

Remimazolam headline data from pivotal U.S. Phase III study in procedural sedation for bronchoscopy



PAION conference call
Dr. Wolfgang Söhngen, CEO

Aachen, 29 June 2017



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Agenda


- Corporate overview
- Study description
- Study headline data
- U.S. status
- EU status
- Japan status
- Q&A


Corporate overview

 PAION AG is a specialty pharma company with a focus on anesthesia products

 Remimazolam, PAION's lead drug candidate, is in Phase III development

 Seven regional partnerships for remimazolam in the U.S., China, South Korea, Canada, Russia (CIS), Turkey and MENA region

 Headcount of 30, HQ in Aachen, Germany: PAION AG with a subsidiary in Cambridge (UK): PAION UK Ltd

 ~ EUR 28.7 million cash and cash equivalents (end of Q1 2017)

 Market capitalization: EUR ~ 200 m

Supervisory Board

Dr. Jörg Spiekerkötter (Chairman)
Background: Former CFO, Schering AG, Organon

Dr. Karin Dorrepaal
Background: Former Schering AG Board Member

John Dawson
Background: CEO Oxford BioMedica

Dr, Dr. Irina Antonijevic
Background: CMO, vasopharm GmbH

Dr. Chris Tanner
Background: Executive Board Cosmo Pharmaceuticals

Management

Dr. Wolfgang Söhngen
Title: CEO, Founder

Abdelghani Omari
Title: CFO

Remimazolam



About remimazolam

- Member of the benzodiazepine family
- Rapidly metabolized by tissue esterases
- Ultra-short-acting intravenous benzodiazepine sedative/anesthetic
- Can be reversed with flumazenil if required
- Results to date indicate:
 - Efficacy and safety in studied populations
 - Rapid onset and offset of action
 - Appropriate depth of sedation
 - Hemodynamic stability

Procedural sedation

- Standards of care: midazolam and propofol
 - U.S. Phase III program vs. placebo
 - Additional data on midazolam

General anesthesia

- Standards of care: propofol and volatile gases
 - EU Phase III study vs. TIVA propofol (discontinued)
 - Japan Phase III program vs. propofol (completed)

Remimazolam – Extensive efficacy and safety database

Completed studies

Studies not yet completed

Procedural Sedation

- 7 Phase I/II trials in the U.S.
- 3 Phase III trials in the U.S.

General Anesthesia

- 3 Phase I/IIa trials in Japan (Ono)
- 2 Phase IIb/III trials in Japan (Ono)
- 1 Phase II trial in Germany

- 1 Hepatic impairment trial in the U.S. (Ono)
- 1 Renal impairment trial in Europe

Procedural Sedation

- 2 Phase I studies

General Anesthesia

- 1 Phase I trial in Germany

More than 1,500 volunteers/patients on drug

Remimazolam U.S. Phase III study program

- Phase III study for procedural sedation in patients undergoing colonoscopy
 - Positive results reported in June 2016
- Safety study in ASA III/IV (high-risk) patients undergoing colonoscopy
 - Positive results reported in March 2017
- Phase III study for procedural sedation in patients undergoing bronchoscopy
 - Positive results reported in June 2017

Phase III bronchoscopy study protocol summary

- To evaluate the efficacy and safety of remimazolam
 - Prospective, double-blind, randomized, controlled multi-center study comparing remimazolam to placebo (with rescue sedative medication; i.e. midazolam)
 - Randomized additional open-label arm for midazolam
 - Procedural sedation in patients undergoing bronchoscopy for diagnostic or therapeutic reasons
- Primary outcome measure
 - Composite endpoint 'Success of procedure' as measured by:
 - completion of bronchoscopy, **and**
 - no requirement for rescue sedative medication (midazolam 'rescue'), **and**
 - no requirement for more than 5 doses of study medication within any 15-minute period (remimazolam/placebo) or no more than 3 doses of midazolam in any 12-minute period

Phase III bronchoscopy study protocol summary

- Secondary objectives
 - Time to start of procedure after administration of the first dose of study medication
 - Time to peak sedation after administration of the first dose of medication
 - Times to readiness for discharge after the end of procedure / after last dose of study drug
 - Times to fully alert (first of three MOAA/S scores of 5) after the end of procedure / after last dose of study drug
 - Recall of the procedure by the Brice questionnaire when fully alert and on Day 4
 - Changes to the patient's cognitive function assessed by the Hopkins Verbal Learning Test Revised (HVLT-R) before study medication and after fully alert
 - Ready to discharge 30, 60 and 90 minutes post injection of the initial dose
 - Drowsiness visual analogue scale to assess for signs of re-sedation
 - Patient's self-evaluation of "back-to-normal" after the procedure
 - Safety of multiple doses of remimazolam following a standard dose of fentanyl
 - Requirement for flumazenil during the procedure
 - Pain on injection at application of study medication
 - Population PK in patients aged 75 or older

Structure of the Phase III trial including midazolam open label in patients undergoing bronchoscopy for procedural sedation

446 patients randomized – 431 treated
Multi-center study placed at 15 enrolling sites in the U.S.
First patient in – 08 June 2015
Last patient out – 28 March 2017

**all patients:
fentanyl 25–75 mcg**

**double-blind
remimazolam
5 mg initial
2.5 mg top-up
n=303**

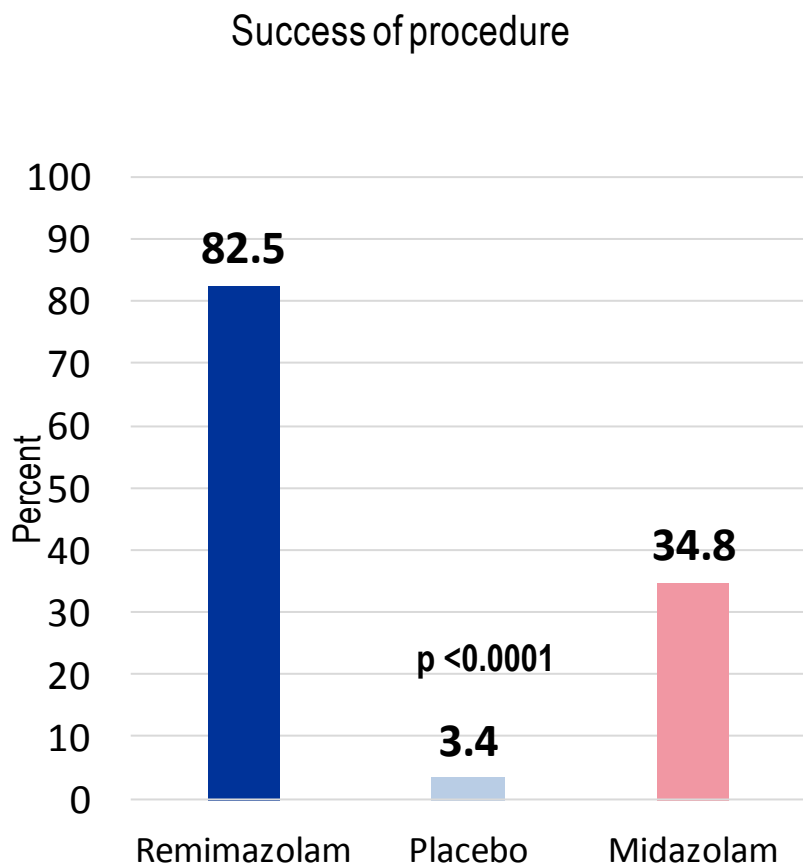
**double-blind
placebo
(midazolam
“rescue”)
n=59**

**open label
midazolam
1.75 mg initial
1 mg top-up
(per FDA insert)
n=69**

Demographics

	Remimazolam Phase III Bronchoscopy	Remimazolam Phase III Colonoscopy
Mean Age [years]	62.3	54.9
Age group >= 65 years [%]	48.5	13.8
Gender male vs. female [%]	45.9 vs. 54.1	47.6 vs. 52.4
Mean Height [cm]	168.6	169.6
Mean Weight [kg]	80.8	83.1
Mean BMI [kg / m ²]	28.3	29.0
ASA III [%]	37.6	6.6

Phase III bronchoscopy study primary outcome measure

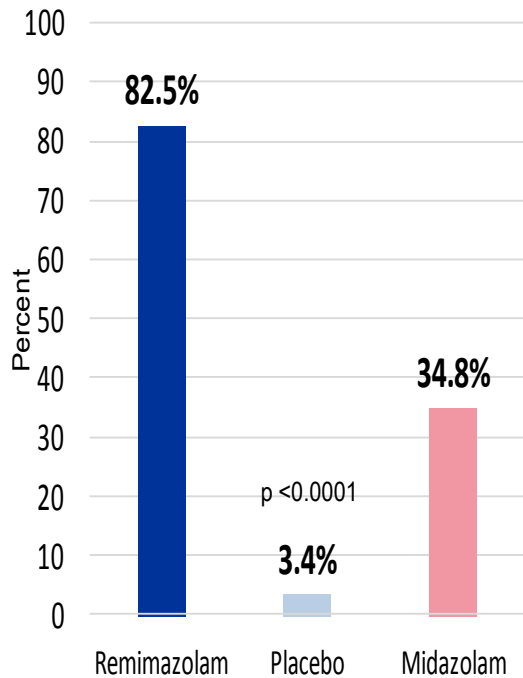


- Success of procedure as measured by:
 - Completion of the bronchoscopy procedure
 - and
 - No requirement for a rescue sedative medication
 - and
 - No more than 5 doses of study medication within any 15-minute window for placebo and remimazolam
 - No more than 3 doses of study medication within any 12-minute window for midazolam

Comparable outcome in different patient populations

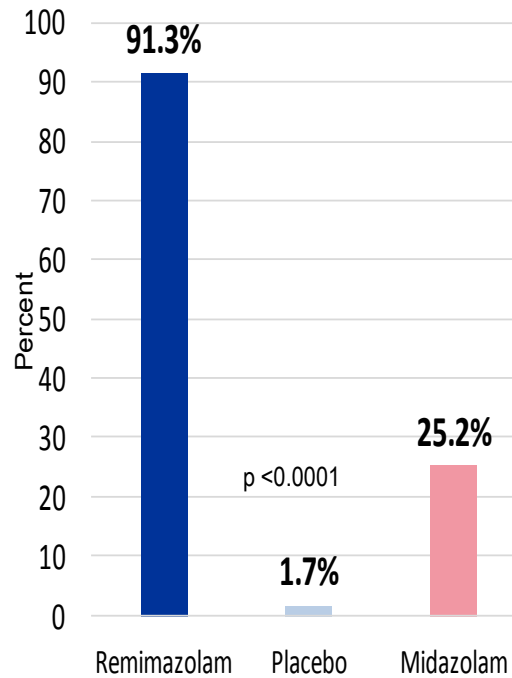
Phase III bronchoscopy (ASA I-III)

Success of procedure



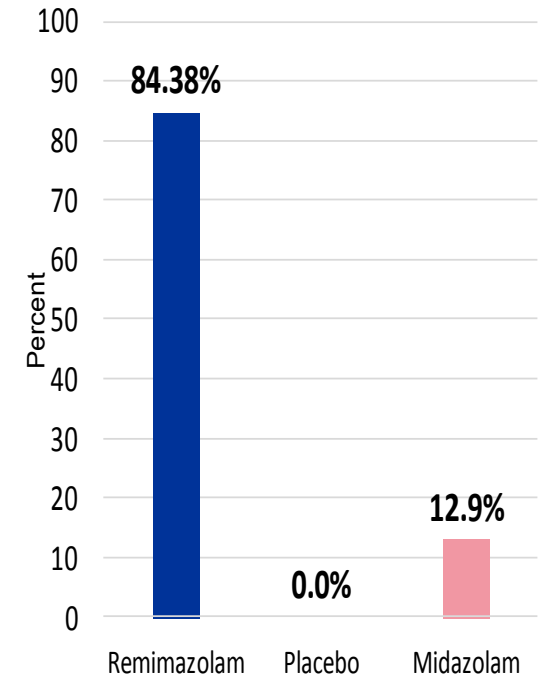
Phase III colonoscopy (mostly ASA I-II)

Success of procedure

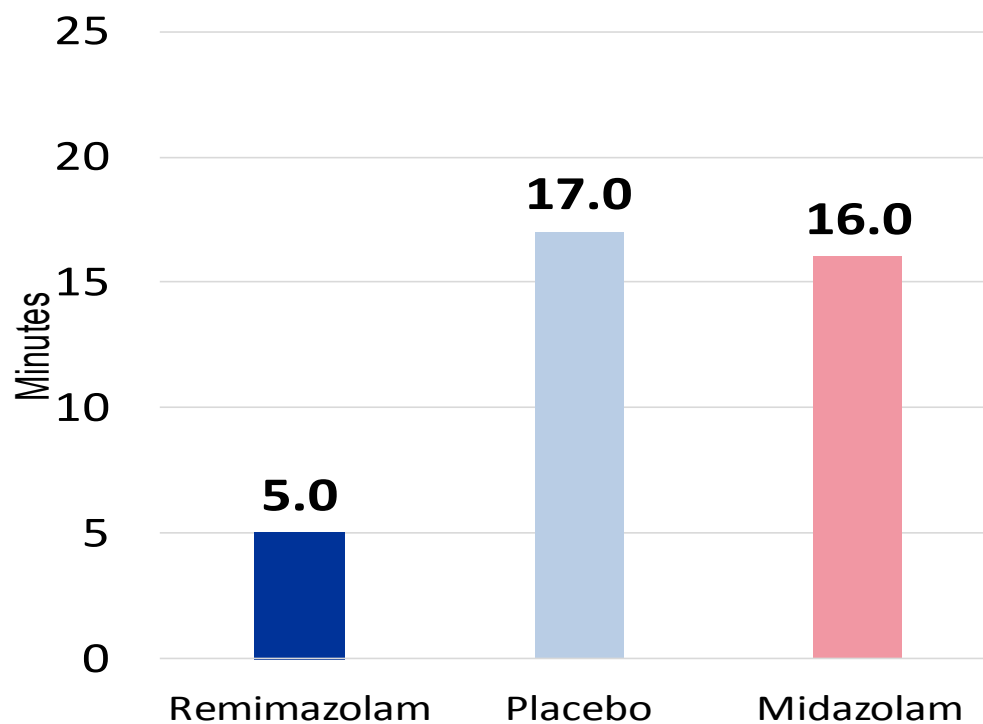


ASA III/IV patients

Success of procedure

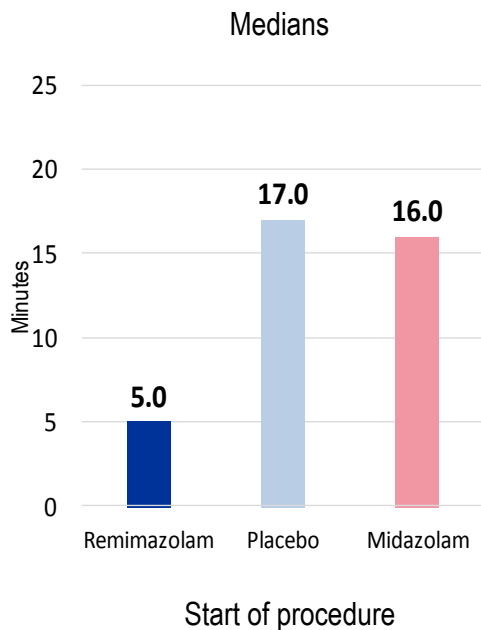


Median times to start of procedure (bronchoscopy)

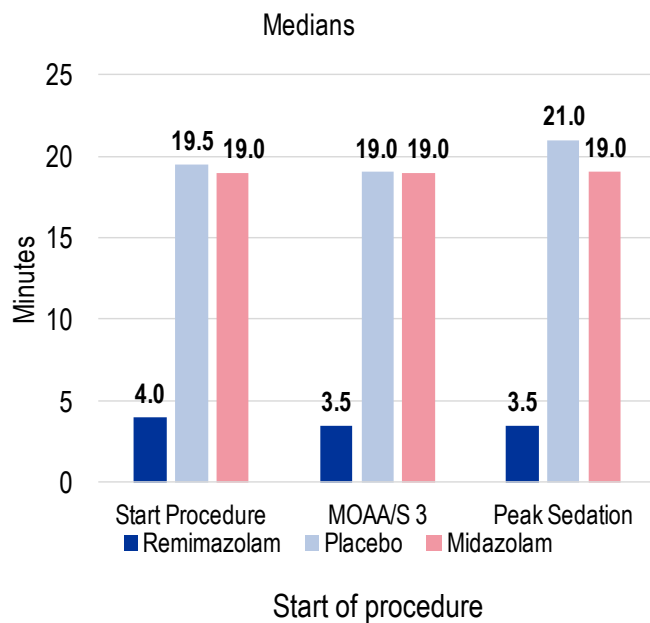


Comparable onset times

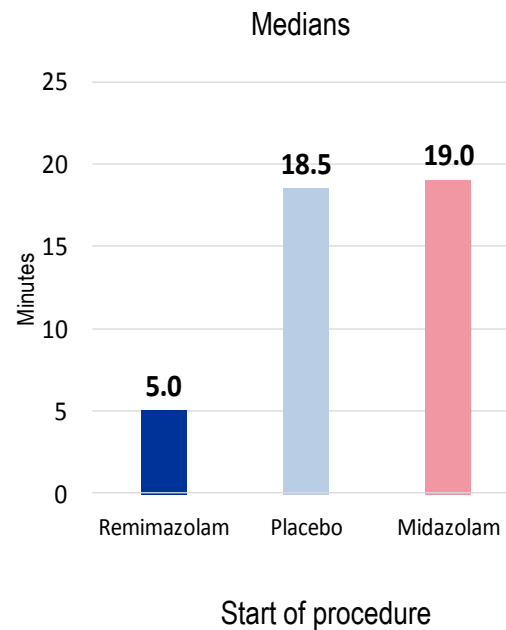
Phase III bronchoscopy (ASA I-III)



Phase III colonoscopy (mostly ASA I-II)

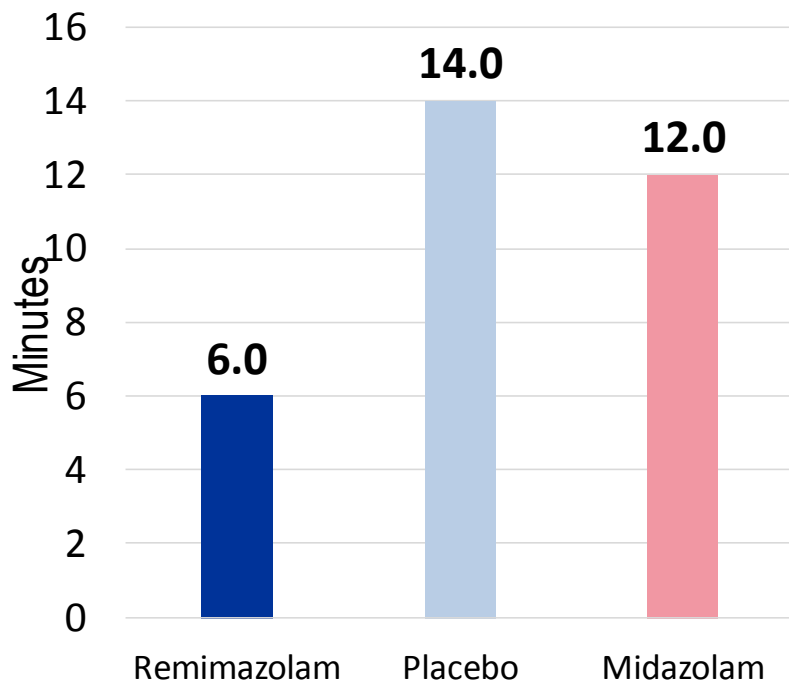


ASA III/IV patients

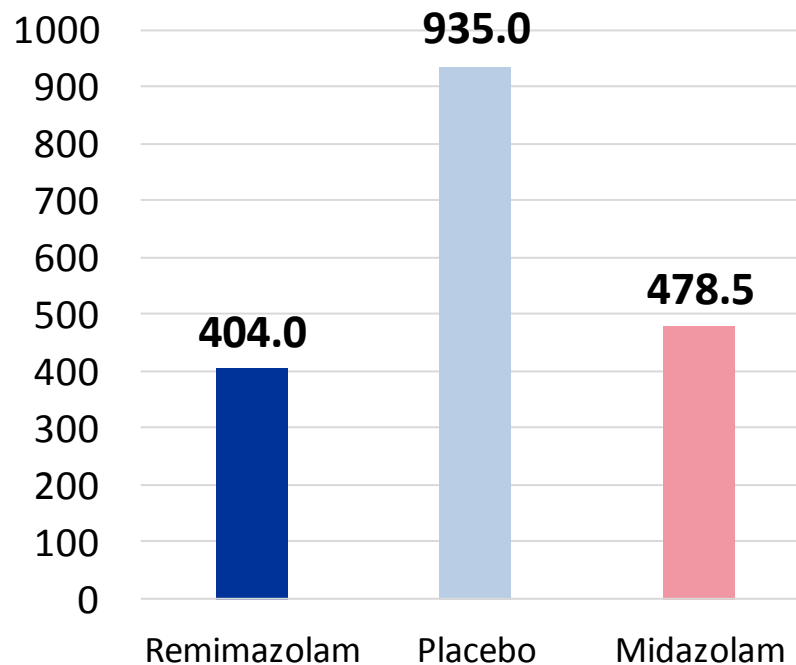


Median Time after end of procedure Phase III bronchoscopy

End of procedure to fully alert



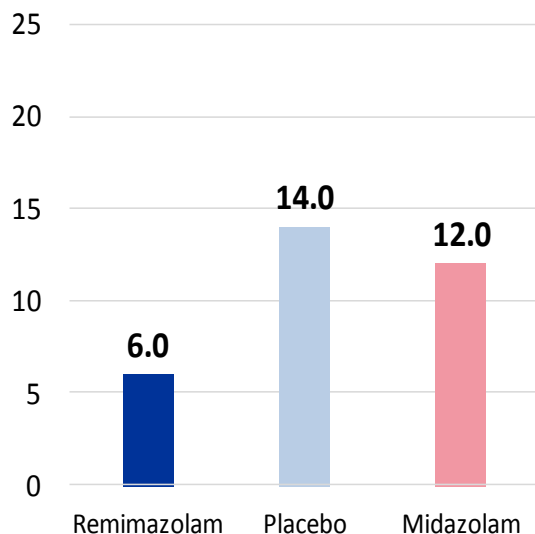
Last dose to 'back to normal'



Comparable time after end of procedure

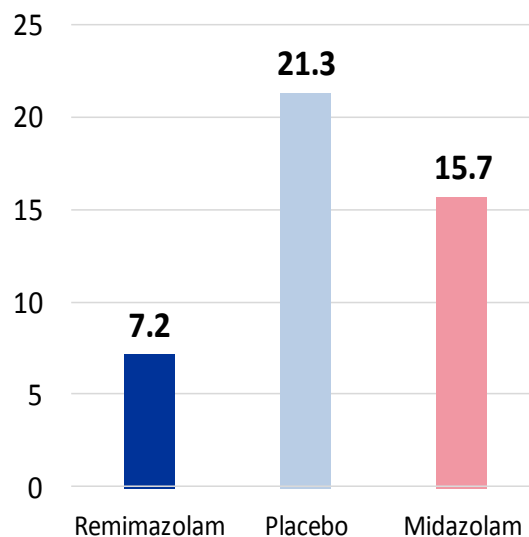
Phase III bronchoscopy (ASA I-III)

End of procedure to fully alert



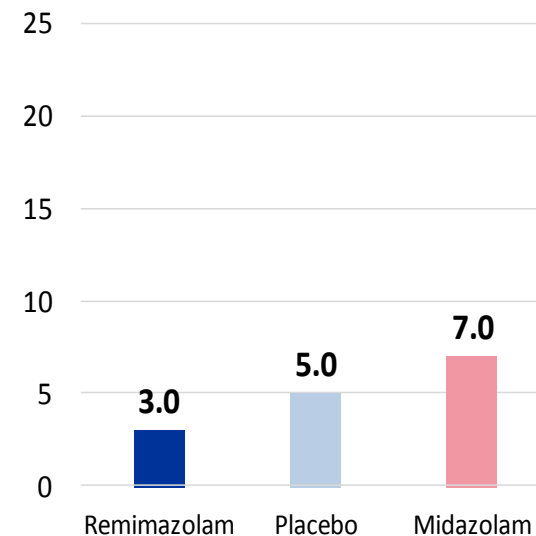
Phase III colonoscopy (mostly ASA I-II)

End of procedure to fully alert



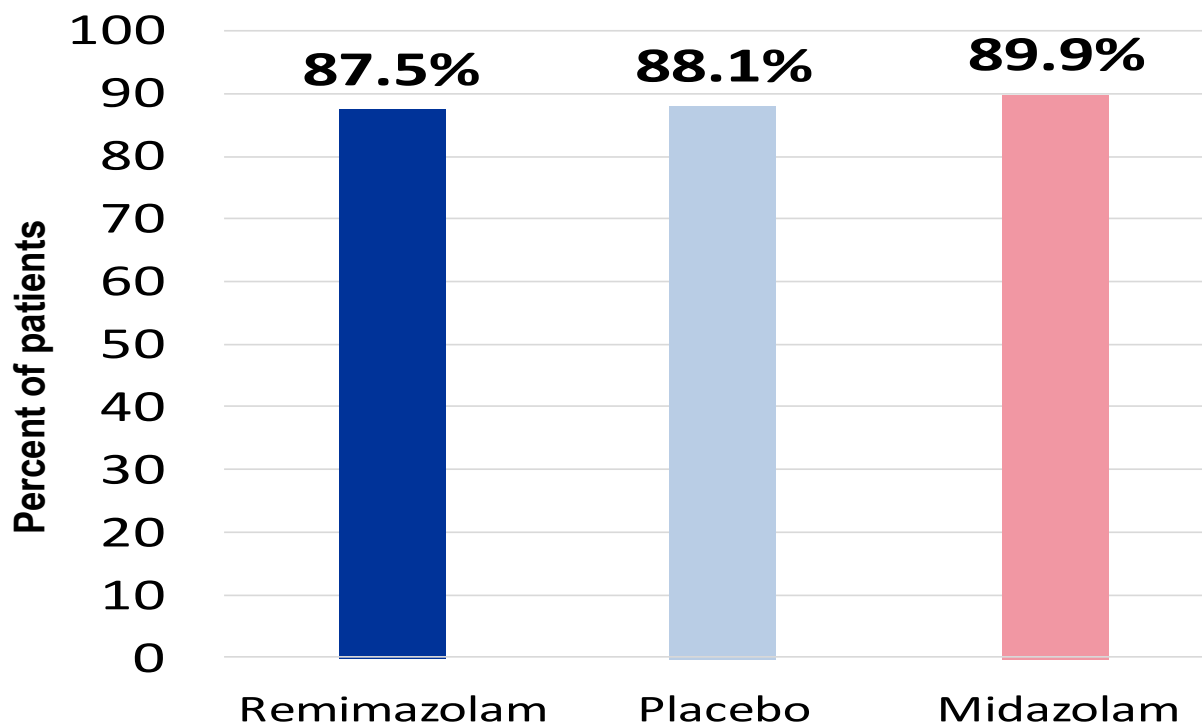
ASA III/IV patients

End of procedure to fully alert



Any AE reported in eCRF in Phase III bronchoscopy

Treatment-emergent adverse events





Remimazolam vs. Fospropofol recruitment speed

Remimazolam Bronchoscopy Phase III trial	Fospropofol Bronchoscopy Phase III trial
<ul style="list-style-type: none">• 15 Centers in the U.S.• 446 Patients• 22 months duration of recruitment <p>➤ 1.35 pt/center/month</p>	<ul style="list-style-type: none">• 25 Centers in the U.S.• 225 Patients• 14 months duration of recruitment <p>➤ 0.64 pt/center/month</p>

U.S. Phase III bronchoscopy: supports business case (ability to treat more patients)

- With an average reduction of 17min/procedure and an average number of procedures of 10-20/day/doctor, centers could increase throughput significantly

Time from start of medication to start of procedure	minutes (Median)
Remimazolam – 5.0/2.5 mg	 5.0
Midazolam – 1.75/1.0 mg (1.0/0.5 mg in the elderly and debilitated)	16.0
Time to end of procedure to fully alert	minutes (Median)
Remimazolam – 5.0/2.5 mg	 6.0
Midazolam – 1.75/1.0 mg	12.0

Conclusion of ASA III/IV and Bronchoscopy study

- Remimazolam appears to be a safe alternative to midazolam in both, patients with and without significant co-morbidities
- Careful use of fentanyl
- Reduced doses of both remimazolam and fentanyl are recommended in patients with significant co-morbidities

Prof. Dr. Gerard A. Silvestri, Medical University of South Carolina, Charleston, South Carolina, U.S., commented:

- *The study results suggest that remimazolam, the first drug in many years to be tested for use in providing procedural sedation in the bronchoscopy lab has the potential to enhance the options for bronchoscopy patients allowing for a more efficient procedure. Remimazolam may be an ideal agent for patients who require bronchoscopy because it is safe, ultra-short-acting, has excellent sedative effects, and allows patients to more quickly wake to an alert state. The results of the trial are under further evaluation but already demonstrate that remimazolam is likely to have a place in providing adequate sedation to patients undergoing bronchoscopy.”*

Remimazolam – U.S. status



Cosmo Pharmaceuticals – Partner for remimazolam in the U.S.

- PAION received EUR 10 million upfront payment from Cosmo
- PAION is entitled to receive up to additional EUR 42.5 million in milestone payments and significant double-digit tiered royalties
 - Royalties on net sales in the U.S. ranging from 20% to 25%, which may be adjusted under certain conditions but not to below 15% of net sales
- Private placement by Cosmo led to gross proceeds of EUR 9.6 million and additional EUR 0.4 million in the course of the capital increase in Feb 2017
- Cosmo is responsible for market authorization as well as sales and distribution
- PAION will be responsible for and bears the costs associated with the completion of the ongoing U.S. clinical development program in procedural sedation

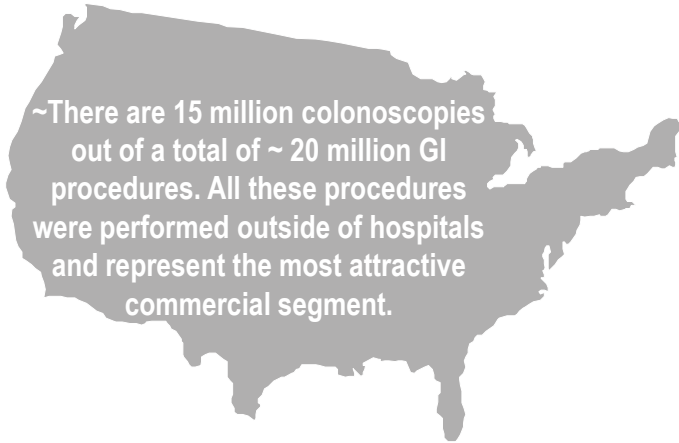
Primary focus – Colonoscopy

Rapidly growing market, big push for colorectal cancer screening:

- Regular and appropriate colorectal cancer screening is both recommended and covered by all major health plans including CMS
- More than 4 million patients turn 50 and are newly eligible each year, baby boomers are all “of age” for screening, i.e. > 50 years
- Millions more covered lives in the U.S. as a result of the Affordable Care Act

U.S. Market Size

Total U.S. market for procedural sedation = 43 million procedures



~There are 15 million colonoscopies out of a total of ~ 20 million GI procedures. All these procedures were performed outside of hospitals and represent the most attractive commercial segment.

26.7 million unique procedure claims for colonoscopy and endoscopy in 2015

Source: *Ambulatory Surgery in the United States, 2006, National Health Statistics Reports Number 11, U.S. Department of Health and Human Services* and PAION projections based on *Symphony Health Solutions (2013), Colonoscopy: Scoping & Mapping*

Various data sources indicate that between 20-27% of procedures are done in hospitals. 2006 CDC/NCHS, National survey of Ambulatory Surgery (NSAS) and National Hospital Discharge Survey (NHDS) (27%). Qualitative market research by Kennedy associates for PAION Inc. 2015 (20%).

Source: *I DATA Market Report on US Gastrointestinal Endoscopic Device Market - 2016*

U.S. colonoscopy market split into 2 main segments

~20 million GI procedures per year outside of hospitals

Providers using midazolam:

- Predominantly in West, Midwest and South
- Lower cost for insurers and CMS
- Problem:
 - Less clinic efficiency
 - Less revenue for providers

Providers using propofol :

- Predominantly in Northeast & Eastern U.S.
- More revenue for providers
- Problem:
 - Higher cost for insurers and CMS
 - Dependency on anesthesia assistance

Considerations

- Market short on innovation
- Sedatives are covered as part of a medical reimbursement; included in cost of the procedure
- Quality of patient experience – efficacy, safety, and recovery time
- Physician experience - predictability of patient response
- Efficiency, throughput, and number of procedures per day
- Total medical resource utilization

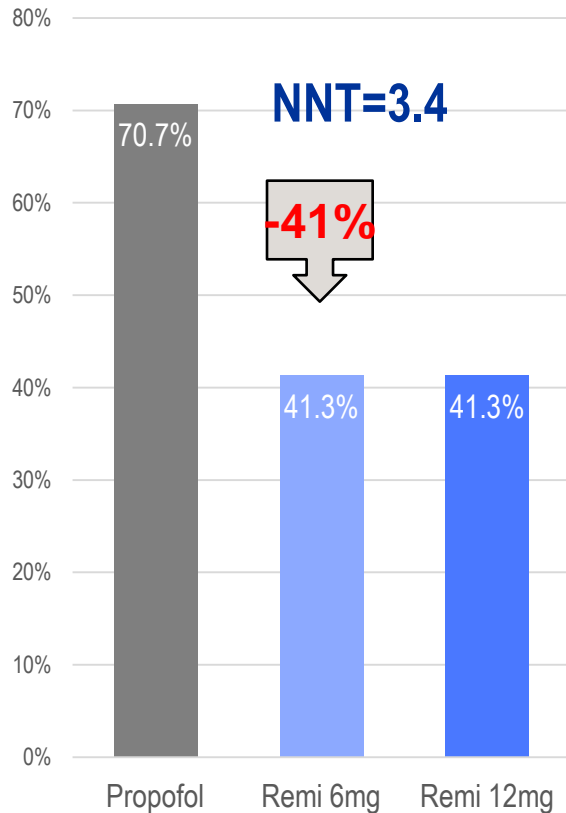
Remimazolam – EU



Our mission in general anesthesia: Reducing the detrimental effects of

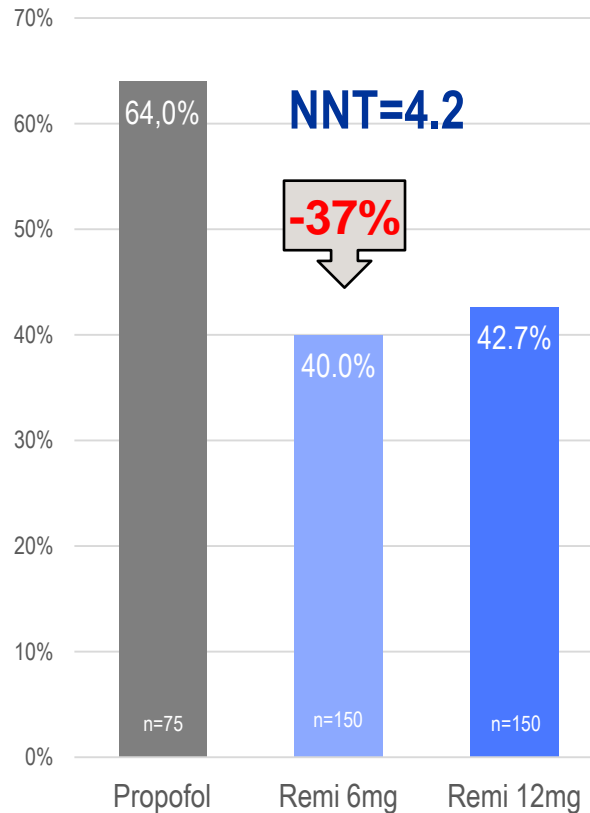
Hypotension

Patients with APM
< 60 mm Hg
first hour after intubation



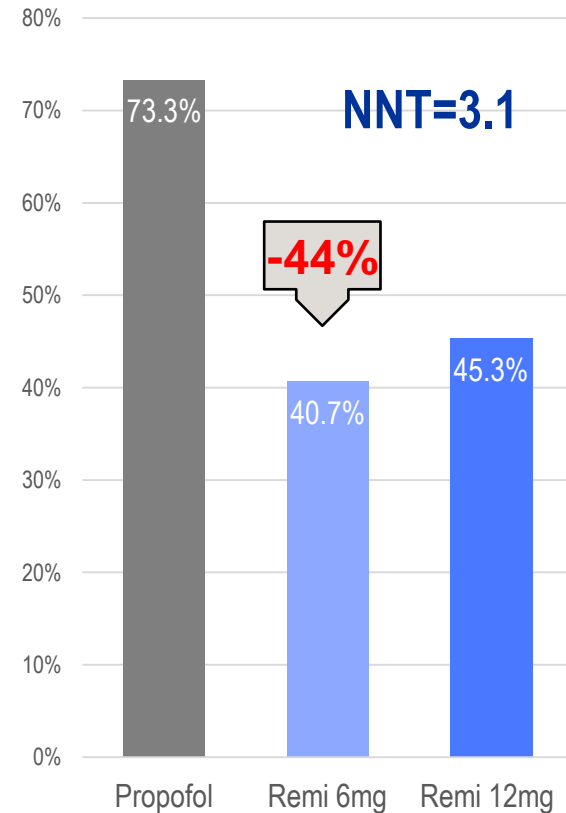
Need for vasopressors

Share of patients who needed
vasopressor
in the entire study



Too deep sedation

Share of patients with BIS
score below 40 until 1 h after
intubation



Source: PAION data on file

Remimazolam – EU program

- In February 2016, PAION discontinued a confirmatory EU Phase III study with remimazolam in patients undergoing major cardiac surgery
 - Due to the complex study design, the trial faced recruitment challenges
 - PAION evaluated how best to resume the clinical development of remimazolam in the EU
 - PAION determined that a study design analogous to the successfully completed Phase III program in general anesthesia in Japan would be the best path forward in the EU
 - Phase III study would thus be conducted with procedures in general surgery and not in cardiac surgery
 - Phase I study to support sample size calculation for a EU Phase III study in general anesthesia will start shortly
 - Seek further guidance from the European Medicines Agency (EMA) to determine the components of the new European development program
-
- PAION plans to commercialize remimazolam itself in the EU. However, PAION is also open to discussing EU partnerships that are value-creating
 - PAION estimates funding needs of approximately EUR 20 million to EUR 25 million until filing

Remimazolam – Japan / Asia



Remimazolam – Japan

- A total of three Phase I, one Phase II and two Phase III trials in general anesthesia have been completed
- PAION has started to prepare filing of remimazolam in Japan
- Activities are important prerequisites to advance ongoing discussions with potential licensees
- PAION seeks to partner in the Japanese market during or after dossier preparation
- Subject to further coordination with the regulatory authority, filing for market approval in Japan is expected by mid-2018



**Thank you very much
for your attention!**

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