Medical Developments International

March 2020

Medical Developments International

Key Achievements

Penthrox®

- → In market sales in the UK grew 42%
- → Australian Penthrox® sales grew 18%
- → Australian Penthrox® sales to GPs grew 54%
- → European sales up 35%
- → China IND approval
- → Russian Marketing Authorisation Application lodged
- → Russian Milestone payment received from partner
- → Penthrox® launch in Italy
- → 386 customers in France
- → 182 customers across the rest of Europe
- → 608 customers in the UK and Ireland
- → Approved for use by UK Military and given a NATA number
- → Progressing USA IND
- → Progressing South Korea approval
- → Progressing South Korea approval
- → Progressed the Paediatric Study in the UK and Ireland (65% recruitment)
- → Nearing finalisation of the Post Authorisation Safety Study Clinical Report
- → Bosnia approval expected in April 2020
- → Europe: Hungary, Greece, The Netherlands and Malta expected approvals in next 6 months
- → Asia: Thailand approval expected in 6 months

Key Achievements

Respiratory Medical Devices

- → USA sales grew 49%
- → UK and European sales grew 73%
- → Australian sales grew 44%
- → Global respiratory device sales up 49%

Key Achievements

Other

- → New 5-year agreement with CSIRO for Continuous Flow technology
- → Continued investment in clinical development programs and trials
- → Received R&D Tax Incentive concession of $431,000

Penthrox® in USA

FDA Update

With FDA for review:

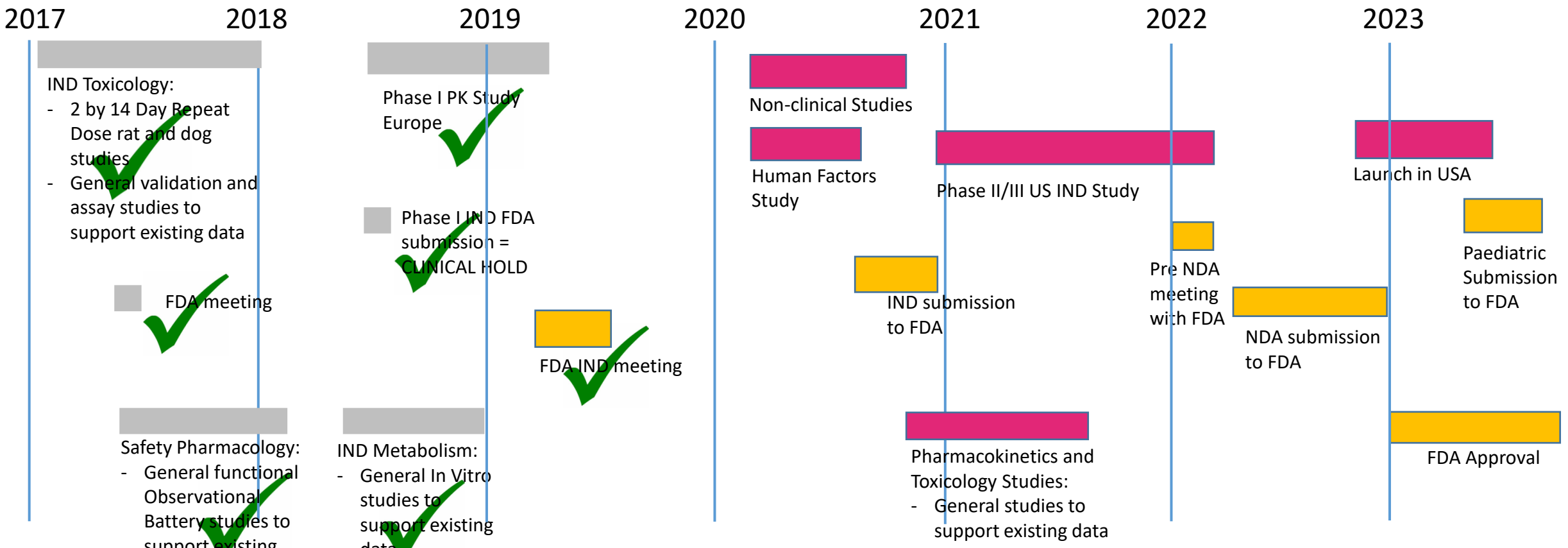
- Pre-Clinical protocol which mimics human dosing regimen
- Human Factors study protocol
- Responses to device questions

Completion of PASS in Europe – awaiting Clinical Study Report in April 2020

IND submission target H1FY21.

NOTE: The next 2 FDA meetings will be Type C meetings, therefore the FDA has 75 days from request to schedule meeting. MDI has 1 month from request to submit briefing pack.
MDI plans to submit the non-clinical study protocols to FDA for feedback prior to conducting study.
MDI plans to submit HF study protocol in FDA meeting briefing pack.

Penthrox® in USA



Penthrox® in China

IND approval November 2019

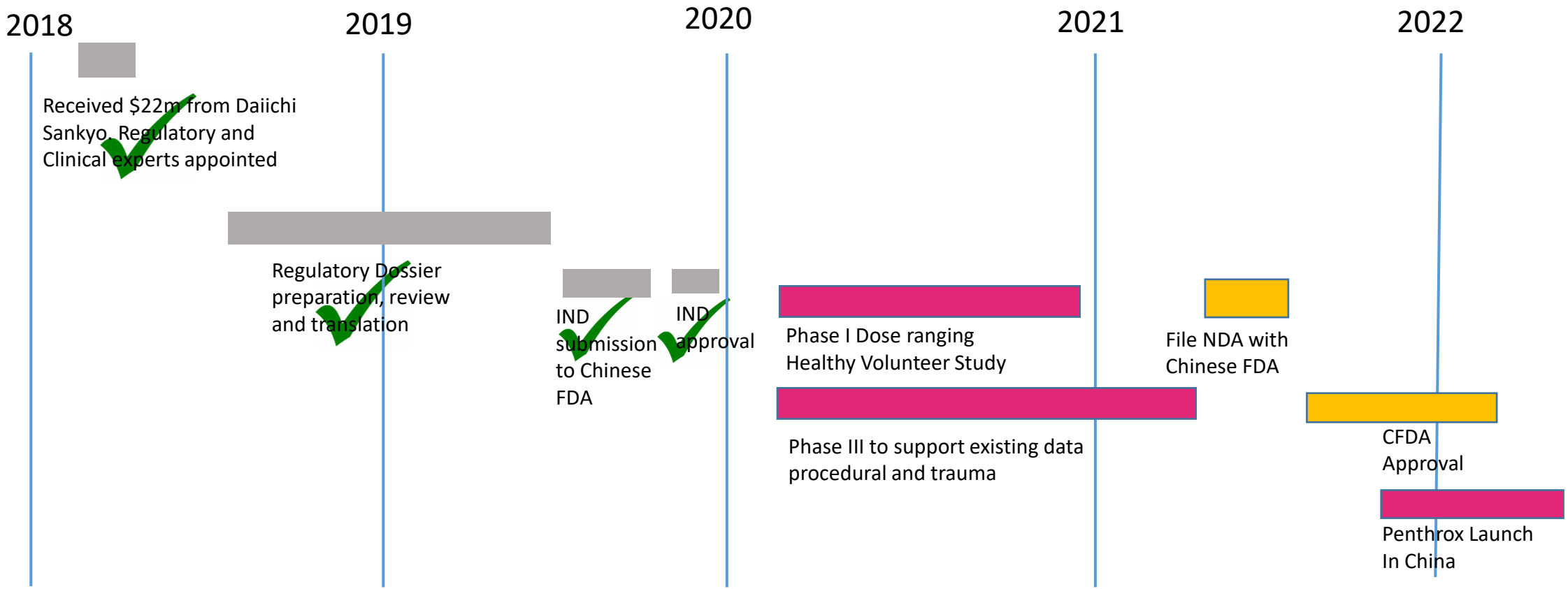
- Phase I PK
- Phase III Bridging Trauma
- Phase III Bridging Acute Pain

MVP site selections completed and protocol training given to partner

Ethics committee submissions on hold due to Coronavirus

NDA approval expected 2022

Penthrox® in China



Penthrox® Clinical

Europe

Paediatric study suspended enrolment due to COVID

Other studies suspended enrolment due to COVID

Penthrox® Publications

MEDITA
Methoxyflurane provided superior short term pain relief to standard analgesic treatment (IV morphine, IV paracetamol, IV ketoprofen) patients with moderate to severe trauma pain

Simple, fast, effective non-opioid treatment option

Mercadante et al 2019

Adv Ther
https://doi.org/10.1007/s12325-019-01055-9

ORIGINAL RESEARCH

Analgesic Efficacy, Practicality and Safety of Inhaled Methoxyflurane Versus Standard Analgesic Treatment for Acute Trauma Pain in the Emergency Setting: A Randomised, Open-Label, Active-Controlled, Multicentre Trial in Italy (MEDITA)

Sebastiano Mercadante · Antonio Voza · Sossio Serra · Germana Ruggiano · Giuseppe Carpinteri · Gianfilippo Gangitano · Fabio Intelligente · Elisabetta Bonafede · Antonella Sblendido · Alberto Farina · Amedeo Soldi · Andrea Fabbri on behalf of the MEDITA Study Group

Received: July 17, 2019
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ABSTRACT

Introduction: Inhaled low-dose methoxyflurane is approved in Europe for emergency relief of moderate-to-severe trauma-related pain in adults, but data versus active comparators are sparse. The phase IIb Methoxyflurane in Emergency Department in ITAly (MEDITA) trial investigated the analgesic efficacy, practicality and safety of methoxyflurane versus standard analgesic treatment (SAT) for acute trauma pain. ***Methods:*** This was a randomised, active-controlled, parallel-group, open-label trial conducted in 15 Italian emergency units. Adults with limb trauma and pain score ≥ 4 on numerical rating scale (NRS) were randomised 1:1 to inhaled methoxyflurane 3 mL or SAT [intravenously administered (IV) morphine 0.1 mg/kg for severe pain (NRS ≥ 7); IV

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.9228326.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-019-01055-9) contains supplementary material, which is available to authorized users.

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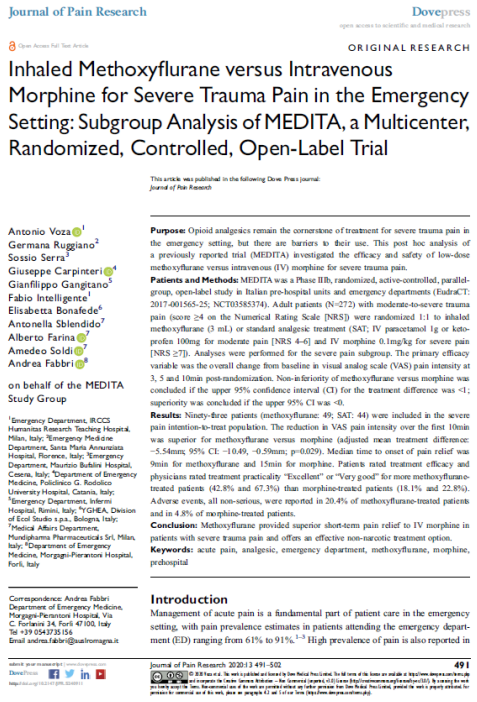
Published online: 12 October 2019

MEDITA
Sub group analysis

Methoxyflurane provided superior short term pain relief compared to IV morphine in patients with severe trauma pain.
Effective non-opioid treatment option

Voza et al 2020



Journal of Pain Research — Dovepress

ORIGINAL RESEARCH

Inhaled Methoxyflurane versus Intravenous Morphine for Severe Trauma Pain in the Emergency Setting: Subgroup Analysis of MEDITA, a Multicenter, Randomized, Controlled, Open-Label Trial

This article was published in the following Dove Press journal:
Journal of Pain Research

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Purpose: Opioid analgesics remain the cornerstone of treatment for severe trauma pain in the emergency setting, but there are barriers to their use. This post hoc analysis of a previously reported trial (MEDITA) investigated the efficacy and safety of low-dose methoxyflurane versus intravenous (IV) morphine for severe trauma pain.

Patients and Methods: MEDITA was a Phase IIb, randomized, active-controlled, parallel-group, open-label study in Italian pre-hospital units and emergency departments (EudraCT: 2017-001565-25; NCT03585374). Adult patients (N=272) with moderate-to-severe trauma pain (score ≥4 on the Numerical Rating Scale [NRS]) were randomized 1:1 to inhaled methoxyflurane (3 mL) or standard analgesic treatment (SAT; IV paracetamol 1g or ketoprofen 100mg for moderate pain [NRS 4–6] and IV morphine 0.1mg/kg for severe pain [NRS ≥7]). Analyses were performed for the severe pain subgroup. The primary efficacy variable was the overall change from baseline in visual analog scale (VAS) pain intensity at 3, 5 and 10min post-randomization. Non-inferiority of methoxyflurane versus morphine was concluded if the upper 95% confidence interval (CI) for the treatment difference was <1; superiority was concluded if the upper 95% CI was <0.

Results: Ninety-three patients (methoxyflurane: 49; SAT: 44) were included in the severe pain intention-to-treat population. The reduction in VAS pain intensity over the first 10min was superior for methoxyflurane versus morphine (adjusted mean treatment difference: −5.54mm; 95% CI: −10.49, −0.59mm; p=0.029). Median time to onset of pain relief was 9min for methoxyflurane and 15min for morphine. Patients rated treatment efficacy and physicians rated treatment practicality "Excellent" or "Very good" for more methoxyflurane-treated patients (42.8% and 67.3%) than morphine-treated patients (18.1% and 22.8%). Adverse events, all non-serious, were reported in 20.4% of methoxyflurane-treated patients and in 4.8% of morphine-treated patients.

Conclusion: Methoxyflurane provided superior short-term pain relief to IV morphine in patients with severe trauma pain and offers an effective non-narcotic treatment option.

Keywords: acute pain, analgesic, emergency department, methoxyflurane, morphine, prehospital

Introduction

Management of acute pain is a fundamental part of patient care in the emergency setting, with pain prevalence estimates in patients attending the emergency department (ED) ranging from 61% to 91%.[1–3] High prevalence of pain is also reported in

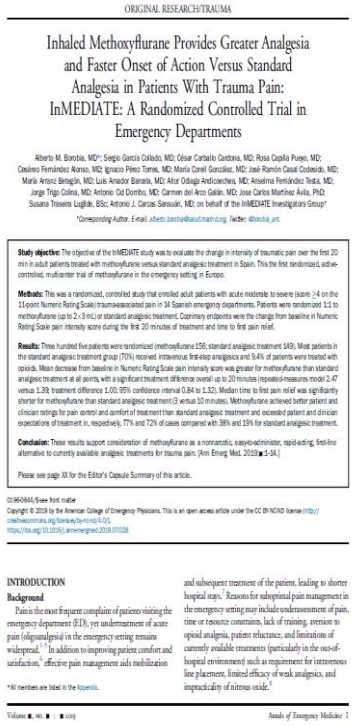
Journal of Pain Research 2020:13 491–502 491

Penthrox® Publications

Immediate

Methoxyflurane provided superior short term pain relief to standard analgesic treatment (mostly NSAIDS, paracetamol, opioids) patients with moderate to severe trauma pain

Borobia et al 2019



ORIGINAL RESEARCH/TRAUMA

Inhaled Methoxyflurane Provides Greater Analgesia and Faster Onset of Action Versus Standard Analgesia in Patients With Trauma Pain: InMEDIATE: A Randomized Controlled Trial in Emergency Departments

Alberto M. Borobia, MD*; Sergio García Collado, MD; César Carballo Cardona, MD; Rosa Capilla Purga, MD; Cesáreo Fernández Alonso, MD; Ignacio Pérez Torres, MD; María Corell González, MD; José Ramón Casal Codesido, MD; María Arranz Belagón, MD; Luis Arnador Barrela, MD; Aitor Odiaga Arciocechea, MD; Anselma Fernández Teira, MD; Jorge Trigo Colina, MD; Antonio Cid Domiho, MD; Carmen del Arco Galán, MD; Jose Carlos Martínez Ávila, PhD; Susana Troseira Lugilde, BSc; Antonio J. Carcas Sansuán, MD; on behalf of the InMEDIATE Investigators Group*

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Study objective: The objective of the InMEDIATE study was to evaluate the change in intensity of traumatic pain over the first 20 min in adult patients treated with methoxyflurane versus standard analgesic treatment in Spain. This the first randomized, active-controlled, multicenter trial of methoxyflurane in the emergency setting in Europe.

Methods: This was a randomized, controlled study that enrolled adult patients with acute moderate to severe (score ≥4 on the 11-point Numeric Rating Scale) trauma-associated pain in 14 Spanish emergency departments. Patients were randomized 1:1 to methoxyflurane (up to 2 × 3 mL) or standard analgesic treatment. Coprimary endpoints were the change from baseline in Numeric Rating Scale pain intensity score during the first 20 minutes of treatment and time to first pain relief.

Results: Three hundred five patients were randomized (methoxyflurane 156; standard analgesic treatment 149). Most patients in the standard analgesic treatment group (70%) received intravenous first-step analgesics and 9.4% of patients were treated with opioids. Mean decrease from baseline in Numeric Rating Scale pain intensity score was greater for methoxyflurane than standard analgesic treatment at all points, with a significant treatment difference overall up to 20 minutes (repeated-measures model 2.47 versus 1.39; treatment difference 1.00; 95% confidence interval 0.84 to 1.32). Median time to first pain relief was significantly shorter for methoxyflurane than standard analgesic treatment (5 versus 10 minutes). Methoxyflurane achieved better patient and clinician ratings for pain control and comfort of treatment than standard analgesic treatment and exceeded patient and clinician expectations of treatment in, respectively, 77% and 72% of cases compared with 38% and 19% for standard analgesic treatment.

Conclusion: These results support consideration of methoxyflurane as a nonnarcotic, easy-to-administer, rapid-acting, first-line alternative to currently available analgesic treatments for trauma pain. [Ann Emerg Med. 2019;■:1-34.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

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https://doi.org/10.1016/j.annemergmed.2019.07.028

INTRODUCTION

Background

Pain is the most frequent complaint of patients visiting the emergency department (ED), yet undertreatment of acute pain (oligoanalgesia) in the emergency setting remains widespread.[1–3] In addition to improving patient comfort and satisfaction,[4] effective pain management aids mobilization and subsequent treatment of the patient, leading to shorter hospital stays.[5] Reasons for suboptimal pain management in the emergency setting may include underassessment of pain, time or resource constraints, lack of training, aversion to opioid analgesia, patient reluctance, and limitations of currently available treatments (particularly in the out-of-hospital environment) such as requirement for intravenous line placement, limited efficacy of weak analgesics, and impracticality of nitrous oxide.[6]

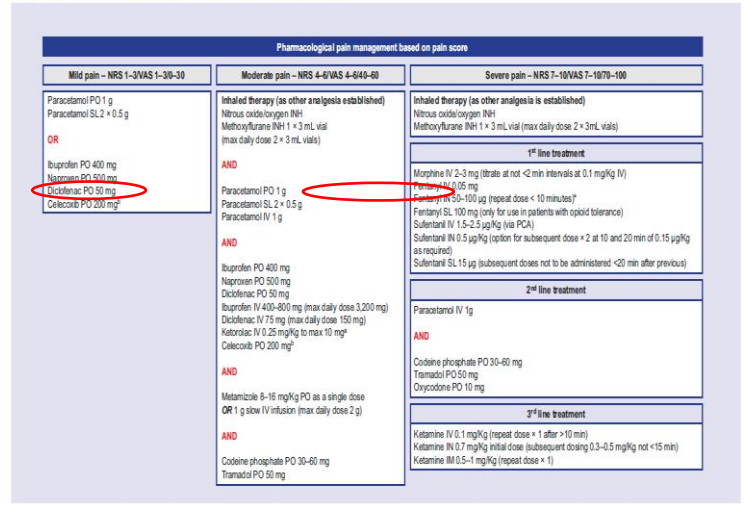
*All members are listed in the Appendix.

Volume ■, NO. ■ : ■ 2019 Annals of Emergency Medicine 1

EUSEM

Penthrox included as a first-line option in both moderate and severe pain while other analgesics are potentially used

Figure 7.1b Pharmacological management of acute pain symptoms – adults



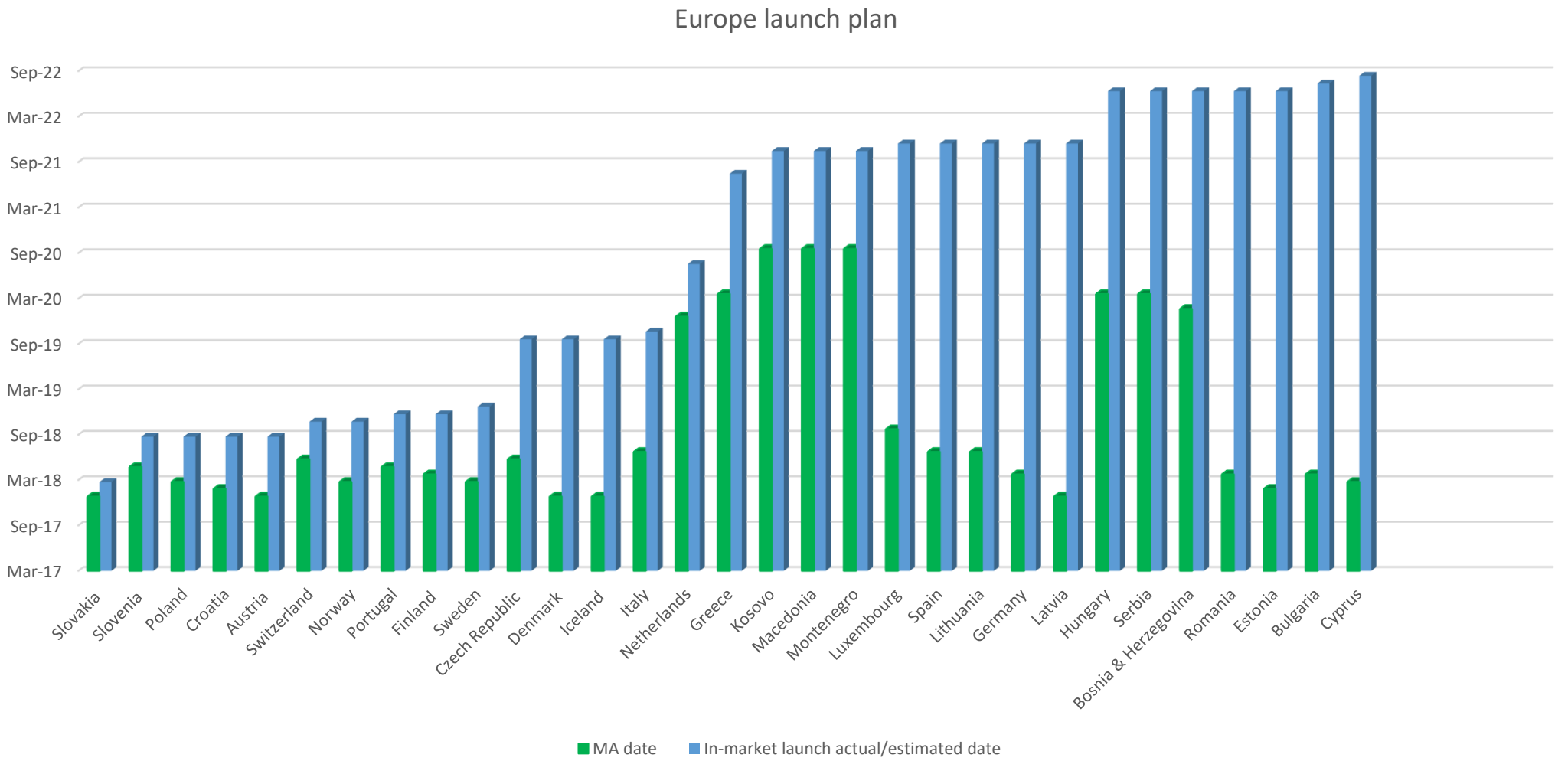
Penthrox® Clinical Pipeline

Start up | Ongoing | Completed | * Partner study

Future for Penthrox®

MVP continues to negotiate with interested parties from around the world in terms of registering and selling Penthrox®, whilst concurrently pursuing other important international regulatory submissions and preparations in countries including USA, China, Russia, Iran, Iraq, Thailand and South Korea.

Penthrox® Future



Continuous Flow

API Manufacturing

Few companies in the generic pharmaceutical industry are investing in the development of new manufacturing technologies.

The single largest development for pharmaceutical markets over the last 30 years has been the introduction of generic manufacturers, who have relied on cheaper labour, larger factories, cheaper raw materials and unregulated marketplaces to reduce the price for generic products

Medical Developments International (MDI) is investing millions in this “disruptive global technology”.

Continuous Flow

Global breakthrough in API manufacturing technology

We intend for our Continuous Flow ‘CF’ process API manufacturing technologies to be covered by Patents (applications and pending) or kept as Trade Secrets depending on the market.

CF has the capacity to reduce the cost of API manufacturing by up to 50%, compared to batch processing and could be applicable to hundreds of pharmaceutical products

We are creating valuable global technology from Australia

Continuous Flow

Our Continuous Flow technology delivers:

- Increased yields – through better process conversion
- Increased purity – through better process control
- Better control over entire process – test in real time
- Lower cost of production
- Lower CapEx
- Less waste
- Less carbon footprint “greener technology”
- Smaller footprint
- Quicker to scale-up
- Safer

Continuous Flow

Globally recognised as the future of manufacturing

Statements from Commissioner of Food and Drugs - Food and Drug Administration - Scott Gottlieb M.D.

”One of todays most important tools for modernising the pharmaceutical industry is a process known as continuous manufacturing (CM)”.

”CM systems means that the process is easier to control than the decades-old, traditional ‘batch’ manufacturing”.

”CM helps to ensure consistently-made products, allows manufacturers to more easily scale their manufacturing operations to meet demand”.

”We’re (FDA) taking additional steps to help facilitate broader adoption of CM by providing guidance and information to interested companies, whether brand name or generic drug manufacturers”.

”CM is a key step towards promoting drug quality and improving the efficiency of pharmaceutical manufacturing. The FDA is committed to helping more companies advance these CM platforms, owing to the public health benefits of these more modern approaches. We support the early adopters that are embracing this innovative technology and we look forward to working with other interested companies”.

Continuous Flow

Future API technologies

MDI is developing its core flow technology into several generic APIs, currently manufactured under standard batch processing.

Examples of this are:

- **LIDOCAINE (USP):** Estimated USD $3.5 billion global sales
- **DICLOFENAC:** Estimated USD $6.0 billion global sales
- **SALBUTAMOL:** Estimated USD $6.0 billion global sales
- **ISO/DES/SEVOFLURANE:** Estimated USA $3.0 billion global sales market. (Significant improvements in handling highly toxic & corrosive Fluoride intermediates under safe flow conditions)
- **LEFLUNOMIDE:** Early stage development under flow

Continuous Flow

Lidocaine Continuous Flow deliverables:

- Lidocaine (base/HCl) to USP & Ph Eur
- Pilot scale capable of producing kilograms/hr (completed)
- Commercial scale expected to produce >100kgs per day (under qualification)
- Minimal change to footprint from Pilot Plant to Commercial scale
- Material has been tested to and passes all specifications of Lidocaine USP monograph
- Continuous Flow process allows ease of scaleup by either:
    - Increasing flow rates & benchtop reactor size
    - Modularise setup (run several systems in parallel)

Continuous Flow

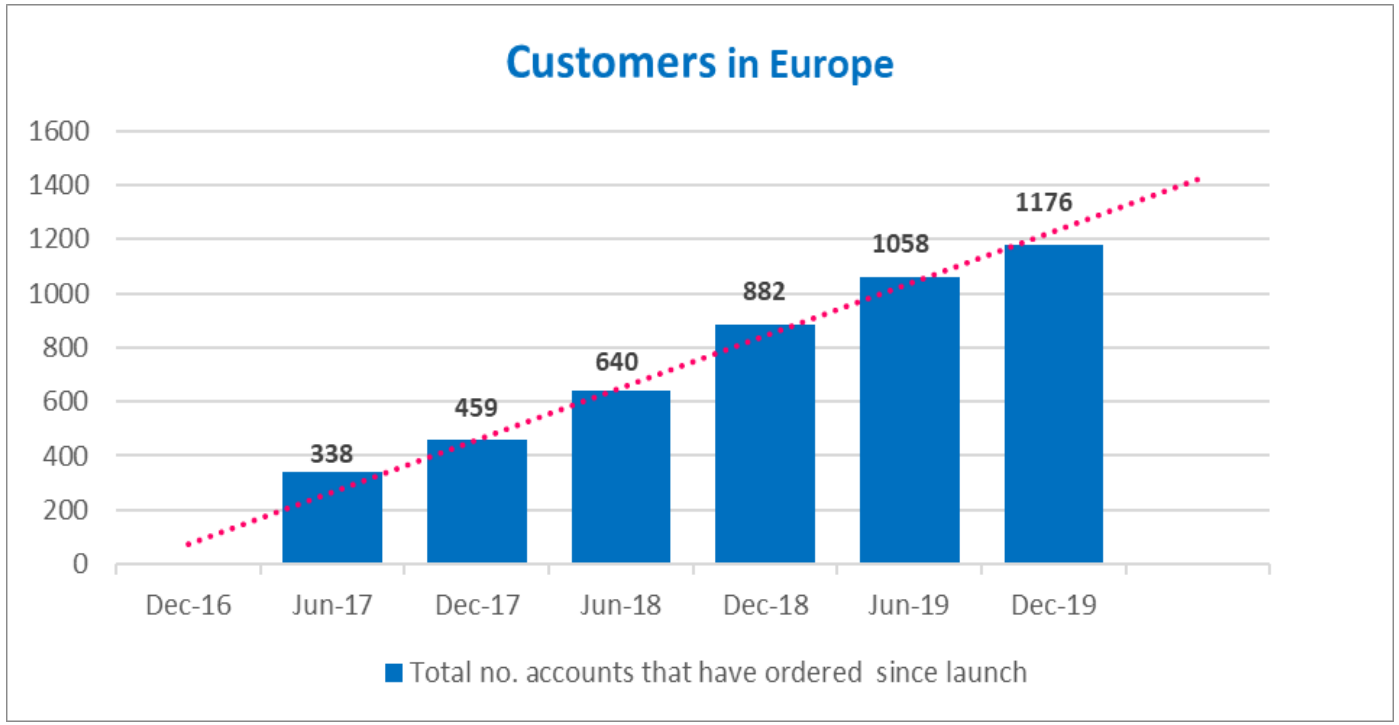
Benefits of Lidocaine manufacture under Continuous Flow v Batch Process

1. We expect better overall process control, which will deliver:
   - A significantly better reaction conversion
   - Better overall yield conversion
   - Significantly reduced impurity profile
   - Significantly reduced price compared to lowest cost producers (>25% tbc)
2. Fast scale-up capability:
   - Increase output by several factors on similar footprint
3. Safer Environment:
   - Reduced manual handling
   - Controlled energetic process (exotherm)
   - Significant energy savings
   - Lower cost for QA and QC

Financial Performance

Penthrox® Sales in Europe

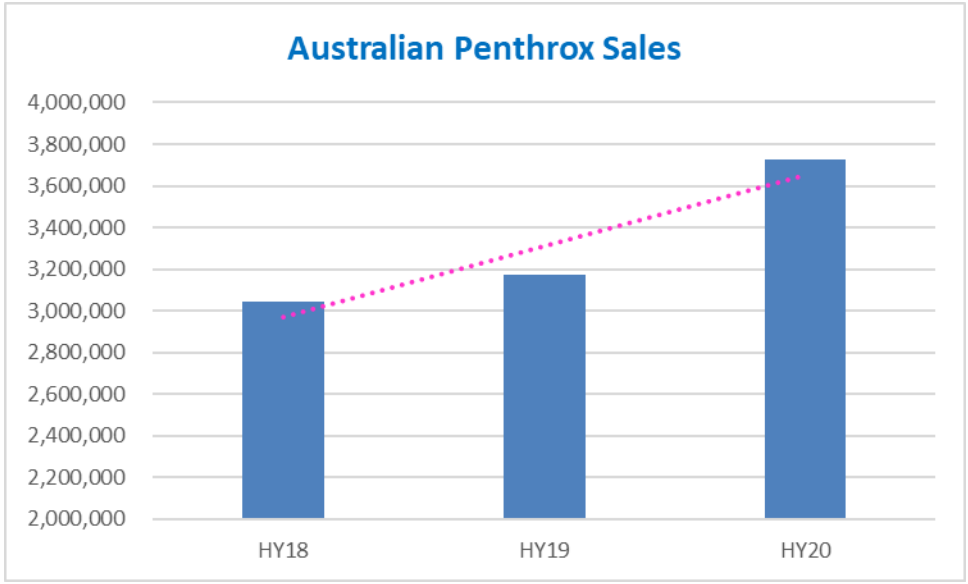
- UK in-market sales grew 42%
- 131 hospitals using in the UK
- In-market European sales grew 35%
- Launched in Italy
- 386 customers in France
- A number of major countries in Europe still to launch including Germany and Spain



Financial Performance

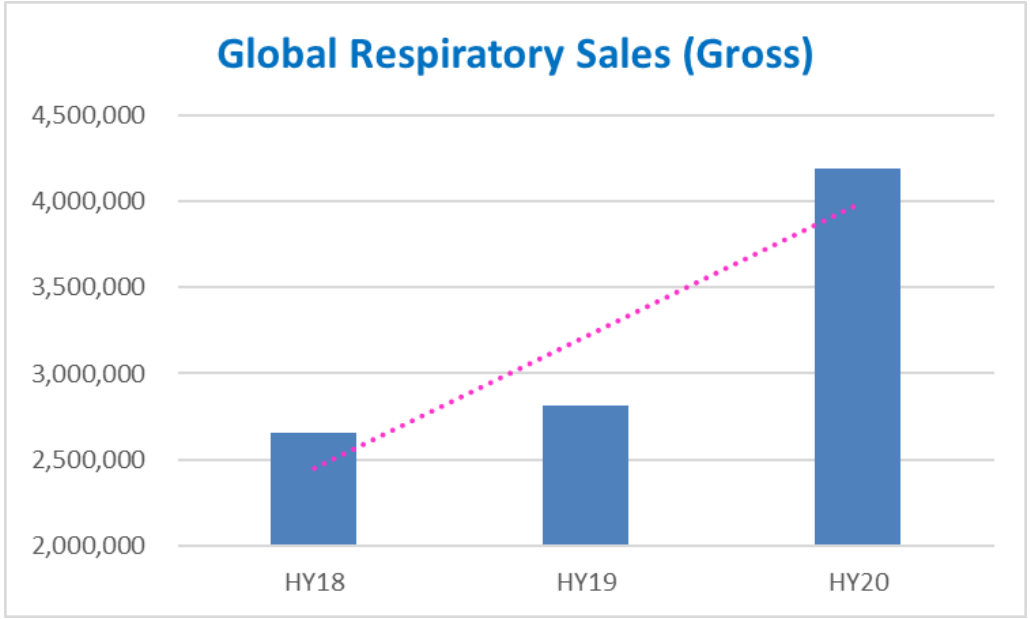
Penthrox® Sales in Australia

- Sales in Australia grew 18%
- New Mundipharma distribution agreement delivering strong sales growth in Australia particularly in GP/hospitals
- Sales for Australian ‘Dr’s Bags’ up 54%



Financial Performance

Global Respiratory Sales



Overall

- Global sales grew 49%
- Improved European sales
- Canada sales grew 207% - strong cardboard spacer sales

Australia

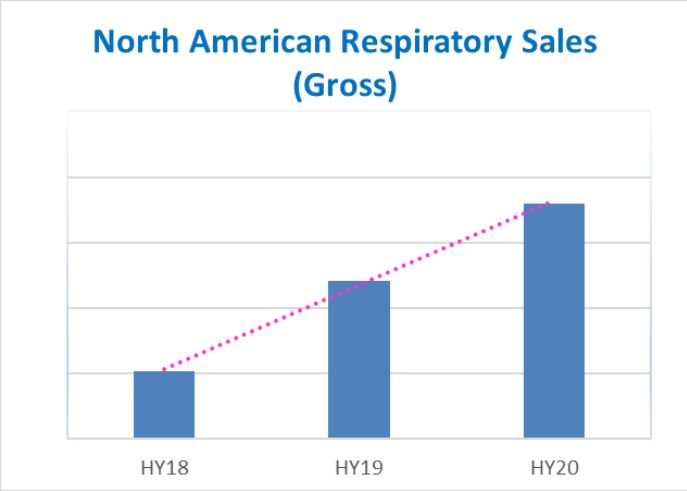
- Sales growth in Australia of 44%
- Breath-A-Tech sales grew 31%

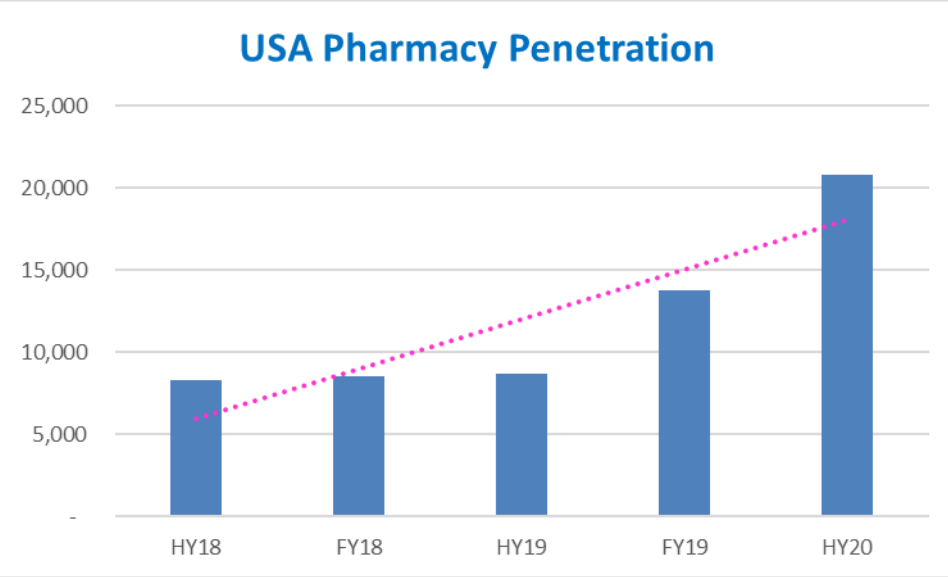
Financial Performance

Respiratory Sales in USA

USA

- Sales to USA grew 49%
- Walgreens launched into 4,750 stores in Feb
- Private label launch into over 4,500 Walmart stores expected in H2 FY20





CVS pharmacy®

Walmart
Save money. Live better.

Walgreens

H-E-B

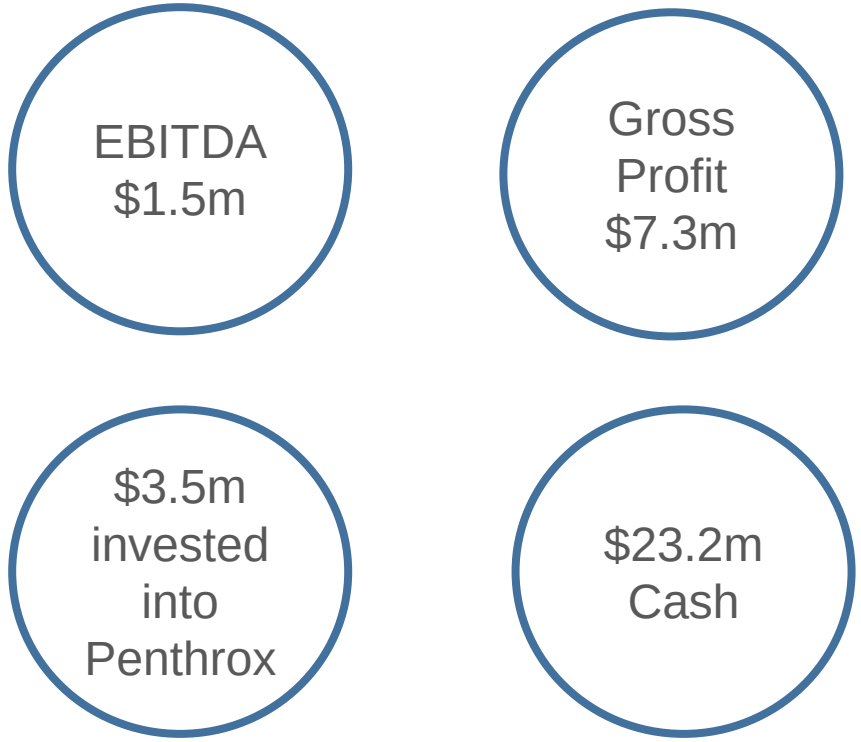
Financial Performance

Gross Revenue increased 15% to $11.2m

EBITDA increased 21%

Net Profit after Tax increased 82%

Fully Franked interim ordinary dividends of 2.0 cps



Penthrox® Future

Outlook

Strong sales growth across Penthrox and Respiratory Devices.

Regulatory approvals for development program in China, USA and Russia.

Commercialisation of first Continuous Flow technology for Lidocaine.

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2. legislative and regulatory developments and economic conditions;
3. delay or inability in obtaining regulatory approvals or bringing products to market;
4. fluctuations in currency exchange rates and general financial market conditions;
5. uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6. increased government pricing pressures;
7. interruptions in production;
8. loss or inability to obtain adequate protection for intellectual property rights;
9. litigation;
10. loss of key executives or other employees; and
11. adverse publicity and news coverage.

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