

# Comparing Relative Effects on Cognitive Function Following Sedation with Remimazolam vs Midazolam as Measured by the Hopkins Verbal Learning Test

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PHARMACEUTICALS

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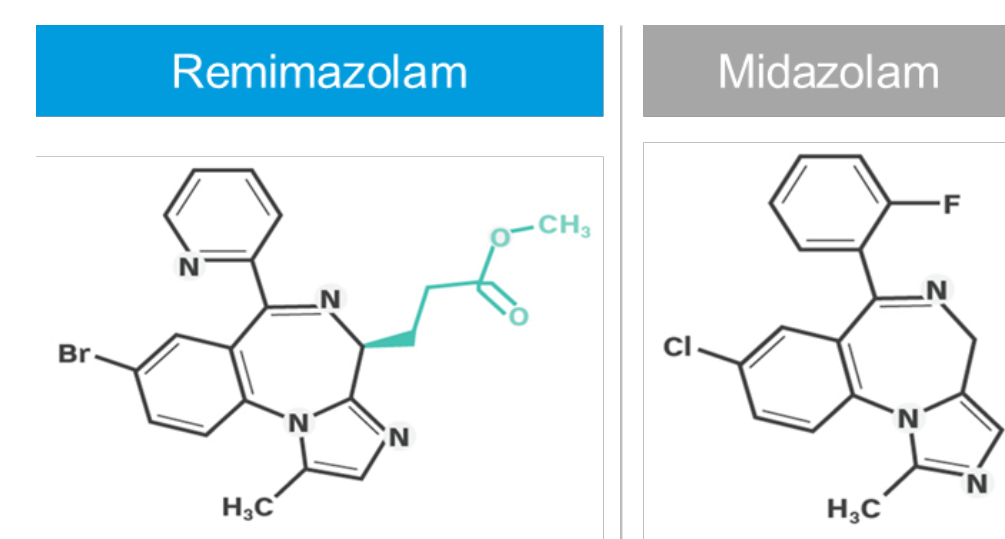
## Background

### Anesthesia/Procedural Sedation and Cognition/Delirium

- The interaction between anesthetic/sedative agents and the CNS, specifically the brain, are not well described
- Untoward effects range from emergence delirium to postoperative cognitive dysfunction (POCD), delayed neurocognitive recovery (NCR), postoperative neurocognitive disorder (PND), and ICU delirium
  - Older patients more susceptible<sup>1</sup>
- Gold standard measurement not elucidated
- The Hopkins Verbal Learning Test-Revised (HVLT-R)<sup>2,3</sup>
  - Validated neurocognitive test
  - Measures 4 parameters
  - Application to anesthesia/sedation?
- Benzodiazepines
  - Used ubiquitously
  - Delirium/exacerbation of dementia in the elderly?<sup>4</sup>

### Remimazolam

- Ultra short acting benzodiazepine recently approved for procedural sedation



- Carboxylic ester side chain
  - Cleavage by non-specific tissue esterases<sup>5</sup>
  - No meaningful contribution by CYP450 enzymes or kidneys
- May not possess same deleterious effects on postprocedural cognition and delirium the other benzodiazepines demonstrate<sup>6</sup>
- Two randomized controlled trials demonstrated remimazolam to be safe and effective for procedural sedation in colonoscopy and bronchoscopy patients<sup>7,8</sup>
- Predictable fast onset/offset pharmacokinetics<sup>9</sup>

RAPID ONSET	RAPID OFFSET
Distribution half-life 0.5-2 minutes <sup>5</sup>	Terminal elimination half-life 37 to 53 minutes <sup>5</sup>
Onset of sedative effects 1.0-1.5 minutes (DOF)	Time to fully alert <sup>5</sup>
Median time to peak sedation 3.0-3.5 minutes <sup>5</sup>	<ul style="list-style-type: none"> <li>11-14 minutes after last dose</li> <li>3-6 minutes after end of procedure</li> </ul>

- No correlation found between sedation level and vital signs in high-risk ASA III-IV patients<sup>10,11</sup>

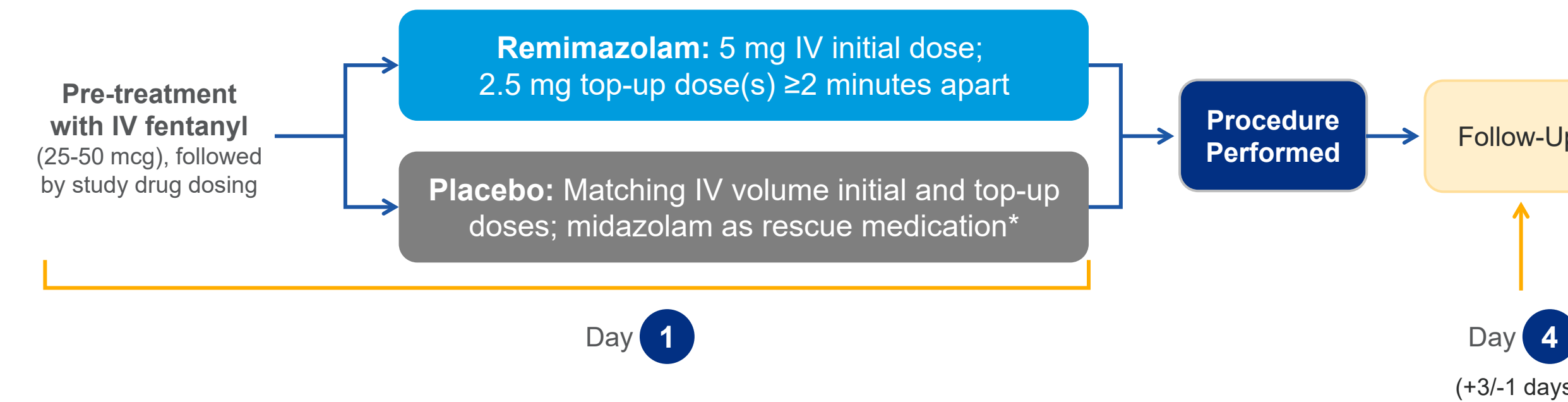
## Study Aim

The aim of this analysis was to identify/compare cognitive changes after remimazolam sedation versus placebo with midazolam rescue sedation

## Methods

This was a post-hoc analysis of two pivotal US phase 3 prospective, double-blind, randomized, multicenter, parallel group trials performed on 719 ASA I to III adults to assess safety and efficacy of IV remimazolam in patients undergoing colonoscopy<sup>7</sup> and bronchoscopy<sup>8</sup>

### Study Design



\*Placebo rescued if required with midazolam dosed per physician discretion  
 \*Colonoscopy study (006): 95% of placebo patients received midazolam rescue dosed per local standard of care  
 \*Bronchoscopy study (008): 91.5% of placebo patients received midazolam rescue dosed per local standard of care

### Key Secondary Endpoint Assessed in this Analysis

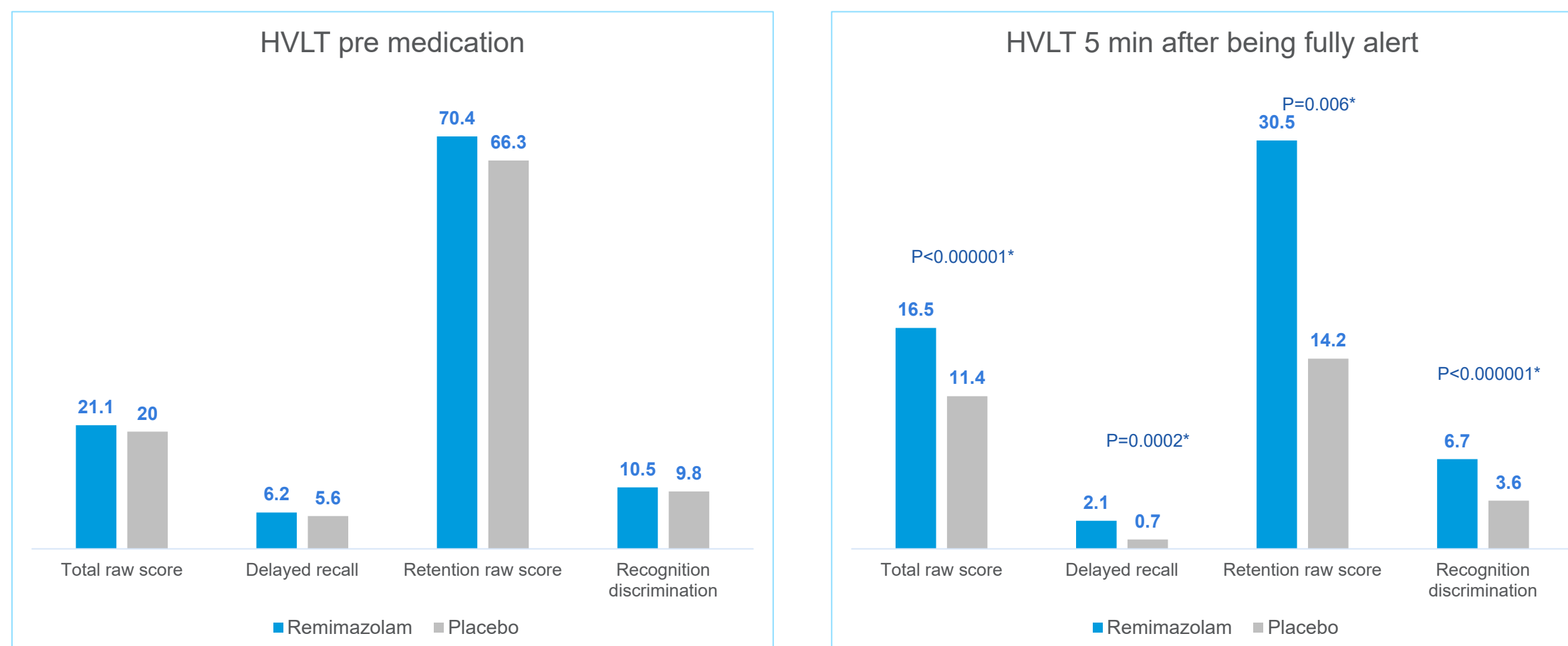
- HVLT scores administered 5 minutes after full alertness was achieved post procedure (compared to baseline HVLT administered 45 min prior to procedure)
  - For inadequate sedation, patients were rescued with midazolam administered according to physician discretion
  - Since > 90% of placebo patients in both trials received midazolam rescue, they essentially represent midazolam standard of care
  - Differences between HVLT scores for remimazolam vs placebo/midazolam rescue

## Results

	Remimazolam/006 (n=296)	Placebo/006 (n=60)	Remimazolam/008 (n=303)	Placebo/008 (n=60)
<b>Age, y:</b>				
Mean(SD)	54.4(10.12)	56.0(9.51)	62.7(12.09)	60.8(12.08)
Min/Max	19.80 / 89.00	24.92 / 89.00	22.95 / 89.00	30.78 / 89.00
≥65, n(%)	42(14.2%)	7(11.7%)	149(49.2%)	27(45.8%)
<b>Sex, Male No.(%)</b>	147(49.7%)	25(41.7%)	139(45.9%)	24(40.7%)
<b>Race:</b>				
Black/African American	52(17.6%)	14(23.3%)	33(10.9%)	10(16.9%)
White	220(74.3%)	43(71.7%)	263(86.8%)	46(78.0%)
Other			7(2.3%)	3(5.1%)
<b>Ethnicity: Hispanic or Latino</b>	46(15.5%)	10(16.7%)	8(2.6%)	0(0.0%)
<b>Weight:</b>				
Mean(SD)	83.2(17.39)	84.6(19.90)	80.9(20.21)	77.7(21.17)
Min/Max	40.128 / 144.00	49.144 / 144.00	41.155 / 144.00	32.327 / 144.00
<b>BMI:</b>				
Mean(SD)	28.9(4.72)	30.0(5.31)	28.4(6.39)	27.9(7.09)
Min/Max	17.40 / 44.00	19.40 / 44.00	16.45 / 44.00	14.44 / 44.00
<b>ASA I</b>	95(32.1%)	11(18.3%)	10(3.3%)	2(3.4%)
<b>ASA II</b>	179(60.5%)	45(75.0%)	185(61.1%)	29(48.2%)
<b>ASA III</b>	22(7.4%)	4(6.7%)	108(35.6%)	28(47.5%)

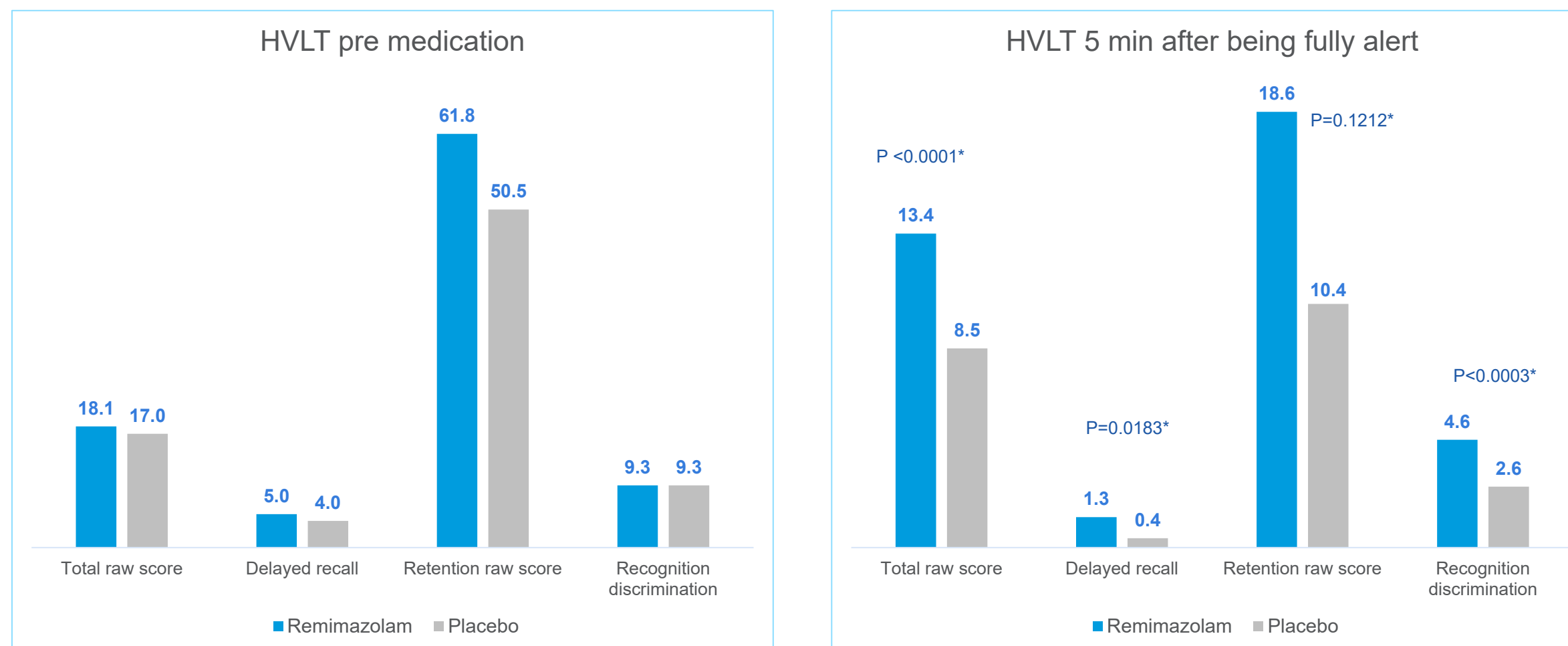
## Results (cont.)

### Hopkins verbal learning test (HVLT-R) Study CNS 7056 -006



\* Anova F-test for equal means in 2 groups

### Hopkins verbal learning test (HVLT-R) Study CNS 7056 -008



\* Anova F-test for equal means in 2 groups

## Results (cont.)

Number(%)	Remimazolam/006 (n=296)	Placebo/006 (n=60)	Remimazolam/008 (n=303)	Placebo/008 (n=60)
<b>TEAEs</b>	218(73.6%)	47(78.3%)	268(88.4%)	52(86.1%)
<b>Serious TEAEs</b>	0(0.0%)	0(0.0%)	17(5.6%)	4(6.8%)
<b>TEAEs Leading to Death</b>	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
<b>TEAEs Leading to Discontinuation/Withdrawal</b>	0(0.0%)	0(0.0%)	1(0.3%)	0(0.0%)
<b>Hypotension</b>	115(38.9%)	25(41.7%)	127(41.9%)	37(62.7%)
<b>Hypertension</b>	59(19.9%)	17(28.3%)	186(61.4%)	31(52.5%)
<b>Bradycardia</b>	33(11.1%)	7(11.7%)	13(4.3%)	4(6.8%)
<b>Tachycardia</b>	23(7.8%)	7(11.7%)	4(1.3%)	0(0.0%)
<b>Hypoxia</b>	3(1.0%)	2(3.3%)	66(21.8%)	12(20.3%)
<b>Decreased respiratory rate</b>	4(1.4%)	2(3.3%)	7(2.3%)	2(3.4%)

## Conclusions

- Ubiquitous benzodiazepine use suggests clinical need in the elderly
- Remimazolam
  - Short acting benzodiazepine
  - No active metabolites, no accumulation
- Consistent results between 2 pivotal trials (006/008) demonstrate
  - Both groups had significant decreases in all 4 HVLT parameters
  - Decreases consistently greater in the placebo with midazolam rescue vs remimazolam patients
- Ultimate interpretation of measurements done with HVLT-R still remains to be elucidated
  - Real life applicability
  - Class vs pK effect
  - Temporary or long term
  - Is dose response relationship important? (for larger doses of GA/ICU sedation vs procedural sedation)

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