PORD are Poor

- Unable to accurately predict which patient will have an episode of PORD
- PACU Staff routinely miss low oxygen, <90% of episodes[1]
  - Incidence of post-operative hypoxemia underestimated[1]
- Up to 62% transferred from floor to ICU had serious abnormalities 8-48 hours prior to transfer[2,3]
  - Not recognized or acted on
  - Alarm-fatigue
- Patients experiencing PORD utilize greater resources, have an increased length of stay and increased healthcare costs
- Education, monitoring, other procedures have not significantly reduced these events[4]
  - Need for a comprehensive and reliable approach to assessment and recognition of PORD

PORD = Postoperative Respiratory Depression
PACU = Post Anesthesia Care Unit
ICU = Intensive Care Unit

1. Sun Z et al. Anesth Analg. 2015;121:709-715
2. Hillman KM et al. Inten Care Med. 2002;28:1629-1634
3. Gong MN et al. BMJ Open. 2016;6::e011347
4. Ayad S et al. Br J Anaesth. 2019;123(3):378-391

Manifestations of PPC

- Respiratory failure
- Pneumonia
- Atelectasis
- Dyspnea
- Prolonged mechanical ventilation
- Unexpected reintubation
- Hypoxemia (blood gas or SpO2)
- Administration of naloxone

Branson Rd et al. Respir Care 2013;58(11):1974 –1984

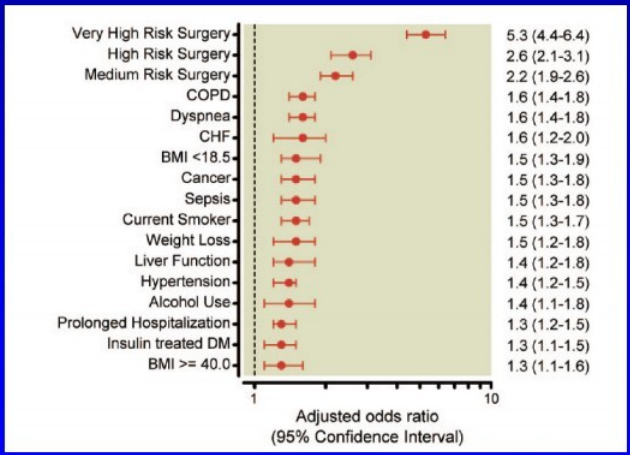
Postoperative Pulmonary Complications (PPC) – Risk Factors

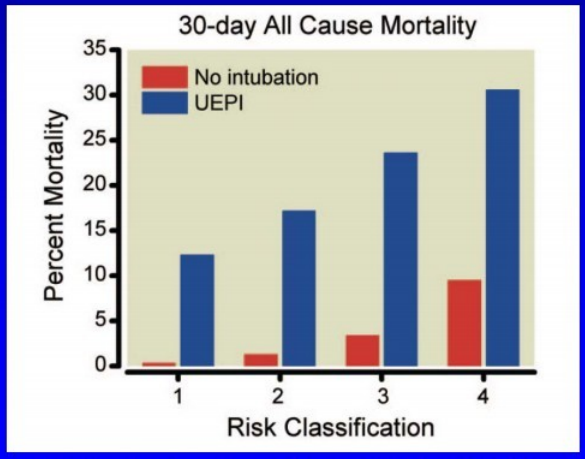
Patient factors	Procedure factors	Laboratory testing
Non-modifiable	**Non-modifiable**	Urea >7.5 mmol litre^{-1} [1 10 25]
Age [4–7 10 13 14 18 20 24 25 27 33 36]	Type of surgery: [4–7 10–13 15–18 23 25 27 29]	Increased creatinine [33]
Male sex [12 19 33]	• upper abdominal	Abnormal liver function tests [15]
ASA ≥II [5 11–14 16 19 27 33]	• AAA	Low preoperative oxygen saturation [4 6 29]
Functional dependence (frailty) [10–13 25 27 34 36]	• Thoracic	'Positive cough test' [20]
Acute respiratory infection (within 1 month) [4 6]	• Neurosurgery	Abnormal preoperative CXR [9 27]
Impaired cognition [7]	• head and neck	Preoperative anaemia (<100 g litre^{-1}) [4 6]
Impaired sensorium [25]	• vascular	Low albumin [5 10 27]
Cerebrovascular accident [25]	Emergency (*vs* elective) [4–6 10 11 16 18 19 23 25 29 33 36]	Predicted maximal oxygen uptake [32]
Malignancy [7 15]	Duration of procedure [8 12 14 20 22 27 29 32]	FEV_1:FVC <0.7 and FEV_1 <80% of predicted [5]
Weight loss >10% (within 6 months) [15 25]	Re-operation [18 23 36]	
Long-term steroid use [25]	Multiple GA during admission [19]	
Prolonged hospitalization [15]	**Modifiable**	
Modifiable	Mechanical ventilation strategy [3 19 63–71]	
Smoking [5 7 12 13 15 25 32 33 61]	GA (*vs* regional) [4 25 27 72]	
COPD [10 12 13 15–19 24 25 27 32 33 36]	Long-acting NMBDs and TOF ratio <0.7 in PACU [73]	
Asthma [20 32]	Residual neuromuscular block	
CHF [15 16 18 27 29 33]	Intermediate-acting NMBDs with surgical time <2 h (not antagonized) [21]	
OSA [62]	Neostigmine [21 74]	
BMI <18.5 or >40 kg m^{-2} [15]	Sugammadex with supraglottic airway [75 76]	
BMI >27 kg m^{-2} [7]	Failure to use peripheral nerve stimulator [21 74]	
Hypertension [15]	Open abdominal surgery (*vs* laparoscopic) [5 26 77–79]	
Chronic liver disease [29]	Perioperative nasogastric tube [18 20 22 23 25 80]	
Renal failure [19]	Intraoperative blood transfusion [19 25 36]	
Ascites [12]		
Diabetes mellitus [15 17]		
Alcohol [17 25]		
GORD [17]		
Preoperative sepsis [13–15 33]		
Preoperative shock [12]		

Miskovic A and Lumb AB. British Journal of Anaesthesia, 118 (3): 317–34 (2017)

Independent Predictors and Outcomes of Unanticipated Early Postoperative Tracheal Intubation after Nonemergent, Noncardiac Surgery

- NSQIP database >220,000 patients
- Incidence of unanticipated early postoperative intubation (UEPI) – 0.9%





Ramachandran SK et al. Anesthesiology 2011; 115:44–53

Postoperative Opioid-induced Respiratory Depression

A Closed Claims Analysis

- Out of 9,799 claims, 92 were due to RD
- 88% occurred within 24 h of surgery
- 97% were judged as preventable with better monitoring and response
- Median payment - $216,750

Lee L et al. Anesthesiology 2015; 122:659-65

Hospital Costs Associated with Surgical Complications: A Report from the Private-sector National Surgical Quality Improvement Program

Justin B Dimick, MD, Steven L Chen, MD, Paul A Taheri, MD, MBA, FACS, William G Henderson, PhD, Shukri F Khuri, MD, FACS, Darrell A Campbell Jr, MD, FACS

Table 3. Total Hospital Costs and Length of Stay for Patients with and without Postoperative Complications in the University of Michigan National Surgical Quality Improvement Program

Complication	Complication present (95% CI)	Complication absent (95% CI)	p Value*
Median total hospital costs, $ (IQR)			
Infectious	13,083 (6,499–20,234)	5,044 (4,490–5,767)	<0.001
Cardiovascular	18,496 (8,262–56,857)	5,236 (4,631–5,916)	0.001
Respiratory	62,704 (27,959–135,463)	5,015 (4,498–5,686)	<0.001
Thromboembolic	33,589 (21,985–61,789)	5,233 (4,611–5,851)	<0.001
Median length of stay, d (IQR)			
Infectious	9 (7–13)	5 (4–5)	<0.001
Cardiovascular	4 (2–35)	5 (1–9)	0.17
Respiratory	19 (9–36)	5 (1–9)	<0.001
Thromboembolic	20 (9–22)	5 (1–9)	<0.001

*Comparison performed using Wilcoxon rank-sum test.
IQR, interquartile range.

Average cost of a complication > $10,000

J Am Coll Surg 2004;199:531–537

Postoperative Opioid-induced Respiratory Depression

- Patients with ≥1 respiratory depression episode had a longer length of stay (6.4 vs 5.0 days) and higher hospital cost ($21,892 vs $18,206)
- Respiratory depression episodes include
  - Respiratory rate ≤ 5 bpm,
  - Oxygen saturation ≤ 85%,
  - End-tidal carbon dioxide ≤15 or ≥ 60mmHg for ≥3 min
  - Apnea episode lasting > 30 seconds; or
  - Any respiratory event requiring intervention

Khanna et al. BMC Anesthesiology (2021) 21:88

The Future of Postoperative Respiratory Care

- Cannot prevent all PORD
- Opioids are not the sole culprit of PORD
  - Anesthetics, paralyzing agents, and sedatives that do not respond to naloxone
- Prolonged apnea at the end of surgery delays wakeup
- Goal: Improved respiratory and ventilatory function
- Proactive Approach
  - Conduct risk assessment
    - Does not identify a specific patient
  - Take a "universal approach"
    - Helps keep everyone below the line of moderate risk
  - Consider respiratory stimulant prior to transfer to PACU

PORD = Postoperative Respiratory Depression
PACU = Post Anesthesia Care Unit

Summary

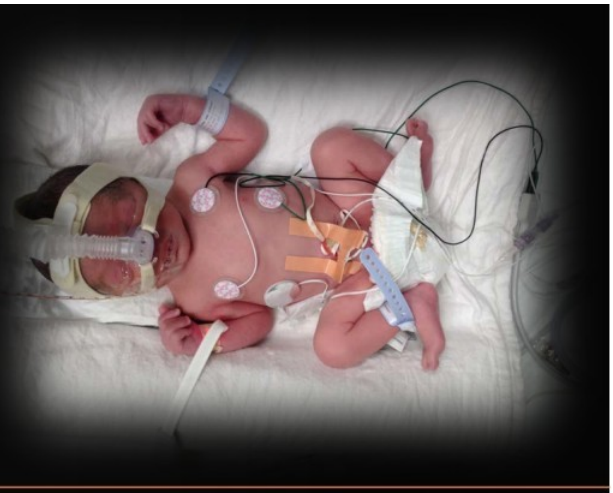
- Postoperative respiratory complications are common and preventable
- 1% of postoperative patients require unexpected reintubation
- Postoperative respiratory complications increase length of stay and substantially increase cost
- Apnea and respiratory depression delay wakeup following surgery and increase cost

Dr. Eugene Vortsman – Potential New Tool for Emergency Settin

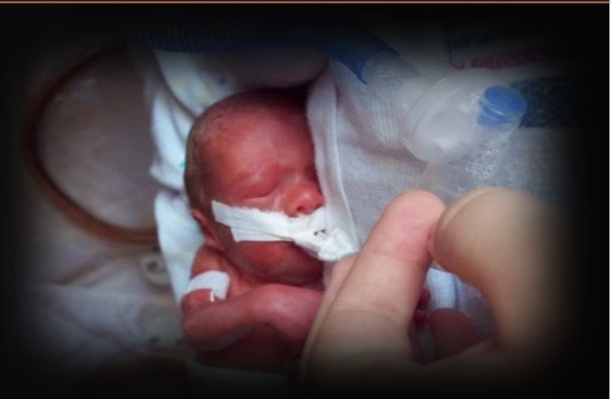
- ***Clinical Director of Addiction Medicine and Disease Management***: Every day, Emergency Departments around the country struggle managing overdoses with only ONE tool available…leading to dangerous situations for staff and patients.
- ***Chair of Pain Advisory Committee***: Every month, hospitals manage iatrogenic overdoses with only ONE tool leading to regulatory scrutiny and worse outcomes for patients.
- ***Co-Chair of the Substance Use and Pain Advisory Committee***: Every day, pre- and post-hospital environment have ONE tool to manage difficult patients leading to dangerous situations for EMS and ambulatory outpatient procedures.

ENA-001 has the potential to be a new effective tool needed in the emergency setting to improve patient outcomes

Apnea of Prematurity and ENA-001

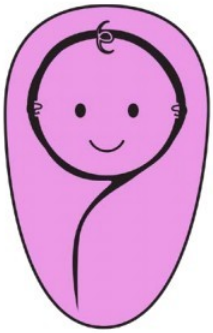


Prem Fort, MD
Chair-MFNI Research Council
Assistant Professor of Pediatrics
Johns Hopkins School of Medicine
Johns Hopkins All Childrens Hospital, FL



https://commons.wikimedia.org/wiki/File:Premature_birth_Alberta,_Canada
https://commons.wikimedia.org/wiki/File:Premature_infant_with_ventilator

Premature Infants



<37 weeks

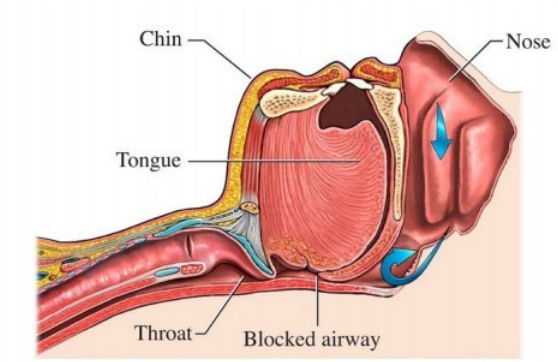
15 MILLION

500,000 US

1 in 10 US

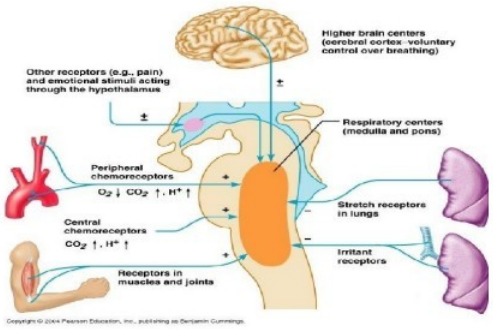
Apnea: Obstructive vs. Central

Obstructive



https://www.nhlbi.nih.gov/health/sleep-apnea/causes

Central



https://slidetodoc.com/patterns-of-respiration-by-ahmad-younes-professor-of/

Apnea of Prematurity

"Apnea of prematurity is defined as cessation of breathing for ≥ 20 seconds or < 20 seconds if accompanied by bradycardia (<100 BPM) and/or cyanosis and pallor in infants < 37 weeks gestational age (GA)"

AAP COFN. Pediatrics 137: 2016

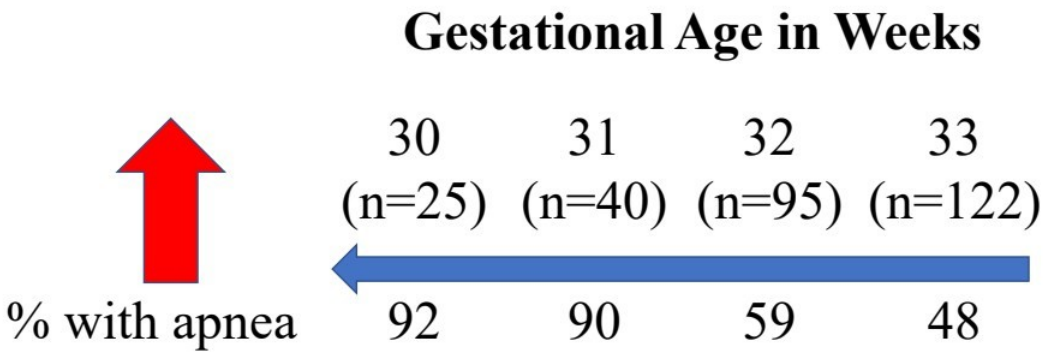
APNEA

Cessation of Breath

12 million a year with APNEA of Prematurity

https://www.whattoexpect.com/first-year/caring-for-a-premature-baby.aspx

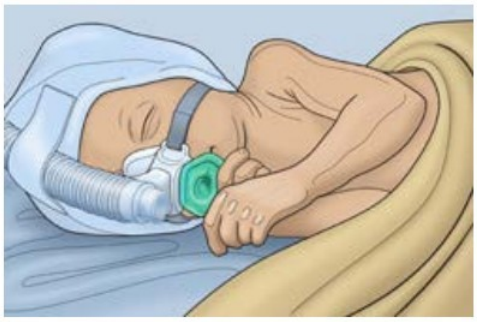
Background: Percentage of Moderate Preterm Infants with Apnea



Eichenwald et al. Pediatrics 108:928-33, 2001

APNEA OF PREMATURITY

How is it treated?

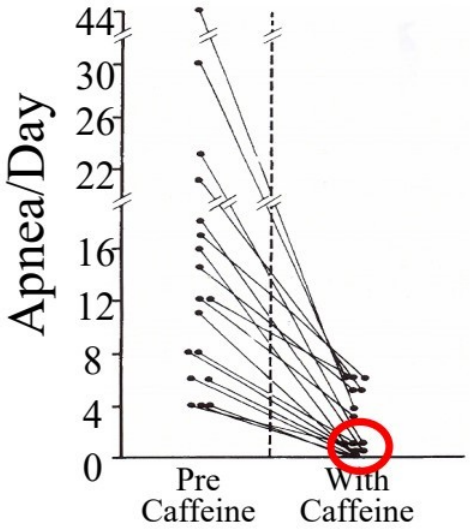


respiratory-care-sleep-medicine.advanceweb.com

neotechproducts.com

APNEA OF PREMATURITY

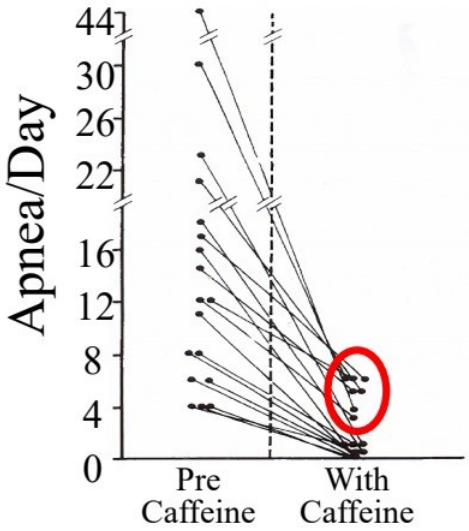
How is it treated?



Aranda et al. J Pediatr 90:467, 1977

APNEA OF PREMATURITY

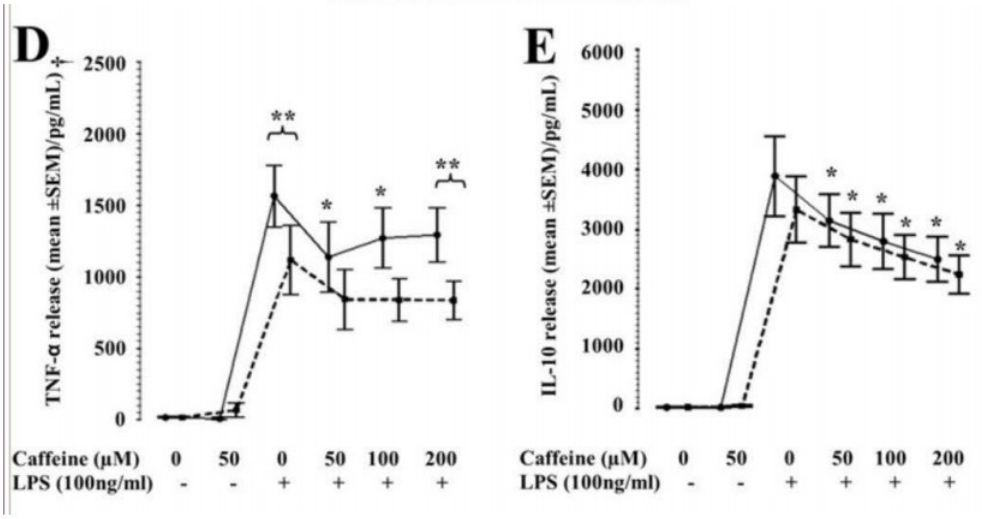
Many left untreated



Aranda et al. J Pediatr 90:467, 1977

Elevated Markers of Inflammation

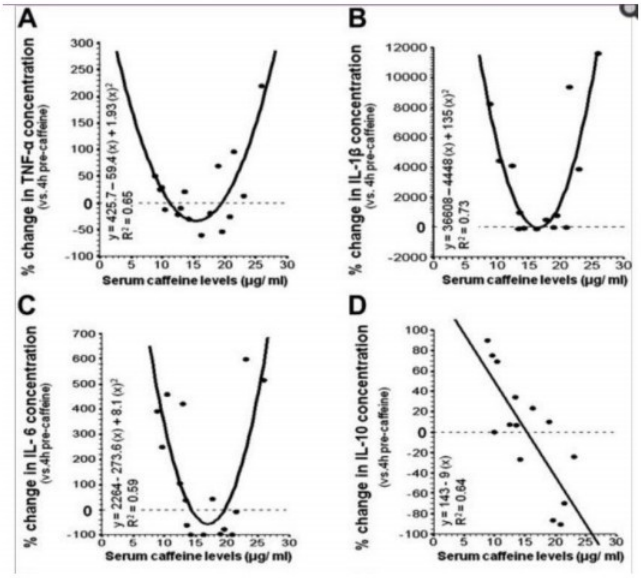
Is Caffeine Safe?



Chavez-Valdez R, Ahlawat R, Wills-Karp M, Gauda EB. Mechanisms of modulation of cytokine release by human cord blood monocytes exposed to high concentrations of caffeine. *Pediatric research*. 2016;80(1):101-109

The Sweet Spot

Caffeine's Limits



Valdez RC, Ahlawat R, Wills-Karp M, Nathan A, Ezell T, Gauda EB. Correlation between Serum Caffeine Levels and Changes in Cytokine Profile in a Cohort of Preterm Infants. *The Journal of pediatrics*. 2011;158(1):57-64.e1.

Meta-Analysis and Systematic Review

Published in final edited form as:
Semin Fetal Neonatal Med. 2020 December ; 25(6): 101178. doi:10.1016/j.siny.2020.101178.

Caffeine for preterm infants: Fixed standard dose, adjustments for age or high dose?

Vivek Saroha, MD, PhD[1], **Ravi Mangal Patel, MD, MSc**[1]
[1]Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

Characteristics of Randomized Trials of Higher vs. Lower Doses of Caffeine

First author (ref)	Scanlon[46]	Romagnoli[11]	Steer[31]	Steer[32]	Gray[33]	McPherso n[35]	Mohammed[47]	Wan[48]
Year published	1992	1992	2003	2004	2011	2015	2015	2020
Design (sample size)	single center (n=44)[a]	single center (n=37)[b]	single center (n=127)	multicenter (n=234)[c]	multicenter (n=287)[c]	single center (n=74)	single center (n=120)	single center (n=111)
Population, GA, weeks	<31	<32	≤31	<30	<30	≤30	<32	<30
Higher LD	50	10	60, 30 (intermedia te dose)[d]	80	80	80	40	20
Higher MD	12	5	30, 15 (intermedia te dose)[d]	20	20	10	20	10
Lower LD	25	10	6	20	20	30	20	20
Lower MD	6	2.5	3	5	5	10	10	5
Primary study outcome	Apnea	Apnea	Extubation failure	Extubation failure	Cognitive outcome at 1 year	Brain structure by MRI and neurobehavioral outcome at 2 years[e]	Extubation failure, apnea	Extubation failure, apnea

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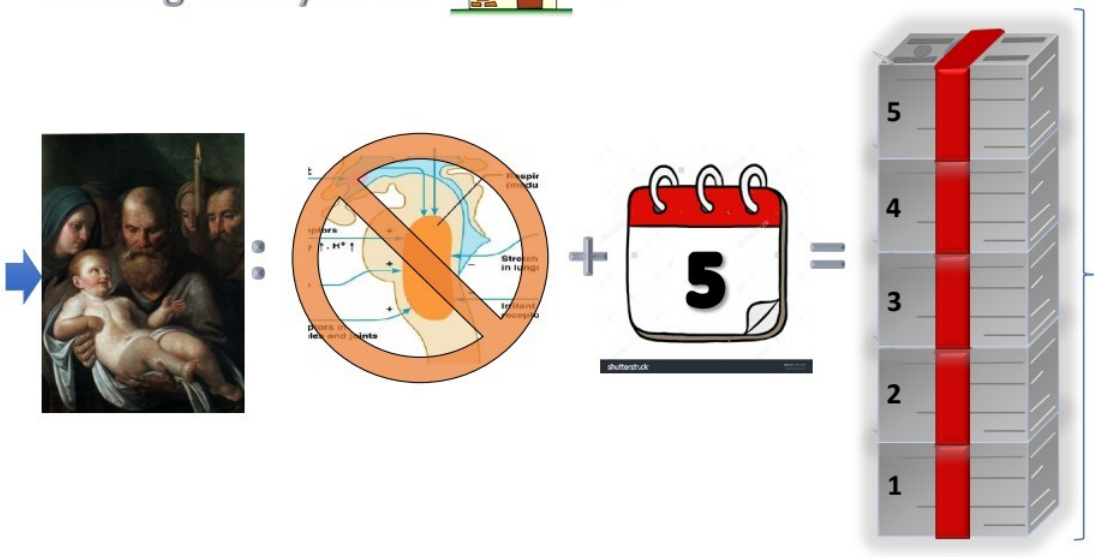
[1]Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

IVH		0.90 (0.63–1.27)	0.98 (0.76–1.27)	
Severe IVH	1.24 (0.65–2.36)	1.41 (0.71–2.79)		
PVL		1.33 (0.48–3.70)	1.35 (0.59–3.07)	
CBL hemorrhage		3.33 (1.00–11.2)[d]		
Abnormal neuroimaging		0.95 (0.75–1.22)		
Seizures		1.47 (0.86–2.50)[d]		
PDA treatment		1.00 (0.66–1.52)[d]		
NEC	0.82 (0.36–1.90)	0.78 (0.39–1.55)	0.54 (0.26–1.12)	
SIP	1.00 (0.22–4.64)[d]			
ROP			0.74 (0.52–1.05)	
Severe ROP	0.60 (0.28–1.29)	0.57 (0.27–1.20)		
Growth ($g.kg^{-1}$ per 24 hours)[b]		−1.1 (−2.4, 0.1)[b]		
Tachycardia	**3.39 (1.50–7.64)**	**2.56 (1.45–4.50)**	**2.02 (1.30–3.12)**	
Electrolyte disturbance			0.75 (0.17–3.28)	
Feeding intolerance			1.13 (0.84–1.51)	
Hypertension			1.75 (0.52–5.89)	
Hyperglycemia	1.92 (0.47–7.94)		0.80 (0.32–1.98)	
Restlessness			1.22 (0.52–2.85)	
Death before 1 year	0.93 (0.47–1.85)			
Major disability	0.58 (0.26–1.25)[d]	0.63 (0.28–1.39)[d]		
Death or disability	1.19 (0.37–3.77)			

Effect estimates are relative risks with 95% confidence intervals in parenthesis, comparing higher vs. lower doses of caffeine noted. Significant effect estimates noted in boldface.

The Effect of Apnea on Hospitalization

Getting Ready to Go  ?



https://slidetodoc.com/patterns-of-respiration-by-ahmad-younes-professor-of/
https://commons.wikimedia.org/wiki/File:Yegorov-Simeon_the_Righteous

Alternate Treatments

Management	Effectiveness	Safety	Comments
Aminophylline	Generally comparable to caffeine	Narrower side effect profile to caffeine. Appears to have no long-term adverse effects	Similar to caffeine
Caffeine	Effectiveness established in several large trials	Well-tolerated. Tachycardia common. Weight loss can occur early but is regained	Frequently used but optimal dose, onset of therapy, and duration of treatment being studied
Doxapram	May be effective, but is considered third-line treatment	Side effects may be treatment limiting	Dose-dependent adverse events may be of concern
Creatinine supplementation	No strong evidence in support of effectiveness	Well-tolerated	Not shown to reduce oxygen desaturation
CO_2 inhalation	Equivocal results, not well studied	Not known	Neonates may accommodate to CO_2 over time, making it less effective
Surfactant administration	Therapeutically effective (indirectly)	Administration can be challenging and pose risks to infant	Reduces preterm mortality
Blood transfusions	Not well-studied	May increase the risk of necrotizing enterocolitis in very preterm infants. Exposure to human blood products	Concept is that it increases oxygen in circulation
Device-based treatments	Neuromodulatory passive limb movement was shown in one study to be effective	No adverse events	Not well-studied or widely used
Noninvasive ventilation (continuous positive airway pressure and/or nasal intermittent positive pressure ventilation	Both approaches appear similarly effective, but some studies are equivocal	Well-tolerated	Variety of approaches (biphasic, flow-synchronized, etc.)
Kangaroo care (skin-to-skin contact)	No clear role in reducing AOP	No adverse events	May reduce morbidity and mortality in low birthweight infants
Postural changes	No evidence for effectiveness in reducing apnoeic events	Well-tolerated	Certain postures may improve infant sleep
Sensory stimulation	Kinesthetic stimulation has not been found effective, but a stochastic resonance effect (vibro-tactile stimulation) reduced apnoeic events	Safe	Variety of approaches (tactile, acoustic, olfactory, etc.)

Pergolizzi Jr, Joseph V., et al. "The limited management options for apnoea of prematurity." *Journal of Clinical Pharmacy and Therapeutics* 47.3 (2022): 396-401.

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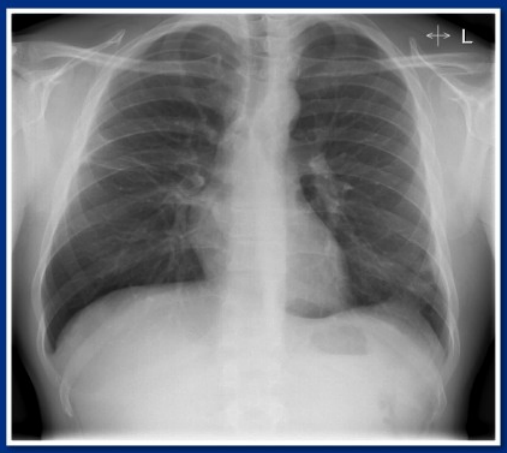
CAL02

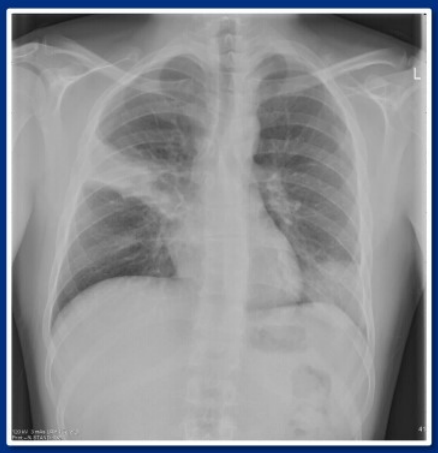
Disease State Overview

Andre Kalil, MD, MPH
Professor of Medicine
University of Nebraska Medical Center

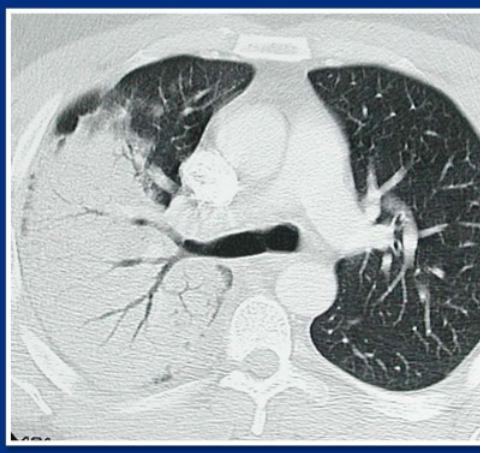
Chest X-ray:
Normal Lungs



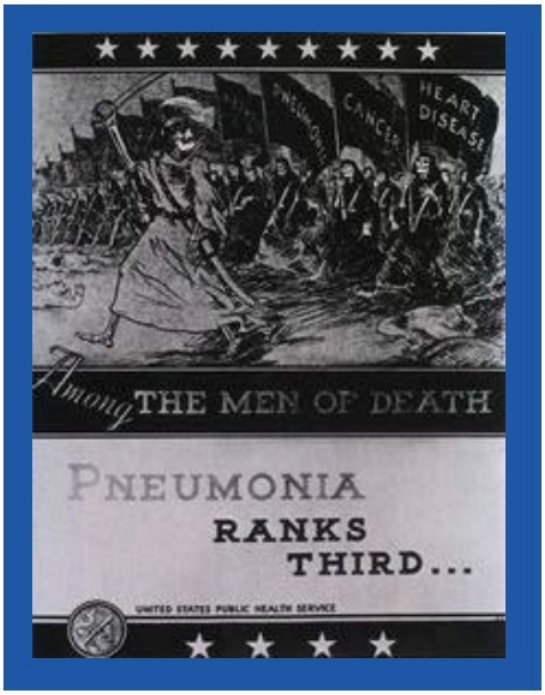
Chest X-ray:
Lungs with pneumonia

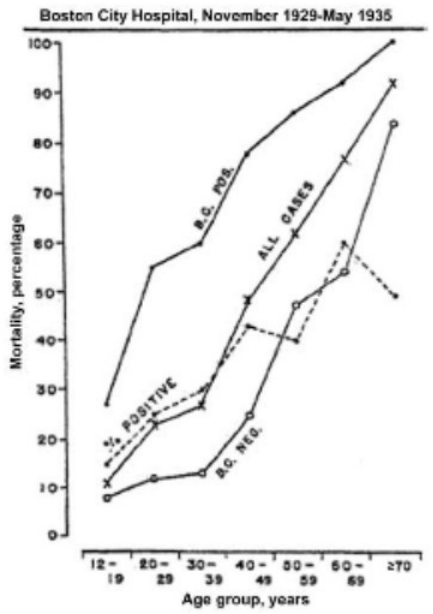


Computerized tomography (CT) scan:
Lungs with pneumonia



Pneumonia before Antibiotics





Tilghman Arch Intern Med 1937;59:602–19.

Pneumonia Overview

Pneumonia is defined as **"new lung infiltrates plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation".** –The Infectious Disease Society & American Thoracic Society

CAP

Pneumonia that is contracted outside of the health care setting is considered community-acquired pneumonia (CAP).

HAP

Hospital-acquired pneumonia (HAP), or nosocomial pneumonia, is a lower respiratory infection that was not incubating at the time of hospital admission and that presents clinically 2 or more days after hospitalization.

VAP

Ventilator-associated pneumonia (VAP) is defined as pneumonia that presents more than 48 hours after endotracheal intubation.

CAP Poses a Significant Public Health Burden

In the US, the annual incidence of CAP was 2.4 cases per 1,000 adults with the highest rates among adults ≥65[1]

Globally mortality with CAP is up to 50% in the ICU.[2-7]

CAP is the second most common cause of hospitalization and the third leading cause of hospital readmission causing direct hospitalization costs of ~17 billion USD.[8-9]

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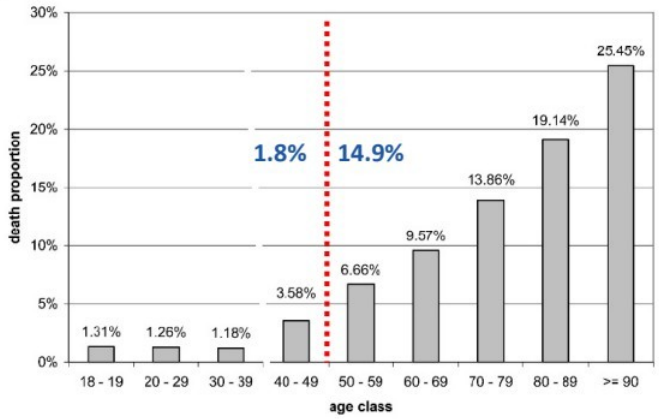
Mortality of Hospitalized CAP

German, 2006-2007

N=388,406 hospitalized CAP
CRB-65

- class 1: 16.55%
- class 2: 71.55%
- class 3: 11.91%
- Mechanical ventilation: 5.1%

hospital mortality: 14.1%



Ewig Thorax 2009;64:1062-1069

Severe CAP

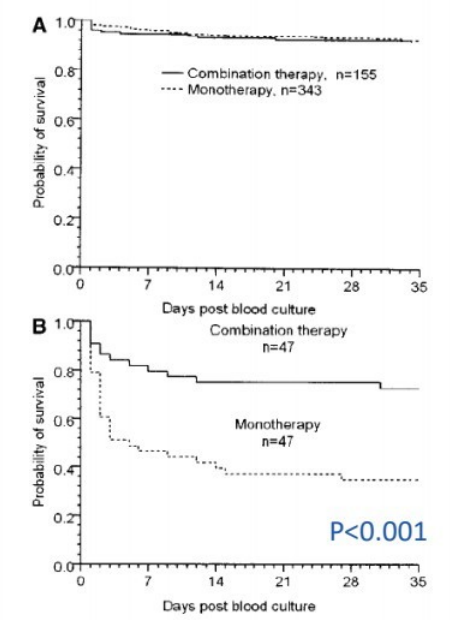
Retrospective study of prospective data, N=844 severe **bacteremic pneumococcal pneumonia**

Pitt bacteremic score ≤/>4

Critically ill pts (30d mortality)

Combination 23.4%

Monotherapy 55.3%



Baddour AJRCCM 2004;170:440

Severe CAP

Retrospective study of prospective data, N=529 ICU admitted CAP

Shock Y/N

Monotherapy vs. combination

β-lactam plus **macrolide**
(HR, 1.73; 95% CI, 1.08 –2.76; p=.**02**)

β-lactam plus **fluoroquinolones**
(HR, 1.77; 95% CI, 1.01–3.15; p=.**05**)

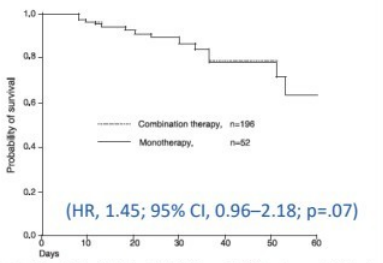


Figure 1. Survival graph for patients without shock stratified by severity of illness (censored at 60 days).

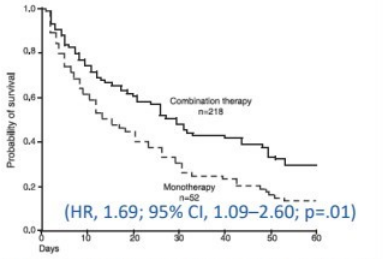


Figure 2. Survival graph for patients with shock stratified by severity of illness (censored at 60 days).

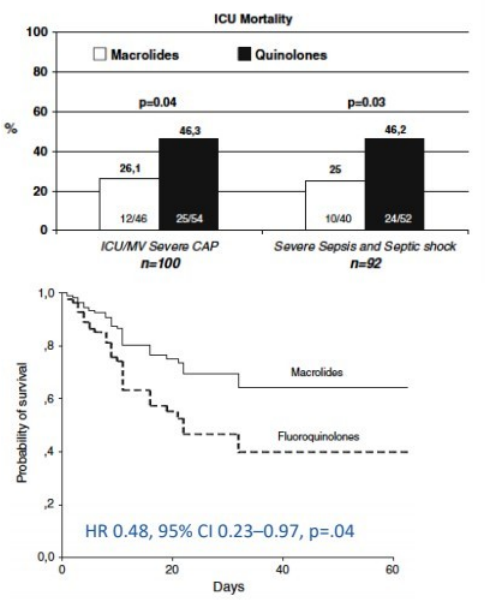
Rodriguez CCM 2007;35:1493

Severe CAP

Prospective observational study
N=217 SCAP requiring MV
Severe sepsis/septic shock 75.5%

Therapy according to ATS/IDSA 2007 guidelines, N=100 (45.9%)

- Combination with fluoroquinolone (N=46) or macrolide (N=56)



Martin-Loeches ICM 2010;36:612

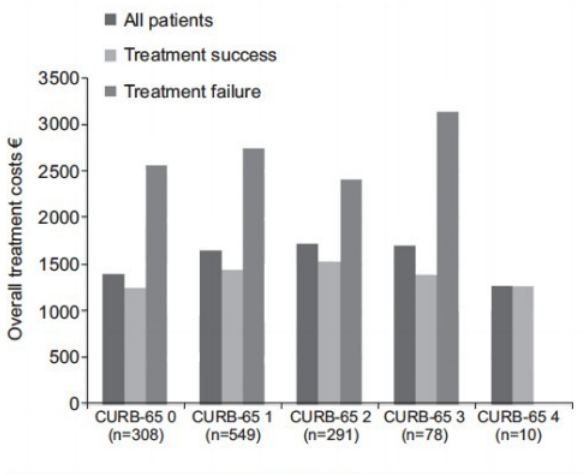
Hospitalized CAP – Treatment Failure

2 open, prospective multicenter studies (moxifloxacin; standard)

n = 1236

Treatment failure (15.9%)

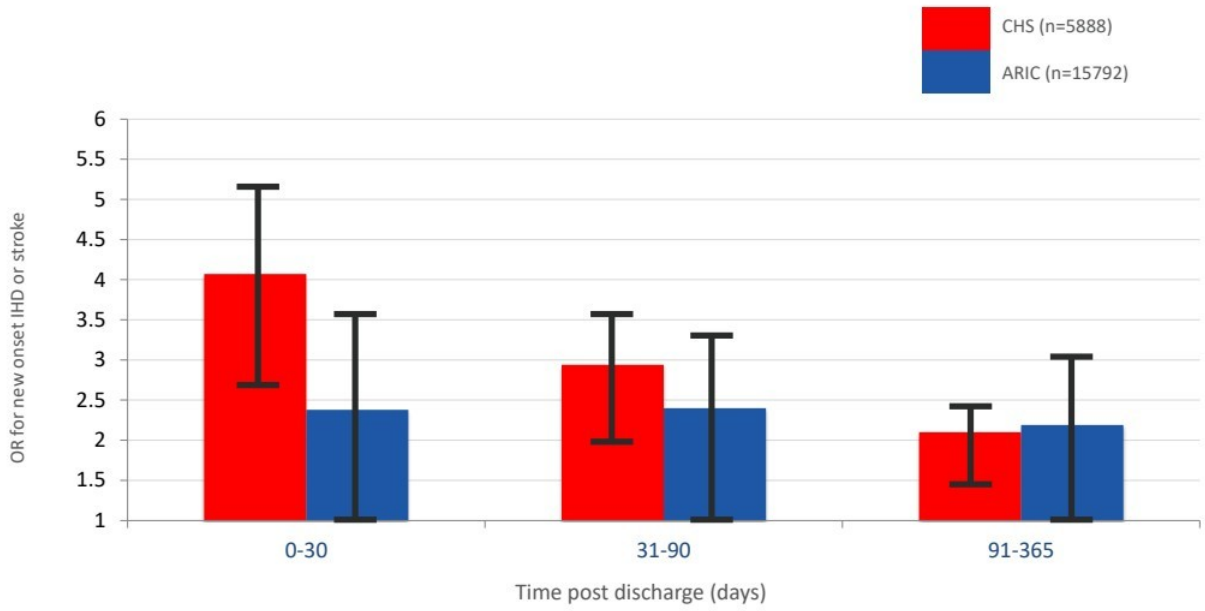
- CURB65≥2 (20.3%, p=.004)
- LOS (15.4 vs 9.8d, p<.001)
- Costs (2206 vs 1284€, p<.001)
- Mortality (17.3 vs 5.2%, p<.001)



Ott ERJ 2012;39:611

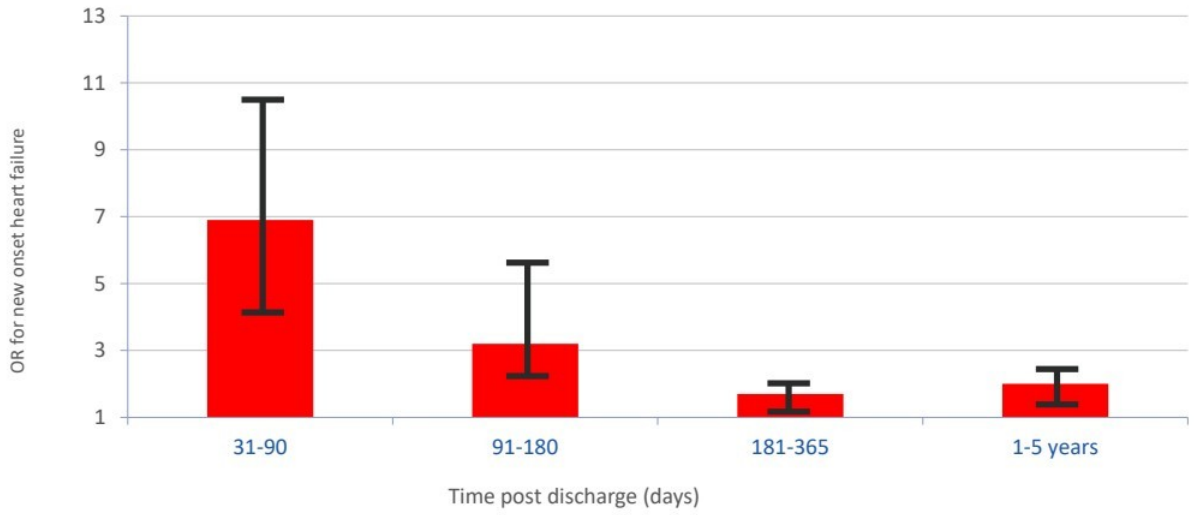
- ✓ **89.1% of group standard received therapy in accordance with guidelines**
- ✓ **Initial therapy with β-lactam + macrolide was less frequently associated with TF compared with β-lactam, particularly in SCAP.**

Pneumonia and Stroke/Acute MI



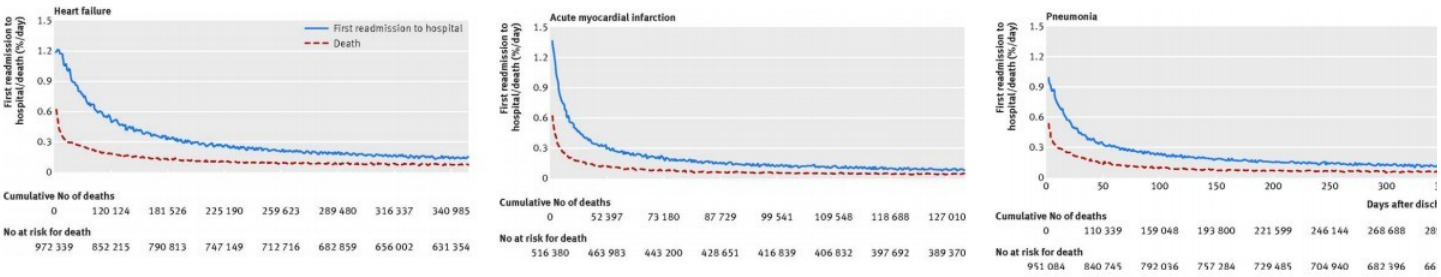
Corales-Medina et al JAMA 2015

Pneumonia and New Onset Heart Failure



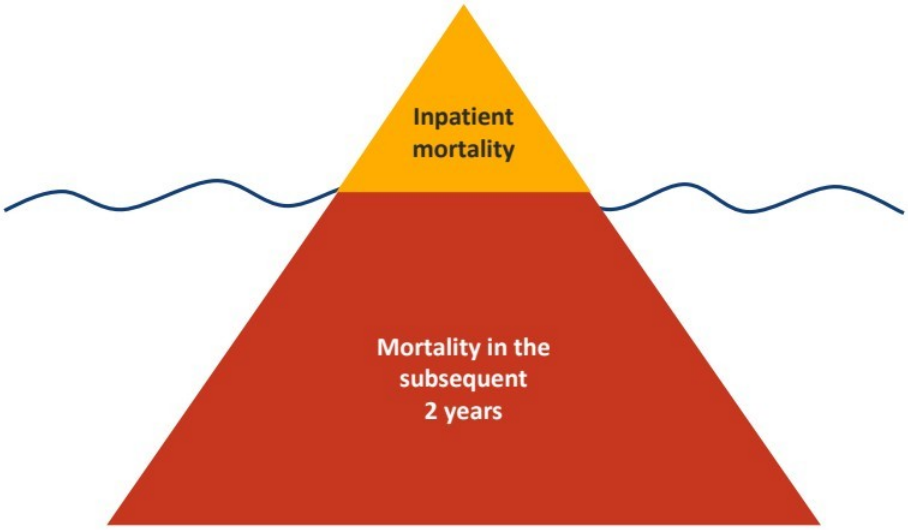
Corales-Medina et al Am Heart J 2015

Risks (hazard ratios) of first readmission to hospital and death for one year after hospitalization for heart failure, acute myocardial infarction, or pneumonia



Dharmarajan K et al. BMJ 2015;350:bmj.h411

Mortality Due to CAP



Mortality and Highly Antimicrobial-Resistant Bacteria

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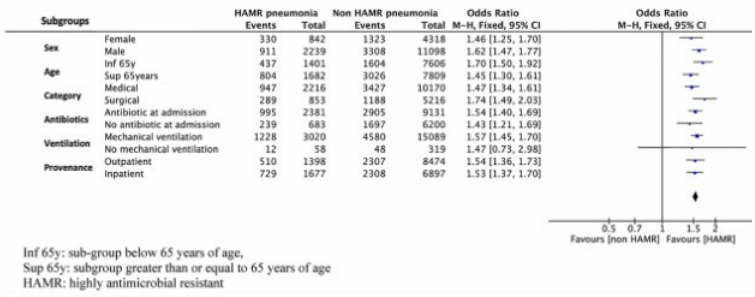
scientific reports

OPEN

Association between mortality and highly antimicrobial-resistant bacteria in intensive care unit-acquired pneumonia

Ines Lakbar[1,2,24], Sophie Medam[1,24], Romain Ronflé[1], Nadim Cassir[3], Louis Delamarre[1,2], Emmanuelle Hammad[1], Alexandre Lopez[1,3], Alain Lepape[4,5,6], Anaïs Machut[5,7], Mohamed Boucekine[6], Laurent Zieleskiewicz[1], Karine Baumstarck[6], Anne Savey[5,7,8], Marc Leone[1,3,9]✉ & REA RAISIN Study Group*

Data on the relationship between antimicrobial resistance and mortality remain scarce, and this relationship needs to be investigated in intensive care units (ICUs). The aim of this study was to compare the ICU mortality rates between patients with ICU-acquired pneumonia due to highly antimicrobial-resistant (HAMR) bacteria and those with ICU-acquired pneumonia due to non-HAMR bacteria. We conducted a multicenter, retrospective cohort study using the French National Surveillance Network for Healthcare Associated Infection in ICUs ("REA-Raisin") database, gathering data from 200 ICUs from January 2007 to December 2016. We assessed all adult patients who were hospitalized for at least 48 h and presented with ICU-acquired pneumonia caused by *S. aureus*, *Enterobacteriaceae*, *P. aeruginosa*, or *A. baumannii*. The association between pneumonia caused by HAMR bacteria and ICU mortality was analyzed using the whole sample and using a 1:2 matched sample. Among the 18,497 patients with at least one documented case of ICU-acquired pneumonia caused by *S. aureus*, *Enterobacteriaceae*, *P. aeruginosa*, or *A. baumannii*, 3001 (16.4%) had HAMR bacteria. The HAMR group was associated with increased ICU mortality (40.3% *vs.* 30%, odds ratio (OR) 95%, CI 1.57 [1.45–1.70], $P<0.001$). This association was confirmed in the matched sample (3006 HAMR and 5640 non-HAMR, OR 95%, CI 1.39 [1.27–1.52], $P<0.001$) and after adjusting for confounding factors (OR ranged from 1.34 to 1.39, all $P<0.001$). Our findings suggest that ICU-acquired pneumonia due to HAMR bacteria is associated with an increased ICU mortality rate, ICU length of stay, and mechanical ventilation duration.



Subgroups		HAMR pneumonia Events	HAMR pneumonia Total	Non HAMR pneumonia Events	Non HAMR pneumonia Total	Odds Ratio M-H, Fixed, 95% CI
Sex	Female	330	842	1323	4318	1.46 [1.25, 1.70]
	Male	911	2239	3308	11098	1.62 [1.47, 1.77]
Age	Inf 65y	437	1401	1604	7606	1.70 [1.50, 1.92]
	Sup 65years	804	1682	3026	7809	1.45 [1.30, 1.61]
Category	Medical	947	2216	3427	10170	1.47 [1.34, 1.61]
	Surgical	289	853	1188	5216	1.74 [1.49, 2.03]
Antibiotics	Antibiotic at admission	995	2381	2905	9131	1.54 [1.40, 1.69]
	No antibiotic at admission	239	683	1697	6200	1.43 [1.21, 1.69]
Ventilation	Mechanical ventilation	1228	3020	4580	15089	1.57 [1.45, 1.70]
	No mechanical ventilation	12	58	48	319	1.47 [0.73, 2.98]
Provenance	Outpatient	510	1398	2307	8474	1.54 [1.36, 1.73]
	Inpatient	729	1677	2308	6897	1.53 [1.37, 1.70]

Inf 65y: sub-group below 65 years of age,
Sup 65y: subgroup greater than or equal to 65 years of age
HAMR: highly antimicrobial resistant

Figure 2. Risk of mortality associated with HAMR status by subgroup.

Lakbar I et al. Sci Report 2021 Aug 13;11(1):164

Secondary Infections in Mechanically Ventilated Patients with COVID-1

Official journal of the Spanish Society of Chemotherapy

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Original

Revista Española de Quimioterapia
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Secondary infections in mechanically ventilated patients with COVID-19: An overlooked matter?

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Article history
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ABSTRACT

Introduction. The susceptibility to infection probably increases in COVID-19 patients due to a combination of virus and drug-induced immunosuppression. The reported rate of secondary infections was quite low in previous studies. The objectives of our study were to investigate the rate of secondary

Conclusions. Our data suggest that the incidence of secondary infection and infection by antimicrobial resistant pathogens is very high in critically ill patients with COVID-19 with a significant impact on prognosis.

Keywords: Acute respiratory distress syndrome, COVID-19, mechanical ventilation, infection, ventilator-associated pneumonia, bacteremia

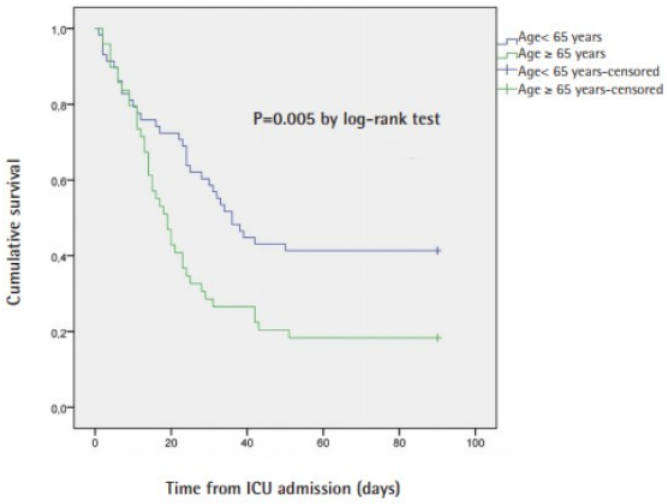
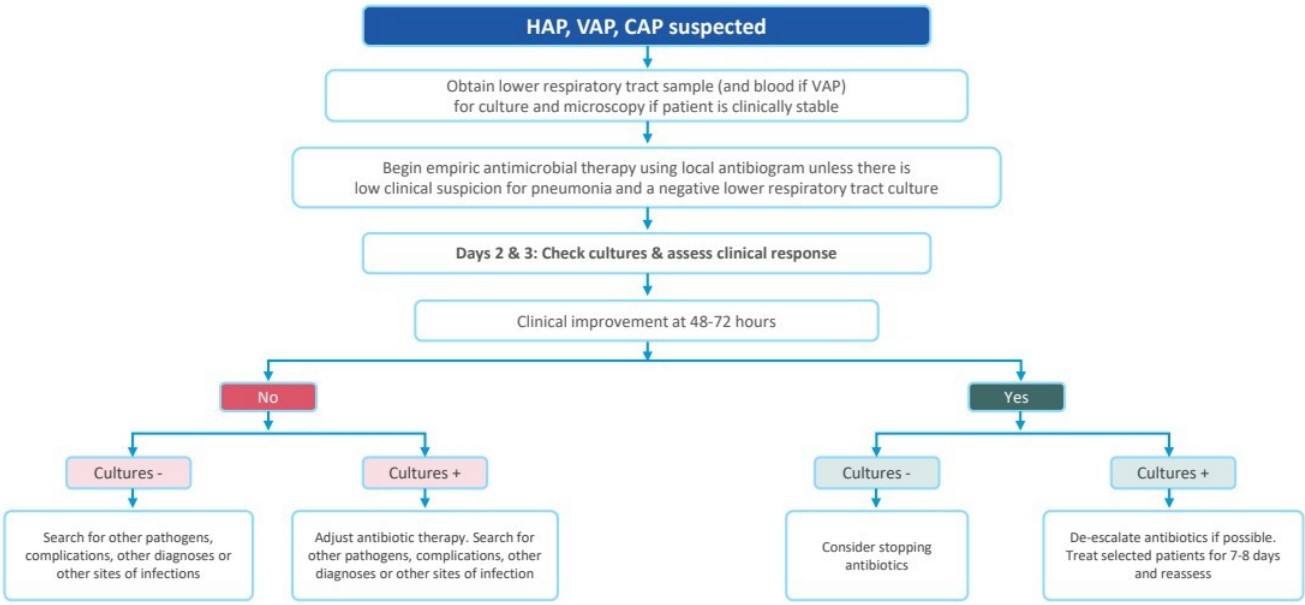


Figure 1 Kaplan-Meier curves for 90-day survival in patients with age < 65 years and ≥ 65 years

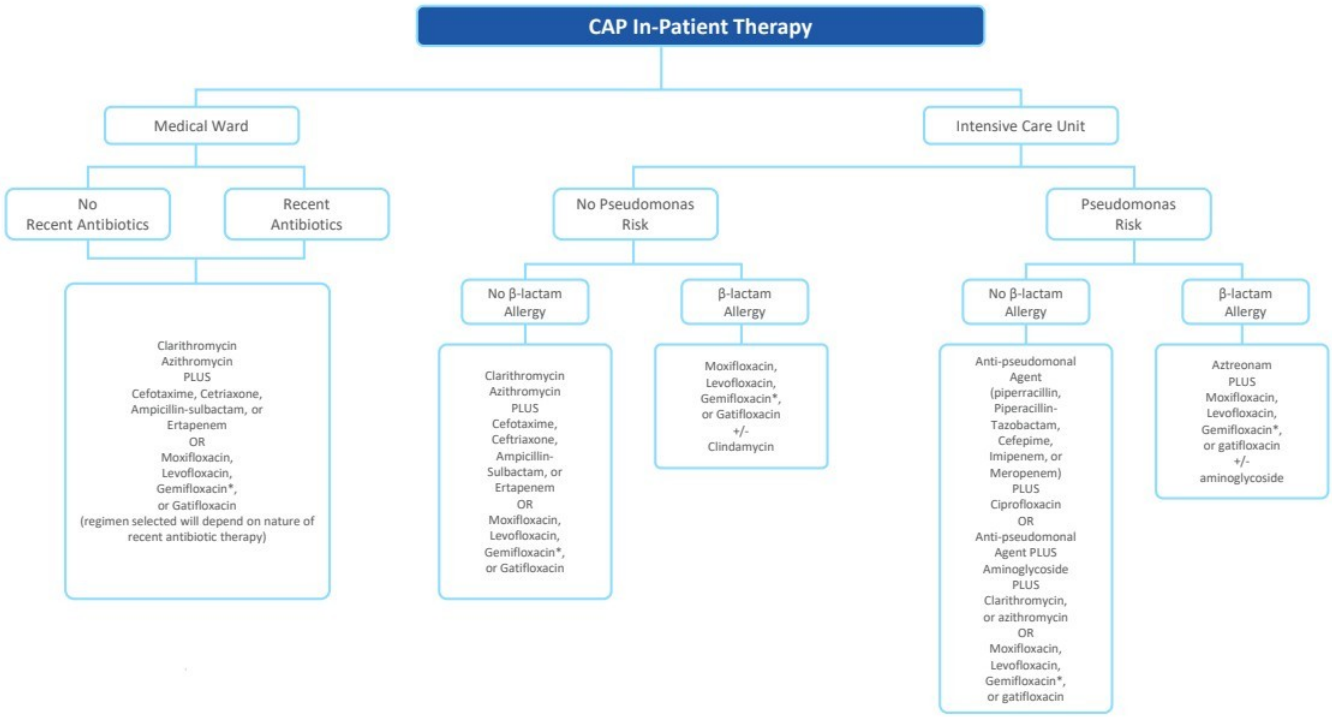
Suarez-de-laRica et al. Rev Esp Quimiot 2021 Aug;34(4):330-336. doi: 10.37201/req/031.2021

Pneumonia Management



Revised: *Trevor Van Schooneveld, MD and Kiri Rolek, PharmaD (July 2015)*

Pneumonia Treatment



Complications Associated with Pneumonia

A Significant Unmet Medical Need

Pneumonia is the most common infection requiring hospitalization and admission to ICU*

3rd most common cause of death globally (2.5million deaths/year)**

In the US about 1 million adults seek care for pneumonia yearly and 50,000 die from this disease*

Admission to ICU and length of hospitalization tightly linked to development of pneumonia complications*

35% - 58% mortality rate due to pneumonia complications such as acute respiratory distress, kidney, liver and heart damage and sepsis***

Adequate empirical antibacterial therapy shows no reduction in risk of death for pneumonia patients admitted to ICU*

Pneumonia complications place considerable burden on healthcare resources through increases in rates of hospitalization, lengthy in-patient care, cost of care and readmission rates*

*American Thoracic Society Top 20 Pneumonia Facts--2019 **Pneumonia & Deaths 2020 American Thoracic Society ***Ibn Saled et al, Crit.Care Med 47, 445-352 2019

Unmet Need in Severe CABP

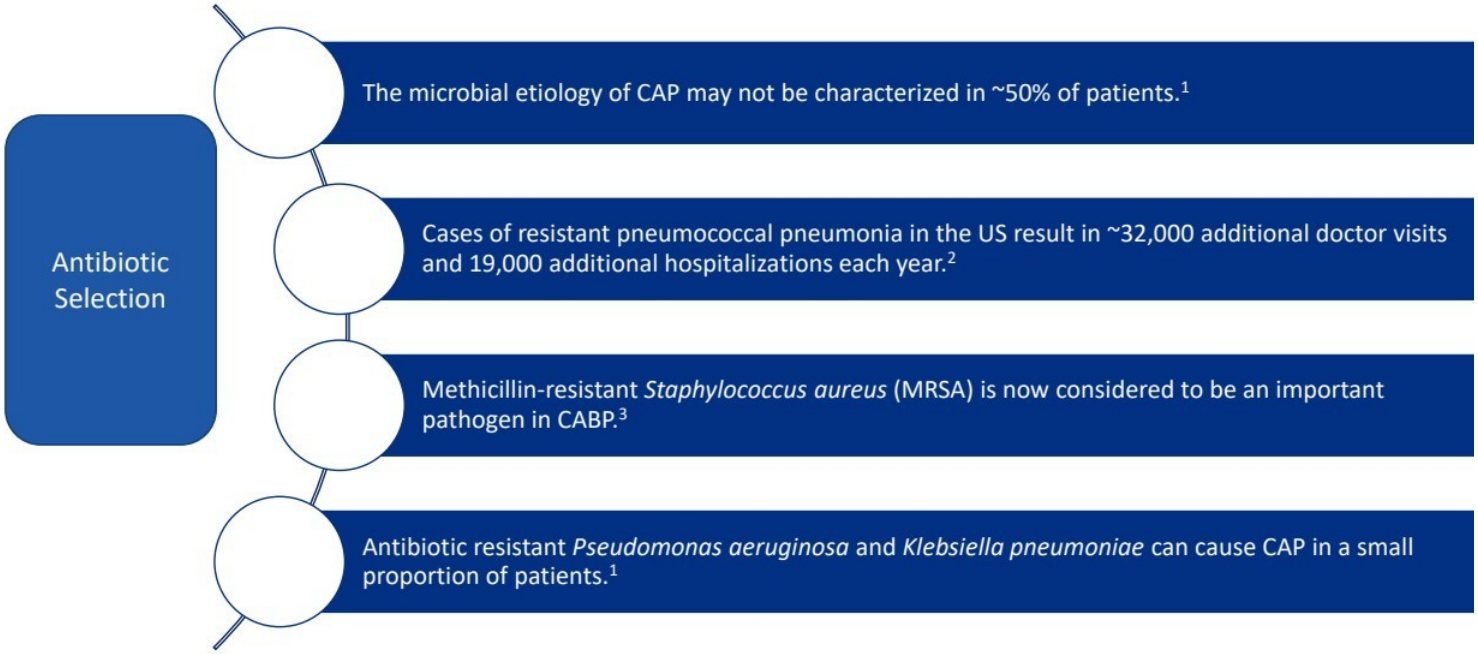
Unknown bacterial speciation upon admission and antibiotic resistance can complicate clinical management

Current CABP treatments have limitations and do not address the propagation of the inflammatory response

Treatment failure and high mortality rates remain problematic for severe CAP patients

There is a current unmet need for new treatment modalities that are effective in decreasing morbidity and mortality in severe CAP

Unknown Bacterial Speciation Upon Admission and Antibiotic Resistance Can Complicate Clinical Management



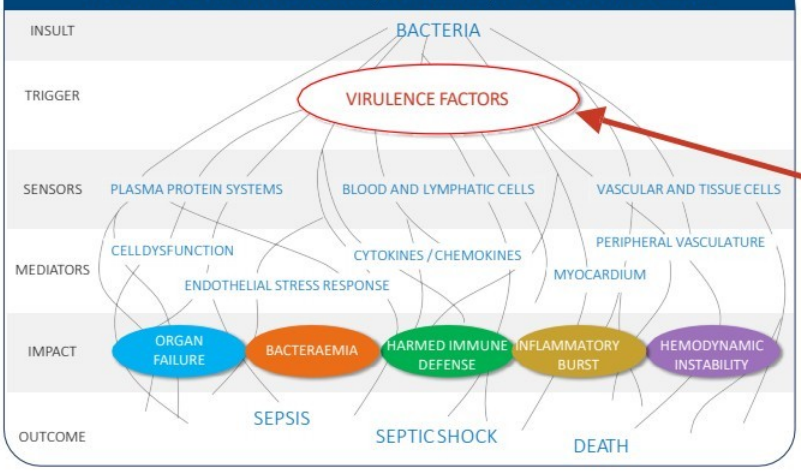
1. Shoar S, Musher DM. Etiology of community-acquired pneumonia in adults: a systematic review. Pneumonia (Nathan). 2020 Oct 5;12:11. doi: 10.1186/s41479-020-00074-3.
2. Centers for Disease Control & Prevention. Antibiotic Resistance Threats in the United States, 2013. US Department of Health and Human Services. Available at: https://www.cdc.gov/drugresistance/threat-report-2013/index.html
3. Mandell ALW, R. Methicillin-resistant staphylococcus aureus and community-acquired pneumonia: An evolving relationship. Clin Infect Dis. 2012;54(8):1134-1136

CAL02 Overview & Development Plan
Valentin Curt, M.D.

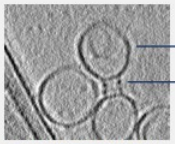
Severe Pneumonia - Key Targets

An underserved patient population:

Mortality rates for ICU pneumonia patients remain as high as 40%, worldwide, due to complications which most often occur even when tissues are already pathogen-free, and the pulmonary process is clearing



CAL02, a novel first-in-class broad-spectrum anti-virulence agent being developed for the treatment of severe community-acquired bacterial pneumonia, could potentially neutralize the most relevant virulence factors in severe pneumonia



Electron micrograph

Virulence effectors have a key role in promoting severe disease:

- play a critical role in the development of severe complications
- reinforce mechanisms of resistance
- facilitate and exacerbate co-infections

EAGLE PHARMACEUTICALS

Bacterial Virulence Factors (VFs)

VFs play a decisive role in the development of long-term, severe, and fatal pneumonia complications

- Currently not targeted by established antibiotics

VFs are a part of the pathogen's armory that triggers multiple pathogenic processes:

- Promote bacterial colonization and growth
- Disrupt tissue barriers
- Facilitate tissue penetration and infection's invasiveness
- Act synergistically to help bacteria evade the innate and adaptive immune response of the host

Ultimately VFs contribute to **edema, inflammation, and organ failure**

EAGLE PHARMACEUTICALS

Bacterial Virulence Factors (VFs) Classification

Pore-forming Toxins (PFTs)

- Single largest category (25-30% of cytotoxic bacterial proteins)
- Function to perforate membranes of host cells
- Classified as α-PFTs and β-PFTs based on the pore-forming mechanism
- β-PFTs and most α-PFTs preferentially target cholesterol and sphingomyelin

Other Virulence Factors

- Toxins with hemolytic activity
- Toxins with destructive enzymatic activities (proteases, lipases, DNase)
- Secreted vesicular or appended virulence effectors

EAGLE PHARMACEUTICALS

Bacterial Causes of Pneumonia

Severe CAP

100%

S. pneumoniae: 50-60% of SCAP cases worldwide
- Leading cause of lower respiratory infection morbidity and mortality globally (1.2 million deaths/year)*

Legionella pneumophila*: 8-12%*

S. aureus (including MSSA and MRSA): 2-12%
- Mortality rates of 50% in SCAP*

H. influenzae: 5-10%*

P. aeruginosa: (3-6%)
- Significant mortality rates*

Gram-negative enteric bacilli (GNEB) such as E. coli and K. pneumoniae: <2%*
- Significant mortality rates

HAP

- *H. influenzae*- early onset HAP
- *P. aeruginosa*
- *S. aureus (including MSSA and MRSA)*
- GNEB *(K. pneumoniae, E. coli)*
- *Acinetobacter** species- ICU patients
- *S. pneumoniae*- early onset HAP

VAP

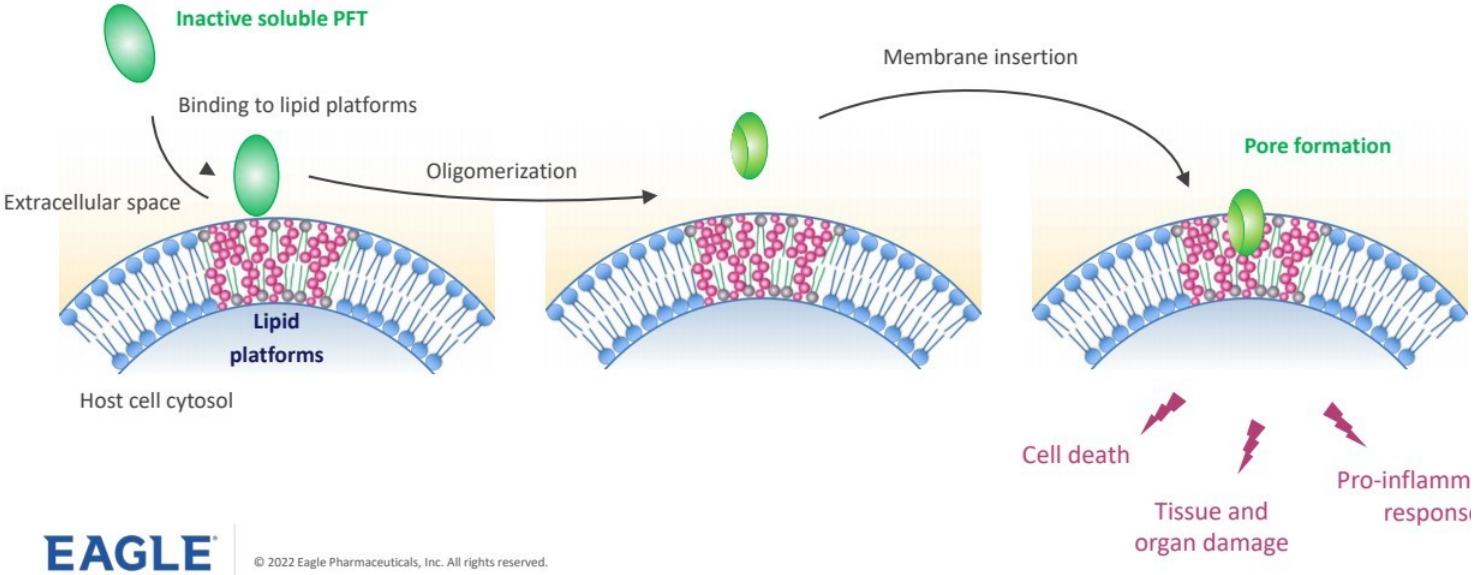
- *P. aeruginosa*
- *S. aureus (including MSSA and MRSA)*
- *S. maltophilia*
- *Acinobacter species*

*Cilloniz C, et al Thorax 66 340-346 2011

EAGLE PHARMACEUTICALS

Virulence Factors: Pore-Forming Toxins

We believe CAL02, a novel first-in-class broad-spectrum anti-virulence agent being developed for the treatment of severe community-acquired bacterial pneumonia, could potentially overcome the limitations faced by current approaches targeting virulence

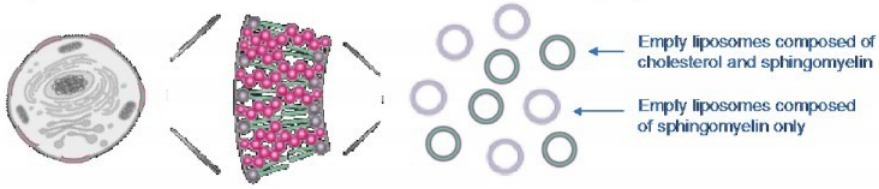


EAGLE PHARMACEUTICALS

CAL02 Mechanism of Action Against Virulence Factors

Lipid microdomains on cell membrane are used as docking stations by many bacterial toxins

CAL02: Specific mixture of empty liposomes engineered to mimic these docking stations to irreversibly trap toxins



DRUG COMPOSITION

Concentrated mixture of empty liposomes composed of cholesterol and sphingomyelin and of sphingomyelin only

MECHANISM OF ACTION

Acts as a winning decoy by mimicking domains targeted by toxins
Neutralizes a large panel of toxins

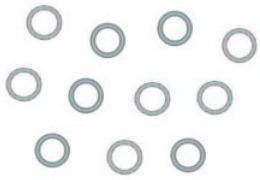
CAL02 is a novel first-in-cl broad-spectrum anti-virule agent being developed for treatment of severe community-acquired bacte pneumonia. It is being developed to neutralize virulence factors produced bacteria that are common associated with severe pneumonia and potentiall add to standard of care t help improve clinical outcomes.

EAGLE PHARMACEUTICALS

CAL02 Product Overview

- **Novel, first in class**
- **Being developed for treatment for patients with severe pneumonia**
- **Phase 2 adaptive design study underway**
- **Potential for Qualified Infectious Disease Product (QIDP) Designation under the Generating Antibiotic Incentives Now (GAIN) Act**
- **Potentially eligible for 10 years marketing exclusivity**

CAL02 (drug product)



Specific mixture of re-engineered empty liposomes solely composed of sphingomyelin and cholesterol capable of capturing and neutralizing a broad spectrum of virulence effectors

- Patented composition of matter
- Sterile liquid solution ready for injection
- Stable for 36 months when refrigerated (6 months when stored at room temperature)
- Route of administration: IV Infusion
  2 doses separated 24 hours apart

EAGLE PHARMACEUTICALS

CAL02 – Novel, First-in-Class Virulence Neutralizer Agent

Mechanism of Action

Address the downstream effects of bacterial VFs/PFTs through competitive inhibition

- Binds to virulence factor molecules secreted by infecting bacteria, prohibiting host tissue cell binding
- Acts as an extracellular "sink" for these toxins
- Potential to attenuate pore forming toxin related effects including host tissue damage, immune dysregulation, and inflammation that contribute to increase disease severity

Lead Indication

Severe Community Acquired Pneumonia

- Significant morbidity and mortality despite advances in direct acting antibacterials
- Significant medical need and burden on health care systems

Differentiated Advantages

- Potential to be used as adjuvant therapy with any traditional antibacterial [therapy agnostic]
- Potential to be used against any bacteria that produces pore forming toxins [bacteria agnostic]
- Potential to carry less risk of antibacterial resistance development

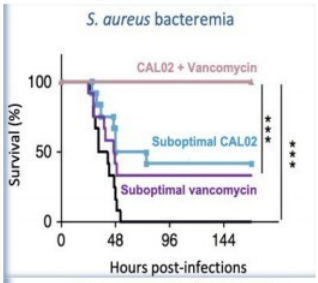
Development Program Progress

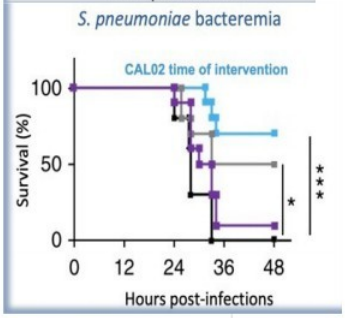
- First-in-Human (FIH) proof of concept study showed tolerability as well as encouraging trends
- Regulatory interactions with FDA and EMA – may be eligible for special designations and review processes
- Global Phase 2 study underway
- Scalable manufacturing process

EAGLE PHARMACEUTICALS

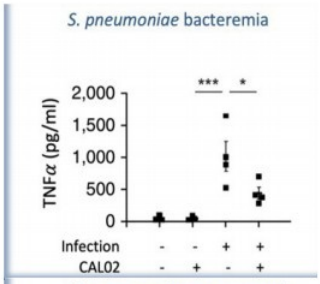
CAL02 Non-Clinical Program Proof-of-Concept

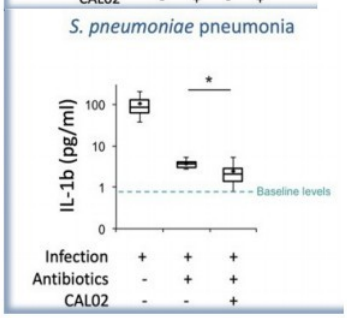
Improved survival



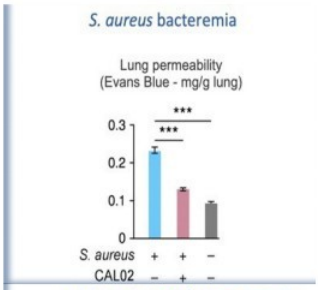


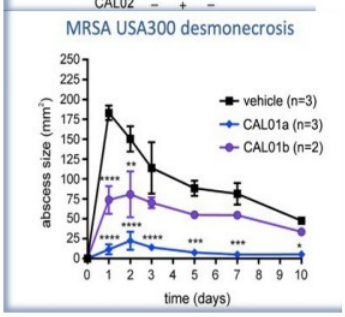
Decreased pro-inflammatory responses



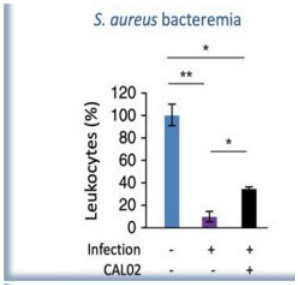


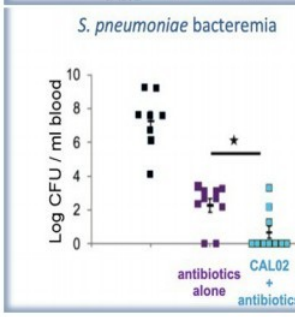
Organ protection (lung, heart injury, tissue necrosis)





Shielded immu defense





EAGLE PHARMACEUTICALS

CAL02 Non-Clinical Safety Pharmacology and Toxicology

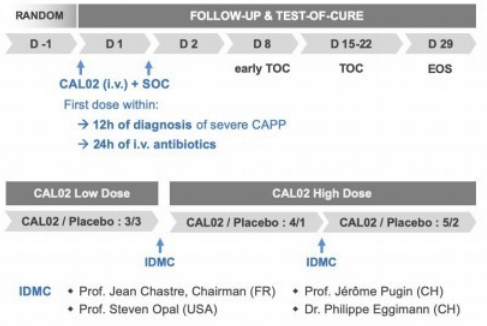
- **Safety pharmacology studies in rats** (respiratory, CNS) **and dogs: no safety signals even at the maximum feasible dose, i.e., a maximum tolerated dose** (MTD) **could not be determined**
- **CAL02 is taken up by macrophages and eliminated via the liver, its half-life in human is estimated to be 24-30 hours**
- **CAL02 toxin complex degradation and elimination do not cause any toxicity, even in critically ill patients with liver failure**
- **Promising biological safety profile** (no impact on flora, non-immunogenic, biologically neutral)

EAGLE PHARMACEUTICALS

CAL02 Clinical Data in Humans: Safety Outcomes

First-In-Human Study Results

- Randomized, double-blind, placebo-controlled
- 3 arms / 19 patients:
  - CAL02 Low dose (4 mg/kg) + Standard of Care
  - CAL02 High dose (16 mg/kg) + Standard of Care
  - Placebo (saline) + Standard of Care
- 2 IV administration 24h apart
- Severe CAPP: At least 1 major criteria (mechanical ventilation/ vasopressors) or 3 minor criteria
- Primary objective: Safety & Tolerability
- Secondary objective : Efficacy & Pharmacodynamics



EAGLE PHARMACEUTICALS

Baseline Characteristics

Disease severity of the study population corresponded to that expected from the inclusion/ exclusion criteria

Severity at baseline:

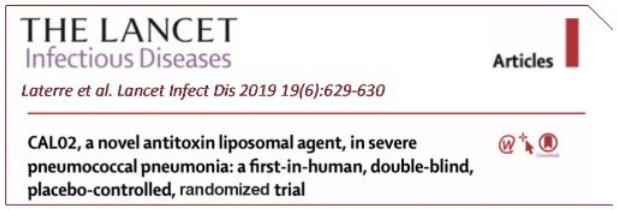
- Mean APACHE II Score: 21.5 (95% CI 19.3-23.7)
- 58% in Septic Shock
- >40% under Invasive Mechanical Ventilation

No differences between treatment groups considered to have a substantial effect on safety and efficacy outcomes

Safety Outcomes

CAL02 showed **the same safety profile as placebo** (saline)

- Adverse Event (AE) occurred in 12 (85%) of 14 patients in the CAL02 groups combined and in al 5 (100%) patients in the placebo group.
- Serious Adverse Event (SAE) occurred in 4 (29%) of 14 patients in the CAL02 groups combined an 2 (40%) of 5 patients in the placebo group
- 1 AE (mild increase in the triglycerides) in a patient in the CAL02 High dose group was reported as related to study drug. However, the analysis of the changes in triglyceride in the CAL02 groups compared with the placebo group revealed no correction with CAL02.
- No AEs were liked to local tolerability events.



CAL02 Clinical Data in Humans: Efficacy Outcomes

	Low-dose CAL02 (n=3)	High-dose CAL02 (n=10)	Placebo (n=5)
Cured at early test of cure (day 8)	0	5 (56%)*	1 (20%)
Cured at test of cure (between days 15–22)	2 (100%)*	10 (100%)	5 (100%)
Median time to cure (days)	15·0 (14 to 16)†	8·0 (6 to 16)	10·0 (7 to 14)
All-cause mortality	1 (33%)	1 (10%)	1 (20%)
Relative change in Sequential Organ Failure Assessment score from baseline to day 8	−65·9% (−34·7 to −97·1)	−64·7% (−46·3 to −83·1)	−29·2% (−12·8 to −45·5)
Relative change in Acute Physiology and Chronic Health Evaluation II score from baseline to day 8	−59·9% (−34·0 to −85·8)	−60·4% (−45·3 to −75·5)	−22·1% (−15·5 to −28·7)
Relative change in PaO_2/FiO_2 from baseline to day 8	153·1 %(116·2 to 189·9)	78·4% (7·4 to 149·3)	58·5% (−27·5 to 137·9)
Median duration of invasive mechanical ventilation (days)†	12·0 (5 to 19)†	4·5 (4 to 14)	12·0 (11 to 56)
28-day ventilation-free days (days)	16·5 (1·8 to 31·2)†	25·1 (22·0 to 28·2)†	17·8 (7·7 to 27·9)
Median duration of intensive care unit stay (days)	15·0 (9 to 21)†	5·0 (2 to 15)	12·0 (6 to 56)
Median duration of stay in hospital (days)	33·0 (12 to 54)†	13·0 (4 to 28)†	21·0 (6 to 56)

Data are n (%), median (range), or mean (95% CI). PaO_2/FiO_2=partial pressure of oxygen in the blood/fraction of inspired oxygen. *One patient was missing for the assessment (because of death). †One patient censored because of death.

Overview of primary and secondary efficacy endpoints in CAL02 and placebo treatment groups (as-treated population)

EAGLE PHARMACEUTICALS

Laterre et al. Lancet Infect Dis 2019 19(6):629-630

CAL02 Phase 2 Study Design

Design	An adaptive, randomized, multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of CAL02 administered intravenously in addition to standard of care in subjects with severe community acquired bacterial pneumonia (SCABP)
Study population	Patients hospitalized with SCABP, with protocol-defined severity criteria
Primary objective(s)	• Time to clinical recovery • Safety and tolerability
Secondary objectives	Length of ICU and hospital stay; Evolution of SOFA score; All-cause mortality; Need for ventilation/oxygen therapy/vasopressors
Exploratory objectives	Evolution of inflammatory biomarkers
Treatment administration	IV infusion, two administrations 24 hours apart
Treatment regimens	• CAL02 • Placebo
Sample size	Approximately 276 subjects
Study sites	Approximately 120 centers across 22 countries
Interim analyses	At 33% of subjects completed and at 50% of subjects completed approximately 1 year after 1st patient in

EAGLE PHARMACEUTICALS

CAL02 Potential Competitive Advantages

Limitations of current approaches
(approved / in development)

Limited use

- Restrictions imposed by stewardship measures and purchasers, as antibiotics are inevitably linked to the emergence of new resistances

Slow and laborious market penetration

- Based on non-inferiority results
- Last-resort treatments
- Increasingly competitive space

Limited scope of application

- Action dedicated against resistant mechanism
- New mechanisms ultimately facing resistance issues
- Monoclonal antibodies targeting a single toxin
- Agents targeting a downstream specific pathway or cytokine dedicated to target patients already in shock

CAL02

- Potentially will not drive resistance; would fill a significant medical gap
- If approved, may offer physicians a new treatment; potential to dramatically improve outcomes
- Potentially combines with any treatment (antibacterial agnostic)
- May lead to a tremendous economy on cost of care; broad-spectrum (used irrespective of pathogen identification or hemoculture or resistance to antibacterials)
- Potential for expedited regulatory pathway to approval

EAGLE PHARMACEUTICALS

CAL02: Potential Unique Therapeutic Benefit

Andre Kalil, MD, MPH
Professor of Medicine
University of Nebraska Medical Center

CAL02: Potential Unique Therapeutic Benefit

Potential to become first line empirical therapy*, if approved

- Compelling **safety** profile
- Did not prompt any new **resistance**
- Unique **broad-spectrum** activity
- **No impact** on flora
- **Non**-immunogenic
- Biologically **neutral**

May offer a unique therapeutic benefit to critically ill patients

Positive trends over placebo in efficacy parameters*+

- Reduction of mortality risk+
- Potentially faster and complete recovery of organ function +
- Shorter duration of mechanical ventilation
- Immediate decrease in inflammatory biomarkers (e.g. IL-6)
- Shorter ICU length of stay+

+ statistically significant

*Laterre et al. Lancet Infect Dis 2019 19(6):629-630

THE LANCET
Infectious Diseases

Comment

Pletz et al. Lancet Infect Dis 2019 19(6):564-565

One step closer to precision medicine for infectious diseases

"A medical breakthrough"

CAL02 represents a milestone"

"Potentially suitable for adjunctive empirical treatment"

Potential to address a significant unmet medical need

A straightforward and innovative approach

A potentially unique therapeutic benefit to critically ill patients

Barhemsys and Byfavo

Hospital Environmental Trends Bolster the Value Proposition of Eagle's Acute Care Portfolio

Profitability within hospitals continues to be a significant challenge	• Rising costs of supplies, wages, and operations • Negative reimbursement trends • Continued staffing shortages
Hospitals taking initiatives to address environmental trends	• Shifting of surgical and procedural volume to outpatient sites of care • Focus on cost containment • Increase focus on quality, safety, and efficiency
Profiles of Barhemsys & Byfavo enable them to be a part of the solution	• Safety and efficacy of both Barhemsys and Byfavo provide new options, contributing to the focus on quality and safety • Both Barhemsys and Byfavo can help improve patient throughput, potentially contributing to the efficiency of the health systems

https://www.aha.org/costsofcaring, https://www.aha.org/fact-sheets/2022-09-13-fact-sheet-advocacy-priorities-fall-2022

EAGLE PHARMACEUTICALS

Barhemsys – Compelling Clinical and Commercial Proposition

Significant unmet need[1]

- Post Operative Nausea and Vomiting (PONV) is associated with increased length of Post Anesthesia Care Unit (PACU) stay and greater resource utilization
- PONV contributes to patient dissatisfaction
- Breakthrough PONV is not being addressed promptly and aggressively

Only FDA-approved product for PONV rescue[2]

- First and only FDA-approved antiemetic for rescue treatment of PONV despite prophylaxis[3]
- Excellent safety profile demonstrated in clinical studies
- Also demonstrated to be effective for prevention

Throughput and health economic benefits

- Is non-sedating – a common complaint of standard antiemetic agents
- Opportunity to reduce PACU and overall hospital stays
- Potential to offer significant economic savings to hospital vs. current standard of care

1. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting; 2 FDA labels for other recommended treatments do not include treatment after failed prophylaxis. Treatment agents recommended by Society for Ambulatory Anesthesiology Consensus Guidelines (2014). Habib et al (2019): no agent has previously been shown in a prospective trial to be more effective than a placebo for treating PONV for patients who have failed prophylaxis. 3 FDA labels f other recommended treatments do not include treatment after failed prophylaxis.

EAGLE PHARMACEUTICALS

Byfavo – Compelling Clinical and Commercial Proposition

Clear unmet need

- No new approved drugs in the sedation space for over 20+ years
- Customers seeking fast and predictable effect with rapid recovery for quick discharge
- Short recovery time enabling efficiency and enhanced patient throughput

Broad label with health economic benefits

- Indicated for procedural sedation in adults in procedures lasting 30 minutes or less
- Substantial clinical data package shows compelling efficacy and safety in colonoscopies and bronchoscopies, including least fit patients
- Commercial use across broad range of procedure and patient types

Strong value proposition

- Benzodiazepine intentionally designed for rapid onset and rapid offset, in dosages independent of patient weight, to offer clinicians a predicable level of sedation and procedural efficiency for procedures lasting 30 minutes or less – maximizing patient comfort and satisfaction

*Important Safety Information (ISI) can be found at: https://bynder.acaciapharma.com/m/403e8c343b2922de/original/Byfavo-PI.pdf

EAGLE PHARMACEUTICALS

Barhemsys: Management of Postoperative Nausea and Vomiting

Management of Postoperative Nausea and Vomiting. The Role of Amisupride.

T.J. Gan, M.D., M.B.A., F.R.C.A., M.H.S.
Division Head of Anesthesiology, Critical Care and Pain Medicine,
The University of Texas MD Anderson Cancer Center
Founding President, American Society for Enhanced
Recovery (ASER) aserhq.org | enhancedrecovery.org
President, Perioperative Quality Initiative (POQI) poqi.org

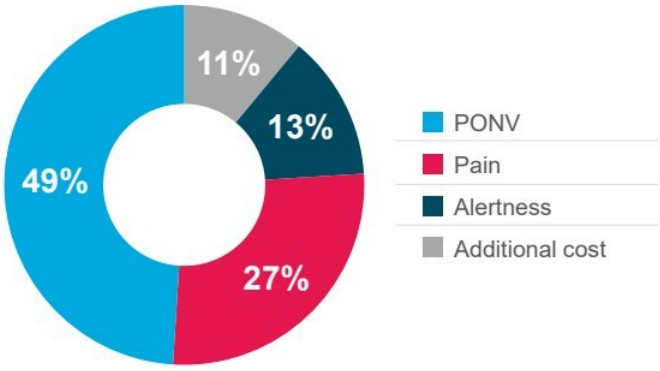
PONV Is Common and Complex

- A common complication of surgery and anesthesia
- Despite prophylaxis, 30% of patients still experience PONV in the PACU
- Unpleasant and associated with patient discomfort and dissatisfaction with perioperative care
- A greater concern for patients than avoiding postoperative pain
- Associated with delayed discharge from the recovery room and unanticipated or extended inpatient hospital stay ($2,607/day); therefore, a cause of potentially avoidable healthcare costs

1. Pierre S, et al. BJA Education. 2013;13(1):28-32. 2. Rahman MH, et al. Pharm J. 2004;273:786-793. 3. White PF, et al. Anesth Analg. 2008;107:452-458. 4. Habib AS, et al. Anesthesiology. 2019;130(2):203-212. 5.Eberhart LH, et al. Anesthesiology. 2002;89(5):760-761. 6. Kaiser Family Foundation. http://kff.org/other/state-indicator/expenses-per-inpatient-day. Accessed September 22, 2021. 7. Gan TJ, et al. Anesth Analg. 2020;131(2):411-448

Patients Perceive PONV to Be Worse than Pain

Relative Importance of Patient Postoperative Recovery Concerns (%) (N=220)[1]



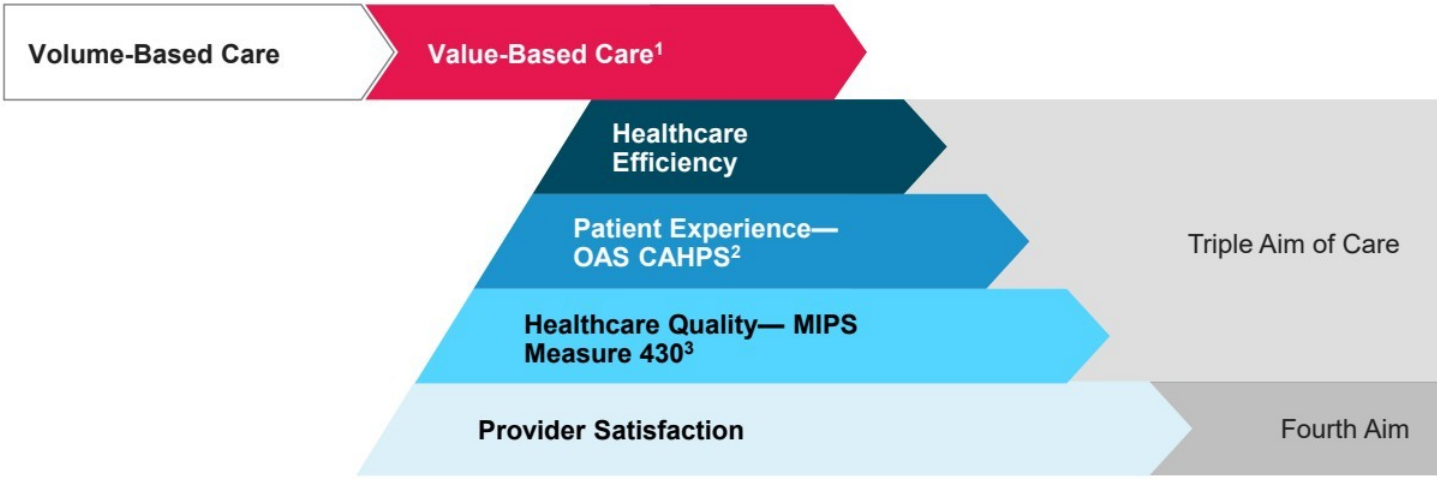
1. Eberhart LH, et al. *Anesthesiology.* 2002;89(5):760-761. 2. Hill RP, et al. Anesthesiology. 2000;92:958-967. 3. Gan TJ, et al. Br J *Anaesth.* 2004;92(5):681-688.

PONV

- The most common reason for poor patient satisfaction during the perioperative period[2]
- A greater concern for some patients than pain, alertness, or additional cost[1,3]

Quality of PONV Management Is Measured by National Performance Metrics

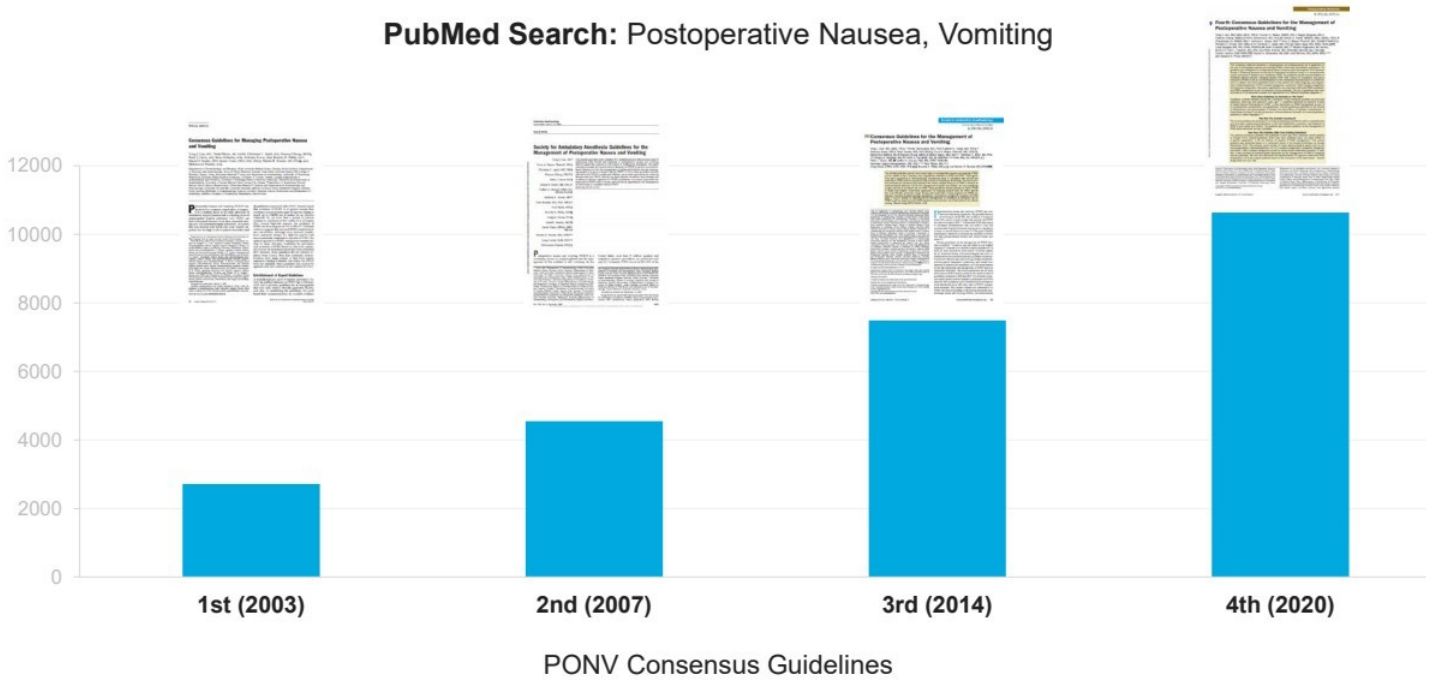
Shifting Towards Patient-Centered Care[1]



OAS CAHPS=Outpatient and Ambulatory Surgery Consumer Assessment of Healthcare Providers and Systems. MIPS=Merit-based Incentive Payment System.

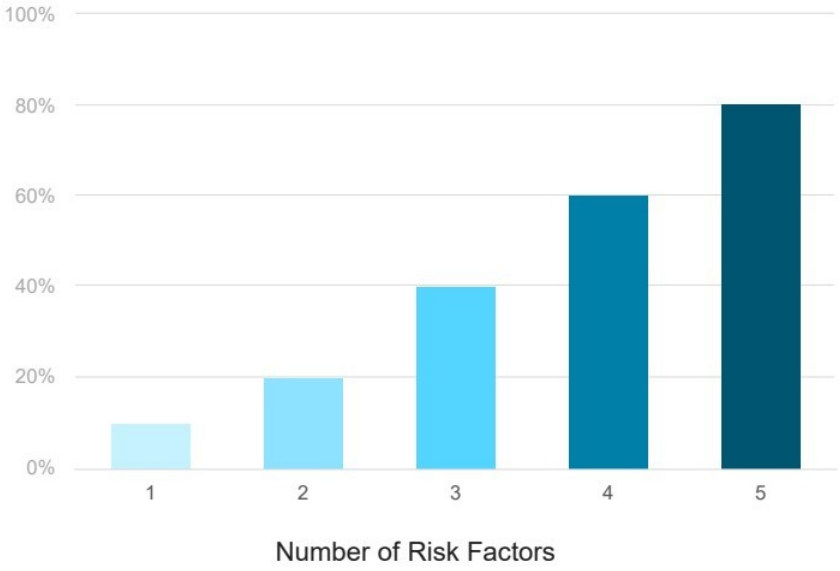
1. Bodenheimer T, Sinsky C. *Ann Fam Med*. 2014;12(6):573-576. 2. Outpatient and ambulatory surgery CAHPS (OAS CAHPS). https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/CAHPS/OAS-CAHPS.html. Accessed September 22, 2021. 3. Merit-Based Incentive System Overview. https://qpp.cms.gov/mips/overview. Accessed September 22, 2021.

Number of Publications on PONV



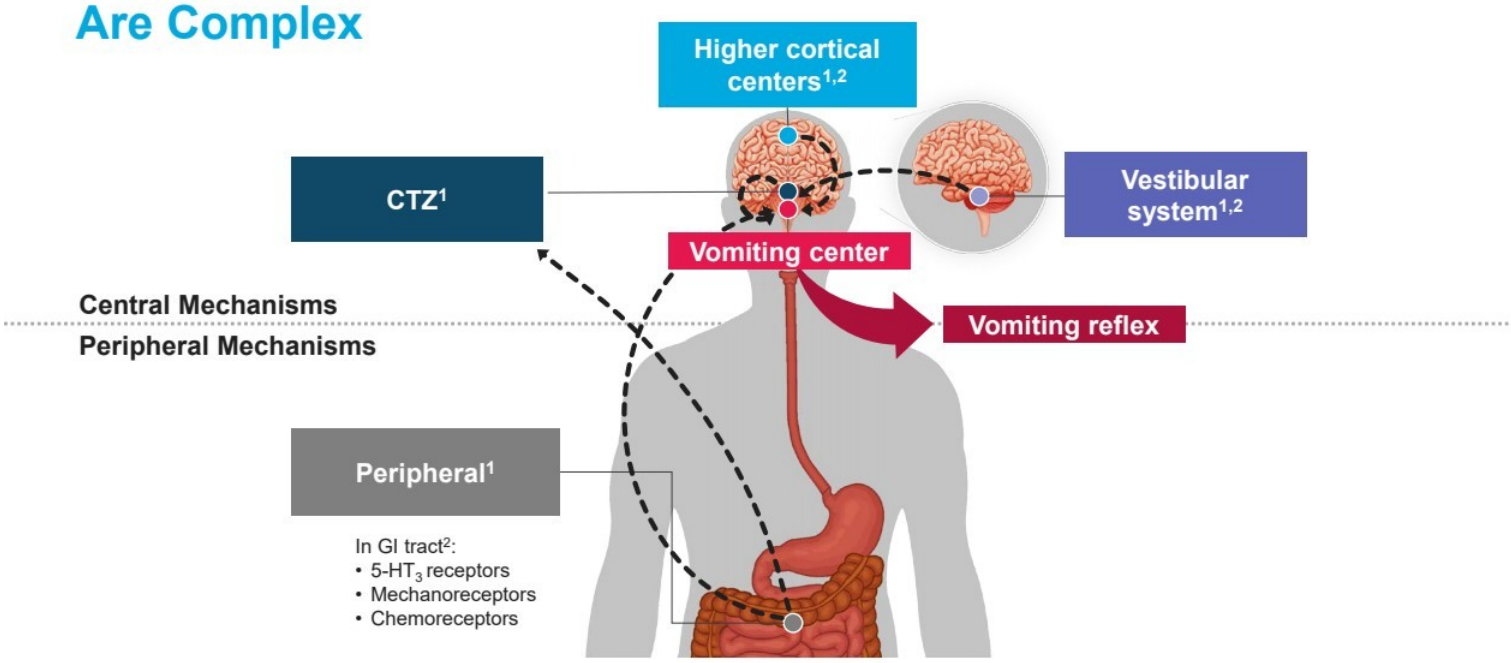
PONV Risk Factors - Adults

Risk Factors	Points
Female Gender	1
Non-Smoker	1
History of PONV	1
Postoperative Opioids	1
Sum of points	1-4



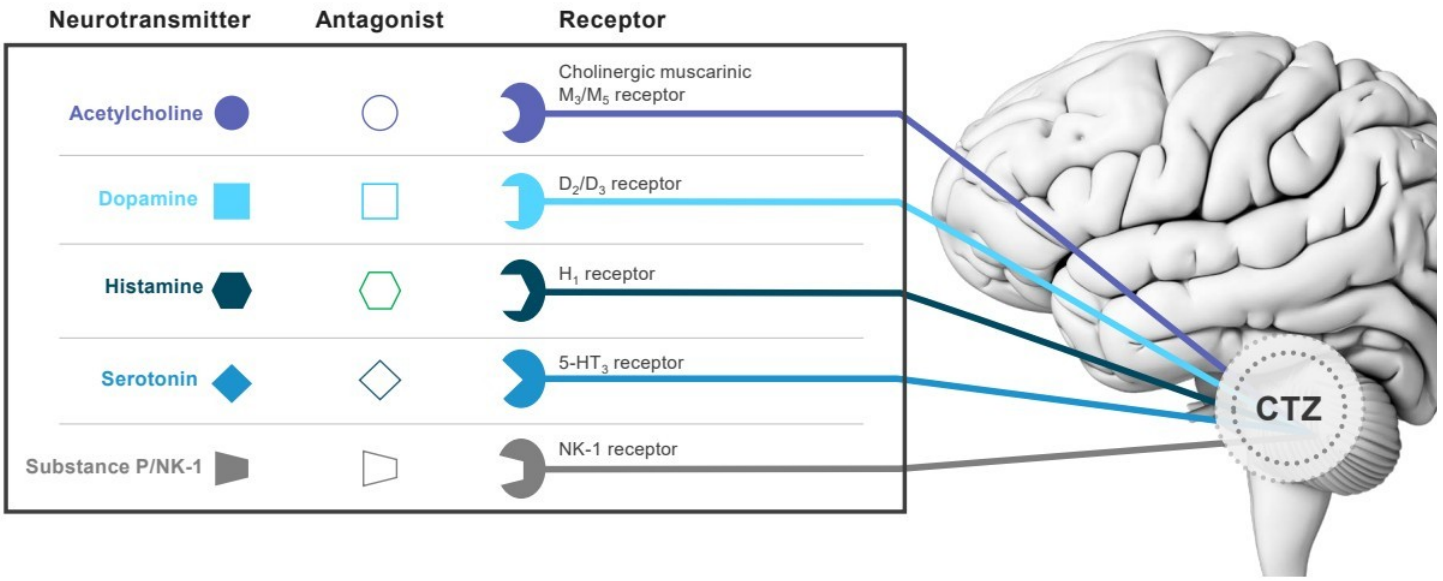
Gan TJ et al. Anesth Analg 2020;131:411–48
Apfel C, et al. Acta Anaesthesiol Scand 1998;42:495-501

Etiology and Pathophysiology of Nausea and Vomiting Are Complex



5-HT_3=5-hydroxytrytamine type 3. CTZ=chemoreceptor trigger zone. GI=gastrointestinal.
1. Rahman MH, et al. *Pharm J*. 2004;273:786-793. 2. Singh P, et al. *Therap Adv Gastroenterol*. 2016;9(1):98-112.

Nausea and Vomiting Are Mediated by Multiple Neurotransmitters and Their Receptors[1-4]



D=dopamine. H=histamine. M=muscarinic. NK=neurokinin.

1. Watcha MF, et al. *Anesthesiology*. 1992;77(1):162-184. 2. Shaikh SI, et al. *Anesth Essays Res*. 2016;10(3):388-396. 3. Kovac AL. In: Gan TJ, Habib A. eds. *Postoperative Nausea and Vomiting: A Practical Guide*. Cambridge, UK: Cambridge University Press; 2016:13-22. 4. Darmani NA, et al. *J Neural Transm*. 1999;106:1045-1061.

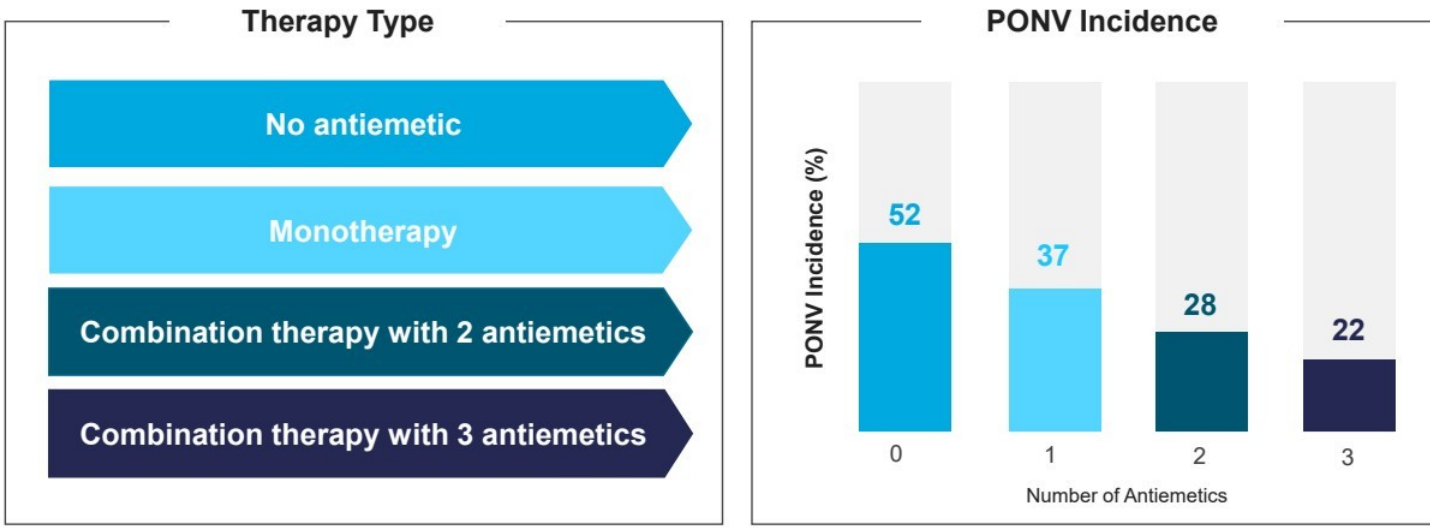
Main Drug Classes Manage PONV

They are classified on the basis of their action over various receptors[1-3]

- **Anticholinergics** (transdermal scopolamine)
- **5-HT_3 antagonists** (ondansetron, granisetron, palonosetron)
- **Dopamine antagonists** (droperidol, haloperidol)
- **NK-1 antagonists** (aprepitant, rolapitant)
- **Antihistamines** (dimenhydrinate, promethazine)
- **Corticosteroids** (dexamethasone, methylprednisolone)

1. Whelan R, Apfel CC. *Pharmacology and Physiology for Anesthesia*. 2013;503-522. 2. Shaikh SI, et al. *Anesth Essays Res*. 2016;10(3):388-396.
3. Gan TJ, et al. *Anesth Analg*. 2020;131(2):411-448.

Combination Therapy in Patients at Moderate or High Risk May Reduce Incidence of PONV



Apfel CC. *N Engl J Med*. 2004;350(24):2441-2451.

Breakthrough PONV Occurs Despite Prophylaxis

In high-risk patients

can experience **PONV**[1,2]

can experience **PONV despite prophylaxis**[3,4]

In patients who failed prophylaxis

can experience **nausea**[4,5]

can experience **vomiting**[4]

1. Gan TJ, et al. *Anesth Analg*. 2014;118(1):85-113. 2. Apfel CC, et al. *Anesthesiology*. 1999;91(3):693-700. 3. White PF, et al. *Anesth Analg*. 2008;107:452-458.
4. Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212. 5. Habib AS, et al. *Curr Med Res Opin*. 2006;22(6):1039-1099.

Limited Treatment Options Exist for Patients Failing Prophylaxis

For patients failing typical pre- or perioperative prophylaxis with 5-HT3 antagonist, rescue treatment choices are limited.[1]

Rescue Treatment Choice	Challenges
5-HT3 antagonists	No benefits if reused within 6 hours[2]
Metoclopramide	Inadequate efficacy[2], Boxed Warning[3]
Dexamethasone	Slow to act[2]
Promethazine	Received Boxed Warning for tissue necrosis concerns[4]
Droperidol	Received Boxed Warning for QTc interval prolongation concerns[5]
Dimenhydrinate	Limited evidence available for use[2]
Aprepitant	Indicated for prophylaxis only[6]

Current guidelines recommend use of an antiemetic from a different class than that used for prophylaxis[1]

1. Habib, et al. *Anesthesiology*. 2019 Feb;130(2):203-212 2. Gan TJ, et al. *Anesth Analg*. 2014;118(1):85-113. 3. Reglan (metoclopramide injection) [Package Information]. Deerfield, IL. Baxter Healthcare Corporation; 2010. 4. Phenergan (promethazine HCL). [Package Information]. Eatontown, NJ. West-Ward Pharmaceuticals; 2012. 5. Inapsine (droperidol injection). [Package Information]. Decatur, IL. Taylor Pharmaceuticals; 2006. 6. EMEND (aprepitant) [Package Information]. Whitehouse Station, NJ. Merck & Co., Inc; 2017.

Barhemsys Characteristics

Amisulpride (active ingredient of Barhemsys)[1]

- Substituted benzamide ($C_{17}H_{27}N_3O_4S$)[1,2]
- Dopamine antagonist with high affinity for D_2/D_3 receptors[1,2]
  - Regional preference for D_2 and D_3 receptors in limbic, but not striatal structures[2-4]
  - No appreciable affinity for any other receptors[1,2]
- Low blood-brain barrier (BBB) penetration at low doses used for PONV[3]
- Elimination half-life is 4-5 hours[1]
- Not metabolized by major CYP450 enzymes[1]
- Plasma protein binding is 25-30%[1]

CYP450=cytochrome P450.

1. Barhemsys [Prescribing Information], Indianapolis, IN. Acacia Pharma; 2021. 2. Schoemaker H, et al. *J Pharmacol Exp Ther*. 1997;280(1):83-97. 3. Möller H-J. *Prog in Neuro-Psychopharmacology & Biol Psych*. 2003;27:1101-1111. 4. Xiberas X, et al. *J Clinical Psychopharmacology*. 2001;21(2):207-214.

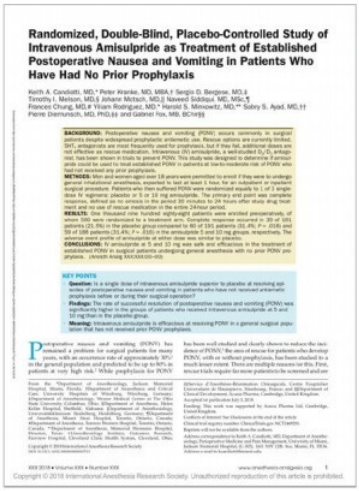
Barhemsys: Evaluated in ~2000 Patients Over 4 Pivotal Clinical Trials[1]

Intravenous Amisulpride for the Prevention of Postoperative Nausea and Vomiting

Two Concurrent, Randomized, Double-blind, Placebo-controlled Trials

Amisulpride Prevents Postoperative Nausea and Vomiting in Patients at High Risk

A Randomized, Double-blind, Placebo-controlled Trial



Randomized, Double-Blind, Placebo-Controlled Study of Intravenous Amisulpride as Treatment of Established Postoperative Nausea and Vomiting in Patients Who Have Had No Prior Prophylaxis

PERIOPERATIVE MEDICINE

ANESTHESIOLOGY

Amisulpride for the Rescue Treatment of Postoperative Nausea or Vomiting in Patients Failing Prophylaxis

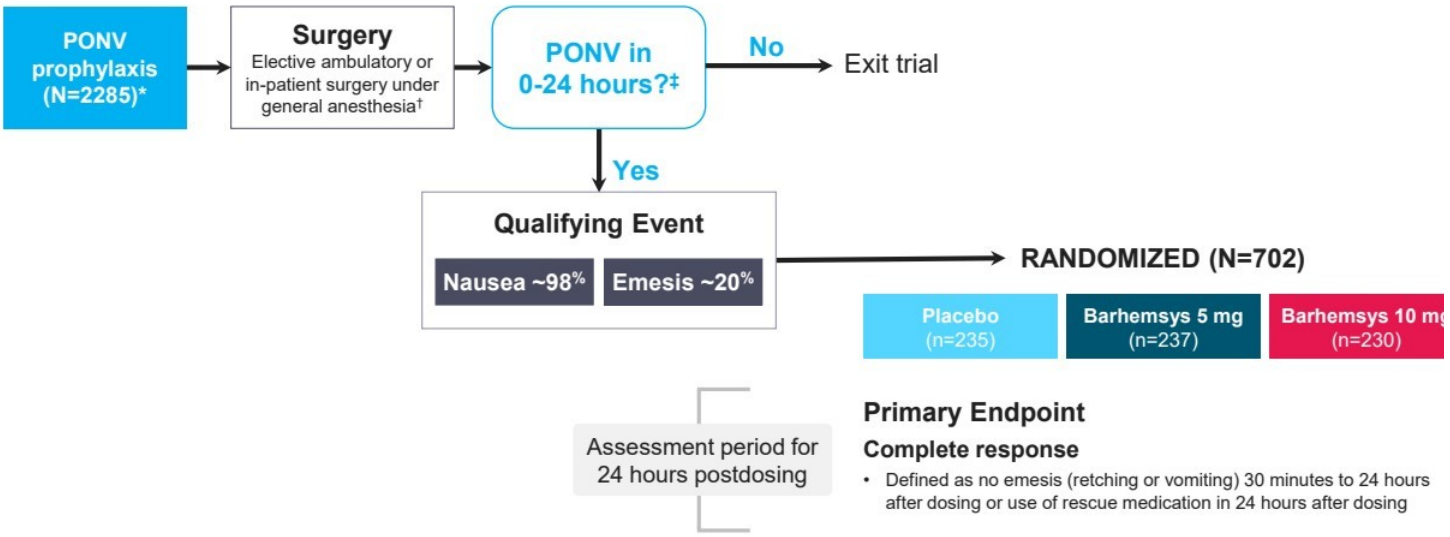
A Randomized, Placebo-controlled Phase III Trial

1. Barhemsys [Prescribing Information], Indianapolis, IN. Acacia Pharma; 2021. 2. Candiotti KA, et al. *Anesth Analg*. 2018. 3. Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212. 4. Gan TJ, et al. *Anesthesiology*. 2017;126(2):268-275. 5. Kranke P, et al. *Anesthesiology*. 2018;128(6)1099-1106

Barhemsys for Rescue Treatment

The First and Only Antiemetic Indicated to Treat PONV After Failed Prophylaxis

Rescue Treatment Clinical Trial Design



Barhemsys 5 mg is not approved for the treatment or rescue treatment of PONV.

*Total IV anesthesia with propofol was not permitted, though a single dose at induction was allowed.
†One or more nondopamine antagonist antiemetics were allowed as prophylaxis. Patients were excluded if they had received a D_2 antagonist antiemetic.
‡As judged by investigator.

Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212.

Rescue Treatment Trial:
Patient Baseline Characteristics at Randomization

	Barhemsys 10 mg (n=230)	Placebo (n=235)
Age, median (range)	47 (18-85)	45 (18-81)
Sex, female	90.4%	90.2%
5-HT_3 antagonist	76.5%	77.4%
Dexamethasone	67.8%	61.7%
Other	12.2%	8.9%
1 antiemetic	52.6%	51.1%
≥2 antiemetics	47.4%	46.0%
Patients with emesis	17.4%	24.3%
Patients with nausea	99.1%	97.0%
PONV in PACU	73.5%	73.2%
PONV 0-2 hours after surgery	67.8%	71.9%

PACU = Post Anesthesia Care Unit

Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212.

Patient Baseline Characteristics

- >90% of patients had 3-4 risk factors
- Most were female, with a median age >45

PONV Prophylactic Treatment

- Majority of patients received a 5-HT_3 antagonist or dexamethasone
- ~50% received ≥2 antiemetics

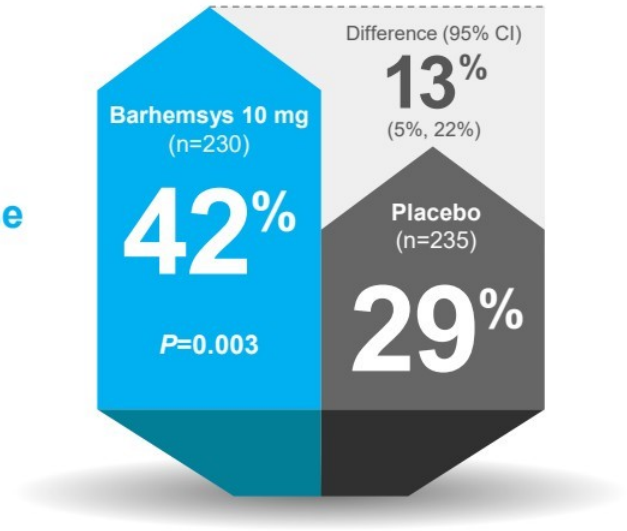
Qualifying PONV Event

- Majority of patients experienced nausea in the PACU or within 2 hours of surgery

Barhemsys Was More Effective than Placebo at Treating PONV in Patients Who Failed Prophylaxis

Patients with Complete Response at 24 Hours*

Defined as: No Emesis or Use of Rescue Medication



42%

of patients who received Barhemsys 10 mg after faili prophylaxis had complete response at 24 hours

Barhemsys 5 mg is not approved for the treatment or rescue treatment of PONV.

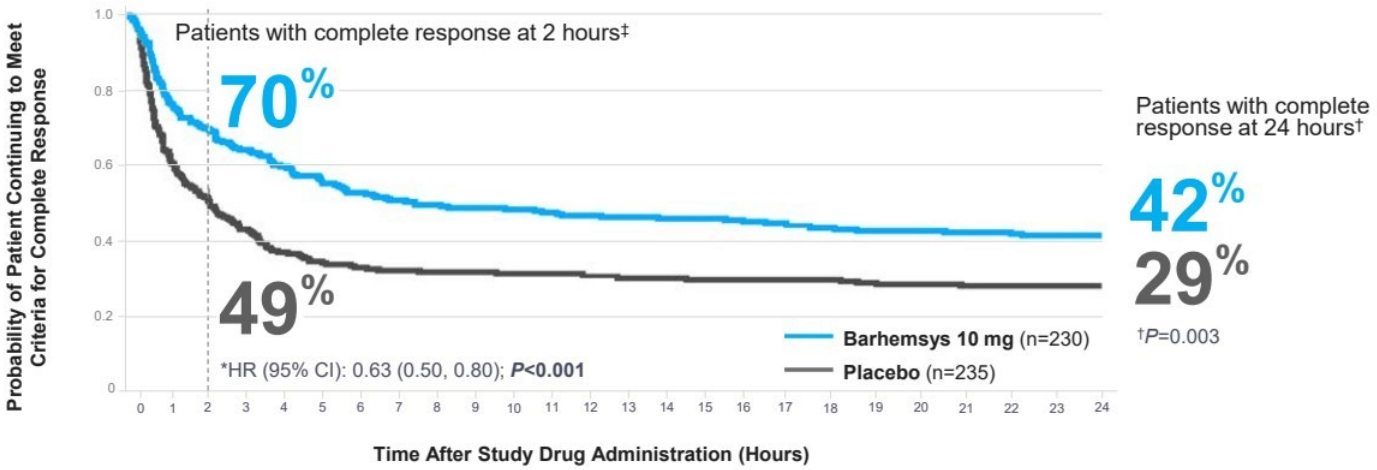
*The primary efficacy analysis was a comparison of the proportion of complete response between Barhemsys 10 mg and placebo in the modified ITT population. Pearson's chi-squared test with a 1-sided 2.5% significance threshold was used to assess the difference between treatment groups. The modified ITT population was composed of randomized patients who received study medication.

CI=confidence interval. ITT=intention-to-treat.

Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212.

Barhemsys Was More Effective than Placebo at Treating PONV in Patients Who Failed Prophylaxis (cont.)

Kaplan-Meier Curves of Complete Response Over Time*



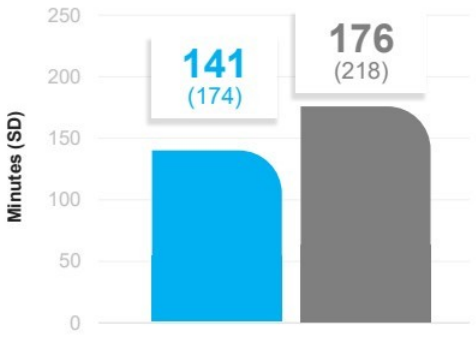
‡The secondary endpoints listed were prespecified. These endpoints were not adequately powered, nor error controlled, and observed treatment differences cannot be regarded as statistically significant.

HR=hazard ratio. CI=confidence interval.

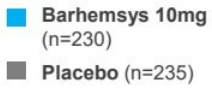
Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212.

Secondary Endpoints: PACU and Hospital Length of Stay

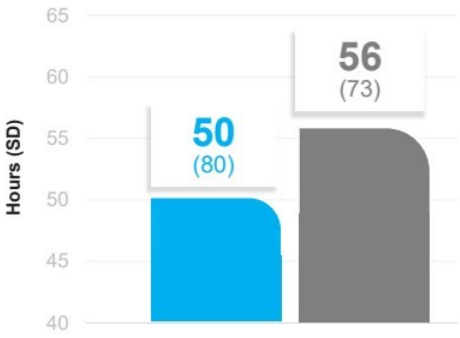
PACU length of stay, minutes



Barhemsys 10 mg-treated patients had 35 minutes shorter mean PACU length of stay than placebo-treated patients



Hospital length of stay, hours



Barhemsys 10 mg-treated patients had 6 hours shorter mean hospital length of stay than placebo-treated patients

The secondary endpoints listed were prespecified. These endpoints were not adequately powered, nor error controlled, and observed treatment differences cannot be regarded as statistically significant.

SD=standard deviation.

Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212.

Efficacy of Amisulpride for Treatment of Postoperative Nausea and Vomiting in Post Anesthesia Care

Ana Mavarez-Martinez, MD[1], Kerri Stafford, B[2], Jason Rosenfield [3], Jamie Romeiser, PhD[1], Sergio D, Bergese, MD[1], and Tong J. Gan, MD[1]

[1]Stony Brook University Hospital, Department of Anesthesiology. Stony Brook, NY. [2]NYIT College of Osteopathic Medicine. Old Westbury, NY. [3]University of Michigan. Ann Arbor, MI

INTRODUCTION

- Postoperative nausea and vomiting (PONV) is a common complication following surgery, adversely affecting up to 80% of high-risk patients. Patients-specific risk factors for PONV include female sex, nonsmoking status, previous history of PONV or motion sickness, and use of opioids postoperatively.
- Amisulpride is a new selective dopamine-2 (D2) and dopamine-3 (D3) receptor antagonist recently approved by the Food and Drug Administration (FDA) for the prevention and treatment of PONV

OBJECTIVE

- We assessed the efficacy of amisulpride when Used for rescue treatment of PONV in the Postanesthesia care unit (PACU)

METHODS

- This review was approved by the Stony Brook University QA/QI committee.
- Data was retrospectively collected from Consecutive patients who:
  1. Underwent elective surgery at Stony Brook University Hospital from October 2020 to April 2021
  2. Had a PONV episode, and requested for an antiemetic during the PACU stay.
  3. Received Amisulpride as the first antiemetic For PONV rescue treatment.
- We collected the following variables: Demographic, PONV risk factors, prophylactic PONV medications, intraoperative anesthetics, Surgical characteristics, and opioid administration (in total IV morphine equivalents).

Patient's characteristics	Treatment Success (N=82)	Treatment Failure (N=30)	p-value
Age – years, mean (SD)[A]	48.7 (18.0)	47.4 (16.2)	0.73
BMI-Kg/m^2, median (IQR)[B]	28.6 (24.4,35.5)	34.1 (29.9,41.0	0.003
Race[C]			
Caucasian	62(75.6%)	23(76.7%)	0.49
Black	5(6.1%)	3(10%)	
Asian	1(1.2%)	1(3.3%)	
Other/Not Reported	14(17.1%)	3(10%)	
Number of PONV risk factors[C]			
1	3(3.7%)	1(3.3%)	0.20
2	23(28.1%)	4(13.3%)	
≥3	56(68.3%)	25(83.3%)	
PONV risks			
Female sex[D]	57(69.5%)	25(83.3%)	0.14
History of PONV[D]	20(26%)	6(23.1%)	0.52
History of motion sickness[D]	24(30.8%)	9(30%)	0.94
Non-smoker[c]	72(90%)	27(90%)	1.0
Number of PONV Prophylaxis[C]			
0	1(1.2%)	1(3.3%)	0.45
1	17(20.7%)	3(10%)	
2	48(58.5%)	20(66.7%)	
≥3	16(19.5%)	6(20%)	
Anethetic Agents			
Inhalation agents[C]	64(78.1%)	27(90%)	0.18
Propofol (total intravenous anesthesia) [D]	17(20.7%)	3(10%)	0.27
Surgical Procedure *(minutes)*			
Surgery duration, *median(IQR)*[B]	94(64,143)	108(73,131)	0.91
PACU duration, *median(IQR)*[B]	120 (90,145)	120 (104,145)	0.25
Opioid administration *(IV morphine eq)*			
Intraoperative opioids, *median (IQR)*[B]	50(40,70)	50(49.5,60)	0.48
PACU opioids, *median (IQR)*[B]	15(0.45)	15(0.40)	0.96

[A] Student's T-Test; [B] Wilcoxon Rank Sun; [C] Fisher's Exact Test; [D] Chi-Square

RESULTS

- Out of 112 patients who received Amisulpride for PONV rescue, 82 (73.2%) had a successful response (defined as no need for additional antiemetic Medication) and 30 (26.8%) failed treatment. Patients failir treatment required an additional antiemetic 50.3 (SD 63.9) minutes af Amisulpride dose.
- Age and race were similar between success and failure groups. BMI w significantly higher in the failure group (p=0.003)
- The number of PONV risk factors were numerically higher in the failur group (83.3% with ≥3 risk Factors) compared to the success group (68. with ≥3 risk factors); but differences did not reach
- Significance (p= 0.20). This may be mostly attributable to the numerica differences in female sex between the failure group and success grou (83.3% vs 68.3%)
- Proportion given inhaled agents was numerically higher in the failure group, but differences did not reach significance (90% vs. 78.1%, p=0.

CONCLUSION

- Amisulpride is associated with a 75% success rate when used as first li rescue therapy in the PACU.
- Failure from PONV prophylaxis is common despite risk-adjusted multimodal antiemetic therapy.

Stony Brook University

In postoperative patients, what is the effect of Barhemsys (amisulpride) as a PONV rescue medication on the recovery length of stay in the PACU as compared with traditional PONV medications?

MaryGrace Hulog, MSN, RN, CCRN

Background

- The term PONV is used to describe nausea, retching, or vomiting occurring within the first 24 hours after surgery[1]
- On average, it was found that the occurrence of PONV increases the PACU stay by an hour[2]
- In a different study, the estimated cost per minute in the PACU was $16.18 US dollars[3]
- PONV is a potential source of patient dissatisfaction. When asked of the relative importance of patient postoperative recovery concerns, 49% of those surveyed ranked PONV more concerning than pain[4]
- The 2020 consensus guidelines rescue treatment for PONV suggests that the medication should be from a different pharmacological class than the prophylactic drug[5]

Defining the Problem

- Current management of PONV at Baylor Grapevine involves the use of antiemetics prophylactically as well as a rescue treatment

Medication	Pre-op	Intra-operative	PACU	Floor	After Discharge
Scopolamine- Transdermal (only 1 patch per op patients with risk for PONV)					
Aprepitant- PO (only certain surgeries)	40mg PO prior to surgery				
Dexamethasone		4mg IV at induction	3rd line: 4mg IV		
Ondansetron		4mg at end of case	1st line: 4mg IV or PO	4mg IV or 8mg PO q 8h PRN	4mg PO q 8h PRN
Promethazine			2nd line: 6.25 IV q15 min up to 12.5mg		
Haloperidol			4th line: 0.5mg IV		
Metoclopramide				10mg IV	

What are our options in the PACU?

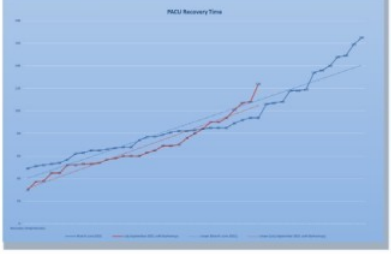
- Ondansetron (Zofran) – a 5-HT3 antagonist; already received at the end of the surgical case
- Promethazine (Phenergan) – histamine H1 antagonist; exhibits anti-emetic and sedative properties[6]
- Dexamethasone (Decadron) – corticosteroid; received at start or surgery
- Haloperidol (Haldol) – antipsychotic, not FDA approved as an antiemetic but low doses (0.5-2mg) could be effective for PONV prophylaxis[5]

Methods and Procedure

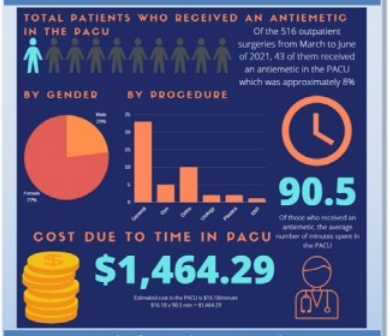
- Data was gathered through our EHR of outpatient surgeries from March 1, 2021, to May 31, 2021.
- Education was provided to the PACU nurses, CRNAs, and anesthesiologists at Baylor Grapevine on the PONV medication Barhemsys (amisulpride) from June to July
- Then, from July 1, 2021, to September 31, 2021, data was gathered through a tracking sheet and the use of our EHR of outpatient surgeries that had received amisulpride.

Group 1 (March 1, 2021 - May 31, 2021)	Group 2 (July 1, 2021 - Sept 31, 2021)
Total Outpatient Surgeries: 516	Total Outpatient Surgeries: 548
Received an antiemetic in the PACU: 43	Received an amisulpride in the PACU: 31
33 Female 10 Male	19 Female 12 Male

Comparison in Recovery Times



Results from March to June



Results from July to September

Observations

- The number of outpatient surgeries in the data se fairly the same as well as the demographic of indi who required an antiemetic
- This was an informal, retrospective study that cou possibly benefit from a longer time frame and a m controlled environment
- Other variables, such as pain, were not taken into consideration in these groups of individuals.
- It is unknown whether PONV continued through p time in PACU.

Conclusion

- There was an observed decrease in the average re time after the addition of Barhemsys (amisulpride management of PONV in our PACU from 90.5 min 68.1 minutes.
- The difference in the time spent in the PACU is 22. minutes. If we were to translate that to the cost sa per minute in the PACU, it could be a potential sav $362.43 per patient who experienced PONV.

References

1. Pierre, S. et al. (2012) Nausea and vomiting after surg *Continuing Education in Anesthesia Critical Care & Pain*. 13(1):28-32. 2. Zhaosheng, J. et al. (2020) Prevention an treatment of postoperative nausea and vomiting (PONV review of current recommendations and emerging thera *Therapeutics & Clinical Risk Management*. 16:1305-131 Sasala et al. (2020) Cost analysis of intravenous propofo monotherapy versus intravenous combination sedation patient undergoing outpatient gastrointestinal endosco *Journal. 88(5)*:373-379 4. Eberhart, L.H. et al. (2002) Pat preferences for immediate postoperative recovery. *Br J* 89(5):760-761. 5. Gan, T.J. et al. (2020) Fourth consensu guidelines for the management of postoperative nausea vomiting. *Anesth Analg*. 13(2):411-448. 6. Deitrick et al. comparison of two differing doses of promethazine for t treatment of postoperative nausea and vomiting. *Journa Perianesthesia Nursing*. 30(1):5-13.

Summary*

- PONV is common and causes patient distress and significant patient dissatisfaction
- PONV is multifactorial and mediated by multiple receptor systems
- The risks of PONV are predictable
- Multimodal prevention strategy is considered the standard of care
- Amisulpride is a new dopamine antagonist
- Almisulpride has demonstrated efficacy in prevention and treatment of PONV
- Amisulpride is the only antiemetic proven safe and effective at the indicated dose for Rescue Treatment

*Important Safety Information (ISI) can be found at: https://bynder.acaciapharma.com/m/5d7c2cd0d58865f7/original/Barhemsys-Prescribing-Information.pdf

Byfavo: Clinical Perspective

- Richard P. Dutton, MD MBA

My Credentials

- Adjunct Professor, Texas A&M
- Anesthesiologist, Baylor University Medical Center
- Chief Quality Officer, US Anesthesia Partners

- 2009-2015: Executive Director, ASA Anesthesia Quality Institute
- 1994-2011: Professor, Chief of Trauma Anesthesia, Chief of Clinical Operations, R Adams Cowley Shock Trauma Center, University of Maryland

USAP in 2022

- **13 states, 16 platforms (cities), 60+ practices**
- **5,000 clinicians:**
  - 1,600 physician partners – majority owners of the practice
  - 800 employed physicians
  - 2,600 CRNAs and AAs
- **700 facilities served:**
  - 200 hospitals
  - 250 ASCs
- **25 healthcare systems**
- **2,500,000 cases**
- **3 equity investors:** WCAS, Berkshire, GIC

Major Issues Confronting Anesthesiology

Workforce: Too much demand, not enough supply
- Driven by Non-Operating Room Anesthesia cases
- Exacerbated by fragmentation, retirement, burnout
- Hospitals generally want more anesthesia coverage

Payment: Increasing downward pressure from payers, including CMS
- Stipends needed to fill gap between cost and revenue
- Universal at hospitals, increasingly at ASCs
- Increasing focus on anesthesia costs

Scope of practice: Interface with CRNAs and other medical specialties

Value Proposition: Hospitals

- Increased access
  - OR time
  - Coverage for NORA
- Increased efficiency
- Decreased cancellations
- Reduced adverse events
- Reduced transfusions
- Increased patient satisfaction
- Reduced use of expensive meds
- **Decreased length of stay**

Value Proposition: Payers

- Increased outpatient surgery
- Decreased:
  - Length of stay
  - Cost of post-acute care
  - Preoperative testing
  - Opioid consumption
  - Readmissions
  - Administrative burden

Workforce Solutions: New Models of Care

- Extended care team coverage ratios
- Autonomous CRNA practice
- Non-anesthesia physician coverage
- “Fire and forget” regional anesthesia blocks

- **Expansion of non-anesthesia nursing sedation services**

Unmet Need in Procedural Sedation: An Ideal Sedative

Characteristics[1-5]	Pharmacokinetics[1-5]	Pharmacodynamics[1-3,6]
Short time to onset	Linear kinetics	A predictable dose-response relation
Ability to titrate to the desired range of sedation	No accumulation	A balanced safety/risk profile
Rapid and consistent recovery leading to a quick discharge	Rapid clearance through CYP450-independent metabolism	Non-weight–based dosing
Predictable amnestic effect	Context insensitive half-time (half-time is independent of infusion duration)[7,8]	
High efficacy rate		

1. Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. *Anesthesiology*. 2018;128:437-479.
2. Sheta SA. Procedural sedation analgesia. *Saudi J Anaesth*. 2010;4(1):11-16.
3. Colao J, Rodriguez-Correa D. Rapidly metabolized anesthetics: novel alternative agents for procedural sedation. *J Anesth Clin Res*. 2016;7(11):1-6.
4. Pambianco D, Cash B. New horizons for sedation: the ultrashort acting benzodiazepine remimazolam. *Tech Gastrointest Endosc*. 2016;18:22-28.
5. Barends CRM, Absalom AR, Struys MMRF. Drug selection for ambulatory procedural sedation. *Curr Opin Anaesthesiol*. 2018;31(6):673-678.
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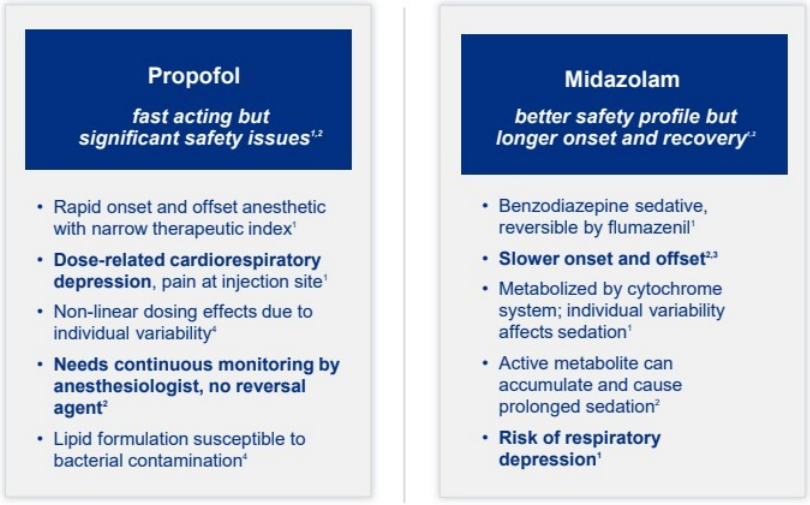
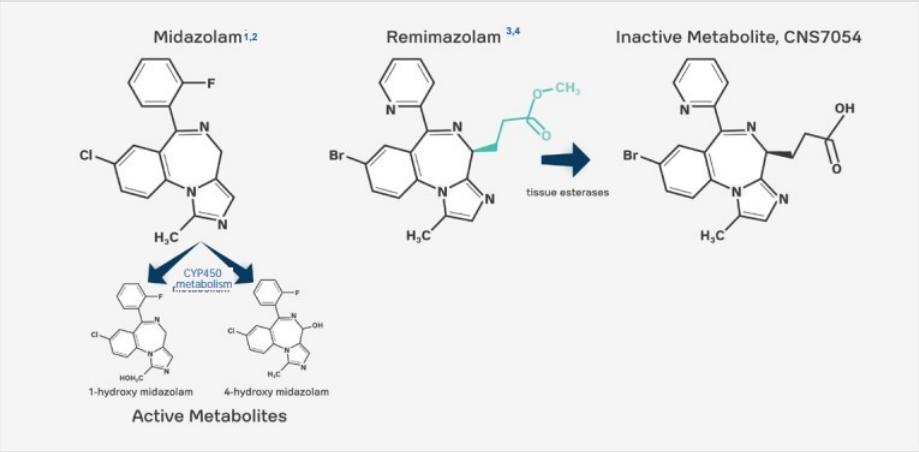
7. Egan TD. Is anesthesiology going soft?: Trends in fragile pharmacology. *Anesthesiology*. 2009;111:229-30.
8. Gepts E. Pharmacokinetic concepts for TCI anaesthesia. *Anaesthesia*. 1998;53:4-12.

Current Select Standards of Care Have Limitations



1 Colao J, et al. *J Anesth Clin Res*. 2016; 7:690. 2 Whizar-Lugo V, et al. *J Anesth Crit Care*. 2016; 4(6): 00166. 3 Rex DK et al. Gastrointest Endosc. 2018 Sep;88(3):427-437. 4 Prescribing label for Propofol. 5 Prescribing label for Byfavo.

Soft, Ester-Based Drug Design



Due to the addition of a carboxylic ester linkage, Byfavo is rapidly hydrolyzed by tissue esterases to an inactive metabolite, with no meaningful contribution by CYP450 enzymes.[3,4] Midazolam undergoes CYP450 metabolism to active metabolites.[2]

1. Reves JG, et al. *Anesthesiology*. 1985;62:310-324. **2.** Midazolam Injection [package insert]. Lake Forest, IL: Hospira; 2018.
3. Byfavo [package insert]. Indianapolis, IN: Acacia Pharma Inc. **4.** Pambianco D, Cash B. *Tech Gastrointest Endosc*. 2016;18:22-28.

Byfavo Rapid Onset/Offset Benzodiazepine

Rapid Onset

- Distribution half-life: 0.5-2.0 minutes[1]
- Onset of sedative effects: 1.0-1.5 minutes[2,*]
- Median time to peak sedation: 3.0-3.5 minutes following initial 5 mg (2mL) bolus IV dose[1]

Rapid Offset

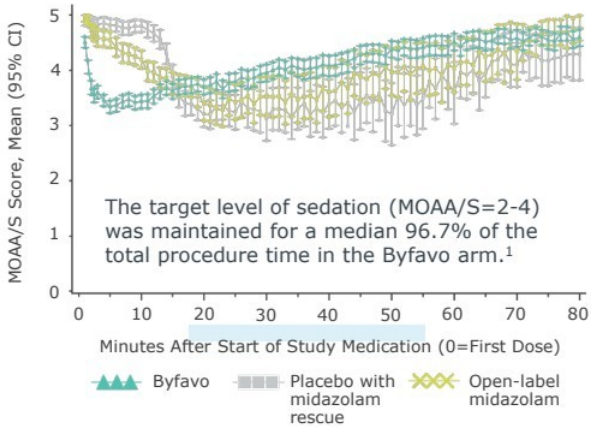
- Median time to fully alert: 11.0-14.0 minutes[1]
- Terminal half-life: 37-53 minutes[1]
- Volume of distribution: 0.76-0.98 L/kg[1]
- Clearance: 54-75 L/hr[1]

*A sedative effect was defined as a MOAA/S score of ≤4. At 1 and 1.5 minutes, 40% and 62% of patients had a MOAA/S score of ≤4, respectively.

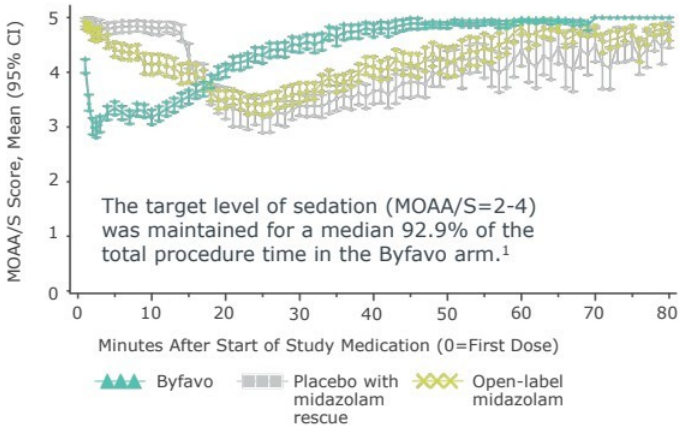
1. Byfavo [package insert]. Indianapolis, IN: Acacia Pharma Inc. 2. Acacia Pharma. Data on File.

Patients Rapidly Achieved an Adequate Level of Sedation for Procedure Start with a Quick Recovery

Bronchoscopy, ASA I-III



Colonoscopy, ASA I-III



1. Acacia Pharma. Data on File.

So What…..Why Byfavo?

- **Predictable effect reducing hemodynamic compromise**
- **Reliable safety**
  - Sedation without post-procedure neurologic dysfunction in at-risk patients
- **Safely administered by non-anesthesia clinicians**
- **Potential for improved throughput in procedural units**

Byfavo – Candidate Populations

- Short CV procedures: cardioversion, TEE, pacemaker battery change, etc. in fragile patients
- GI, Pulmonary, Radiology sedation in at-risk patients (older, frail)
- Bedside sedation (ED, PACU, ICU) for short painful procedures: dressing changes, fracture reduction

Landiolol

Overview of Landiolol: An Ultra-Short-Acting Intravenous β-adrenergic Blocker

EAGLE
PHARMACEUTICALS

Landiolol Overview: NDA Under Review by FDA

- Ultra-short acting cardioselective beta1-blocker
- Rapid rate control
  - Supraventricular tachycardia
  - Ventricular rate
- Simple intravenous dosing
- Multiple use settings
  - Critical/Intensive Care
  - Perioperative
  - Emergency Department

- Safety and efficacy qualified by approved marketing authorizations in the EU and Japan*

*FDA has not determined the safety or efficacy of landiolol and landiolol is not approved for use in the United States. The safety and efficacy of landiolol have been established in Japan and the European Union.

EAGLE PHARMACEUTICALS

Proposed Indications of Use*

Landiolol is an ultra-short-acting β1-antagonist with limited effect on blood pressure and inotropy[1,2]

Proposed Indication[3]

- Short-term reduction of ventricular rate in patients with supraventricular tachycardia, including atrial fibrillation and atrial flutter

**FDA has not determined the safety or efficacy of landiolol and landiolol is not approved for use in the United States. The safety and efficacy of landiolol have been established in Japan and the European Union.*

1. Shibata S, et al. *J Pharmacol Sci.* 2012;118(2):255-265. 2. Wada Y, et al. *J Arrhythm.* 2016;32(2):82-88. 3. Eagle Pharmaceuticals. Press Release, January 31, 2022. https://investor.eagleus.com/press-releases/news-details/2022/Eagle-Pharmaceuticals-on-Track-to-Support-Submission-of-New-Drug-Application-in-Second-Quarter-2022-for-Landiolol-a-Beta-1-Adrenergic-Blocker/default.aspx.

EAGLE PHARMACEUTICALS

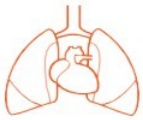
Landiolol Potentially Addresses an Important Unmet Clinical Need

- Designed for potential use in acute-care patients in whom it is necessary to safely and rapidly reduce heart rate with limited effect in blood pressure and inotropy (e.g. patients in sepsis, patients with heart failure)
- Current therapeutic options for these patients are limited
- Comorbidities are common in this population:

HEART FAILURE

RENAL IMPAIRMENT

HEPATIC DYSFUNCTION



RESPIRATORY INSUFFICIENCY

EAGLE PHARMACEUTICALS

Reference Borianni G., et al. European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devic in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Societ Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS)

Landiolol Features

Rapid onset of action (≤1 min) and short duration of action (10-15 min)[1]

Limited effect on blood pressure due to pure S-enantiomer molecular structure[2,3]

Minimal negative inotropic action due to limited effect on the refractory period of the action potential in cardiomyocytes[2]

1. Krumpl G, et al. *Eur J Clin Pharmacol.* 2017;73(4):417-428. 2. Shibata S, et al. *J Pharmacol Sci.* 2012;118(2):255-265. 3. McKee JS, et al. *Anesthesiology.* 2014;121(6):1184-1193.

EAGLE PHARMACEUTICALS

Landiolol Features

Low volume of distribution (0.3-0.4 L/kg) leading to less distribution to tissues and fewer possible toxicities[1,2]

Compatible in patients with respiratory disease (eg, asthma, COPD) due to high cardioselectivity (β1/β2-selectivity = 255:1) among β1 blockers[1,4]

Metabolized in the plasma (CYP450 is not involved) and eliminated primarily in urine[3,4]

- No dose adjustment is necessary in renal impairment and careful dosing is recommended in patients with hepatic impairment due to limited data[3,4]

COPD, chronic obstructive pulmonary disease. CYP450, cytochrome P450.

1. Landiolol. Summary of Product Characteristics, current version. 2. Krumpl G, et al. *J Cardiovasc Pharmacol*. 2018;71(3):137-146. 3. Nasrollahi-Shirazi S, et al. *J Pharmacol Exp Ther*. 2016;359(1):73-81. 4. Balik M, et al. *Eur Heart J Suppl*. 2018;20(A):A10-A14.

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Comparison of Landiolol and Other Rate/Rhythm Control Agents

Medication	Onset of Action	Elimination Half-Life	Duration of Effect	β1:β2 Ratio	Effect on HR and B
Beta Blockers					
Landiolol[1-3]	**1 min**	**4 min**	**15 min**	**255**	**HR ↓↓ BP →**
Esmolol[1,4,5]	2 min	9 min	10-20 min	33	HR ↓ BP ↓
Atenolol[6,7]	5 min	6-7 hours	12 hours	4.7	HR ↓ BP ↓
Metoprolol[7-10]	20 min	3-7 hours	5-8 hours	2.3	HR ↓ BP ↓
Other Rate/Rhythm Control Agents					
Amiodarone[11,12]	1-30 min	9-36 days	1-3 hours	--	--
Digoxin[13]	5-30 min	1.5-2 days	1-4 hours	--	--
Diltiazem[14]	3 min	3.4 hours	0.5-10 hours	--	--

Landiolol has a **rapid onset of action** and short duration of action with **limited effect on BP**[1-3]

BP, blood pressure; HR, heart rate.

1. Krumpl G, et al. *Eur J Clin Pharmacol.* 2017;73(4):417-428. 2. Landiolol. Summary of Product Characteristics, current version. 3. Nagai R, et al. *Circ J.* 2013;77(4):908-916. 4. Esmolol [prescribing information]. Paramus, NJ: WG Critical Care, LLC; 2016. 5. Domanovits H, et al. Eur Heart J Suppl. 2018;20(A):A1-A3. 6. Rehman B, et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. 7. Baker JG. *Br J Pharmacol.* 2005;144(3):317-322. 8. Metoprolol [prescribing information]. Lake Forest, IL: Hospira, Inc.; 2020. 9. Frishman WH, et al. *Am J Ther.* 2008;15(6):565-76. 10. Kelly D, et al. *Intern Med J.* 2015;45(9):934-938. 11. Latini R, et al. *Clin Pharmacokinet.* 1984;9(2):136-156. 12. Amiodarone [prescribing information]. Deerfield, IL: Baxter Healthcare Corporation; 2011. 13. Digoxin [prescribing information]. Kirkland, Canada: Jubilant HollisterStier General Partnership; 2016. 14. Diltiazem [prescribing information]. Bedford, OH: Ben Venue Laboratories, Inc.; 2007.

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Landiolol Conclusions

- Landiolol is intended to be a differentiated, ultra-short acting cardio-selective beta blocker that results in rapid control of ventricular rate
- Landiolol potentially addresses important unmet clinical needs
- If approved, landiolol has the potential to provide clinicians with a unique therapeutic option

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Question & Answer Panel