CGRP pathway - targeting the underlying biology of migraine

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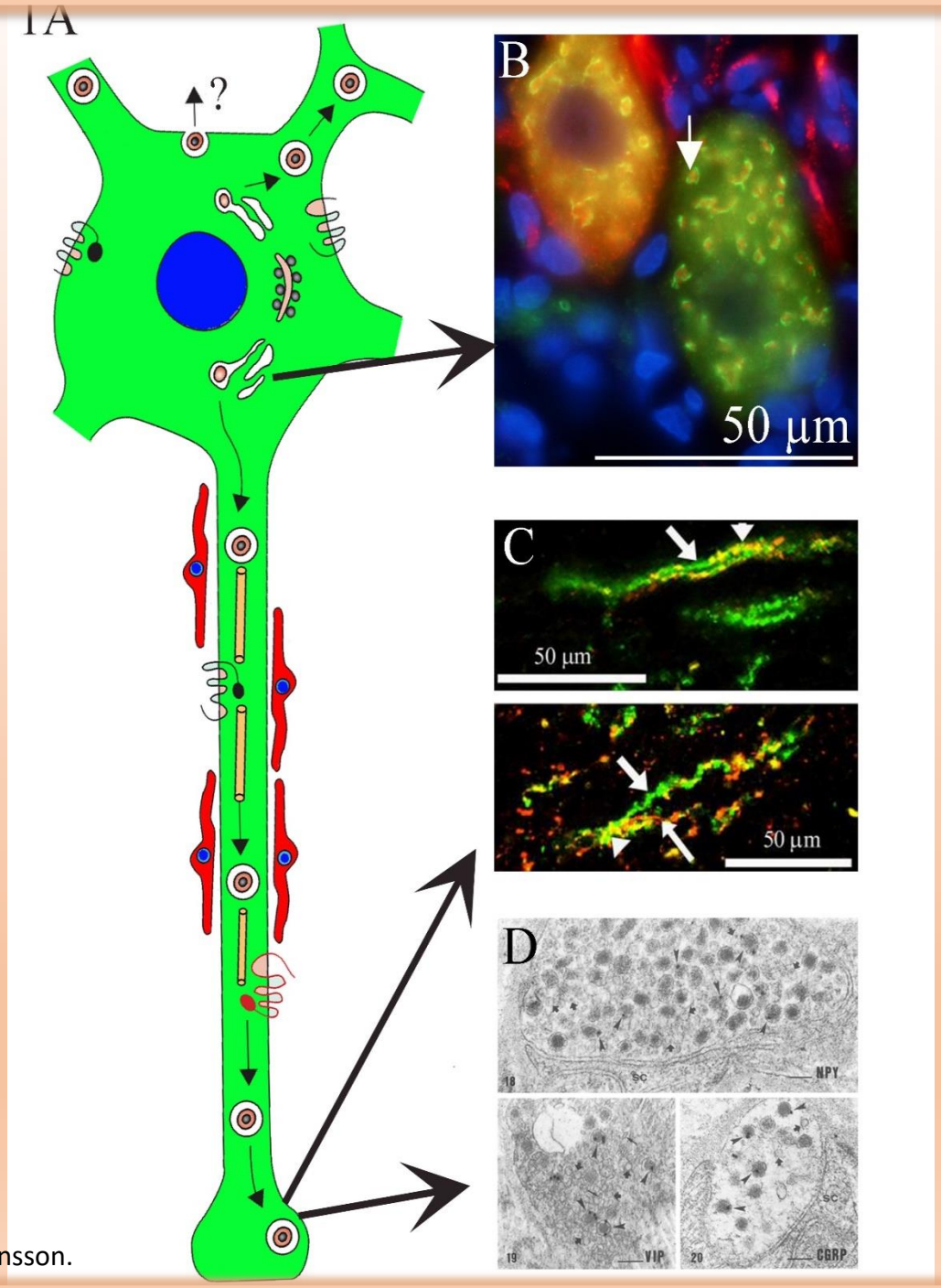
Trigeminal neuron: Illustrating different parts



Vesicular CGRP in Golgi complex

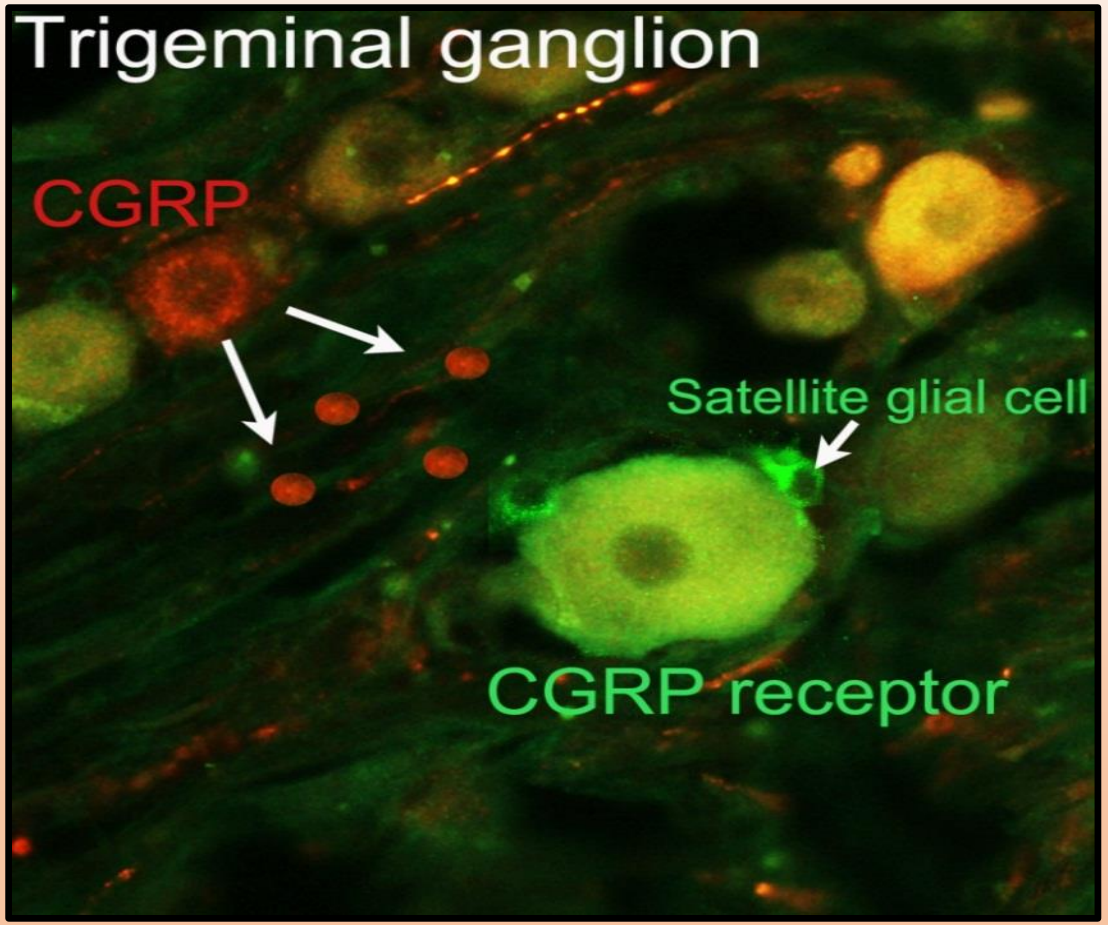
Duramater; C-fibers with CGRP and A-fibers with CLR/RAMP1

Immunoelectromicroscopy showing CGRP containing vesicles in human temporal artery

Image presented with the permission of Prof. Edvinsson.

Trigeminal ganglion and CGRP

- CGRP is expressed in small/ medium-sized neurons
- Receptor expression in large-sized neurons (CGRP negative)
- Receptor (CLR/ RAMP1) expression in satellite
  glial cells
- The trigeminal ganglion may be a key site of action for drugs acting as CGRP antagonists



CLR; calcitonin-like receptor; RAMP1, receptor-activity-modifying protein 1.
Edvinsson L, Linde M. *Lancet* 2010; 376: 645–655.

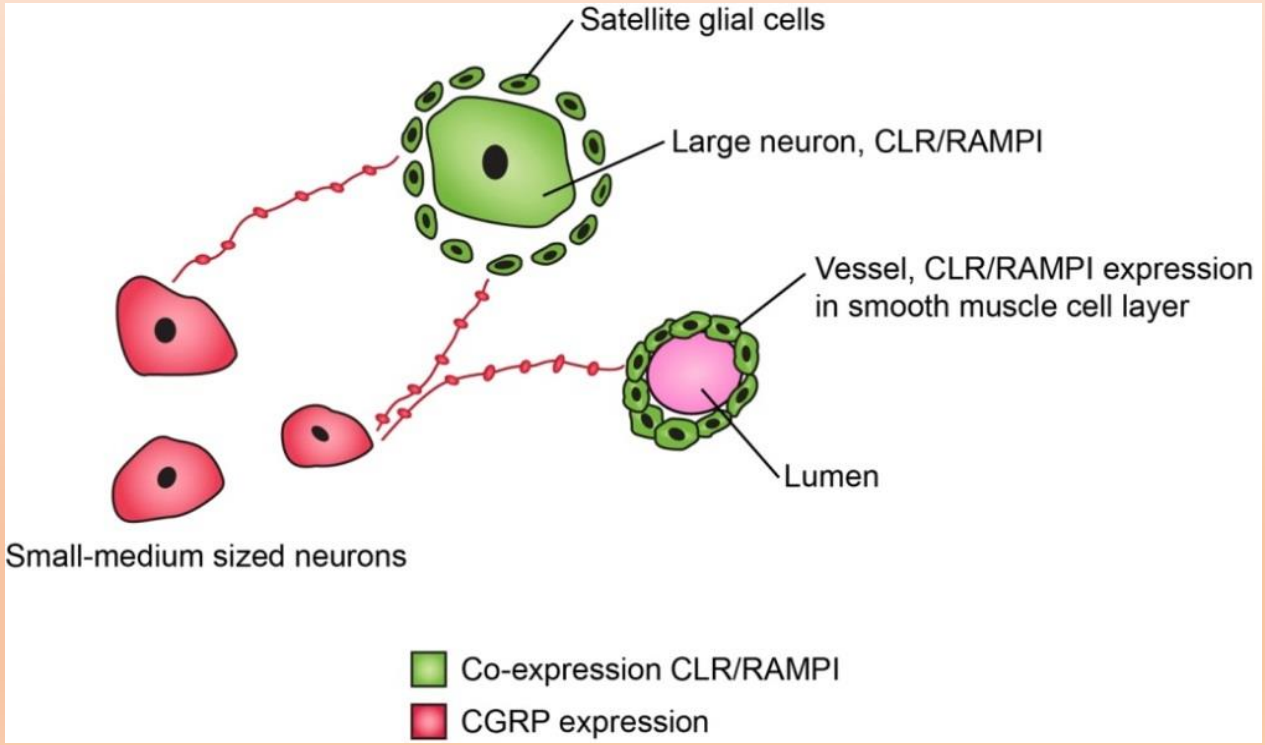
Is there a key regulator in headache?

- CGRP receptor binding sites and protein expression of CGRP and its receptor are found in trigeminal ganglion of rat, monkey and man

- Trigeminal ganglion is located outside the BBB in rodents

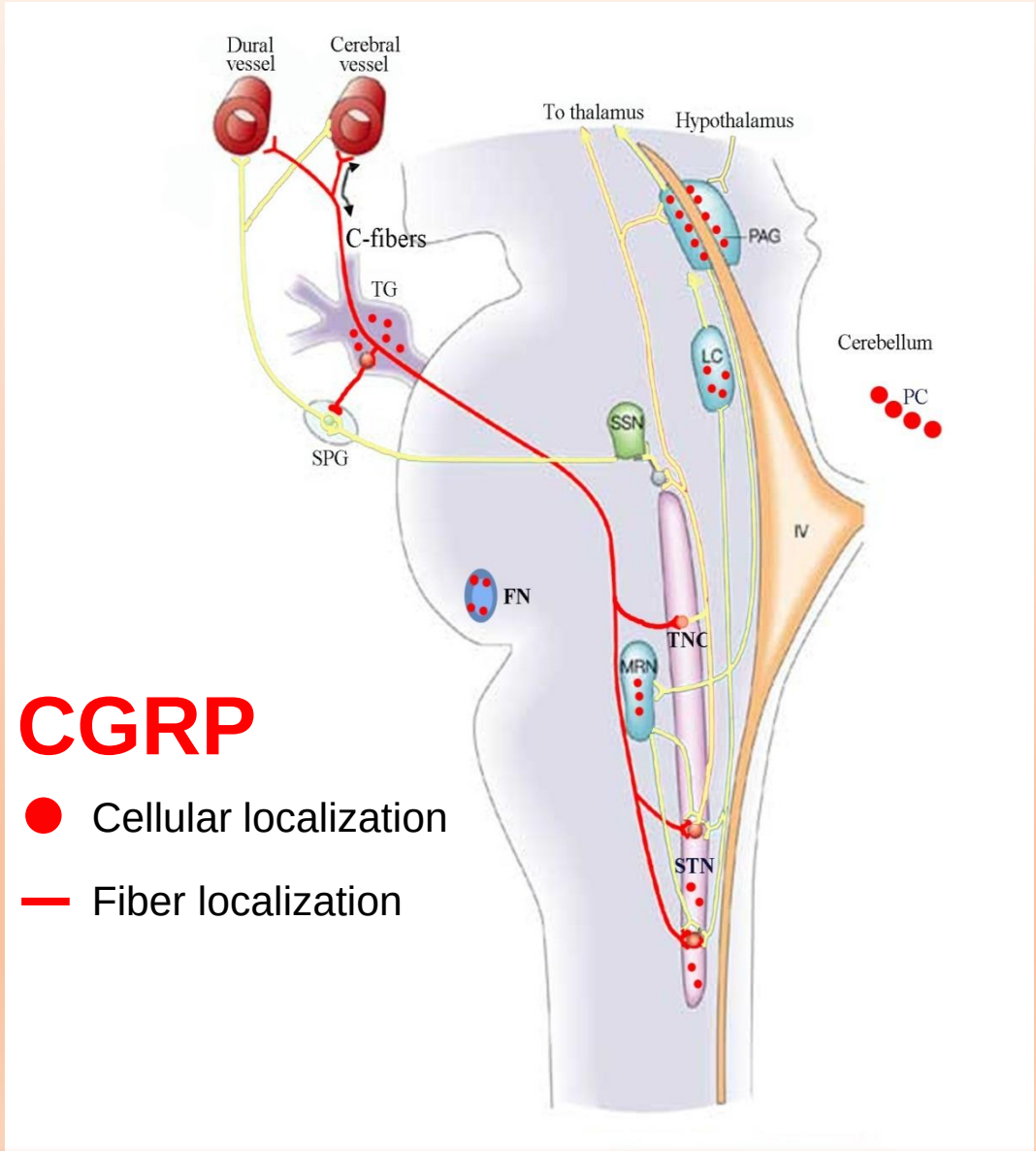
- CGRP receptor antagonists do not need to be CNS-penetrating to block receptors in the trigeminal ganglion

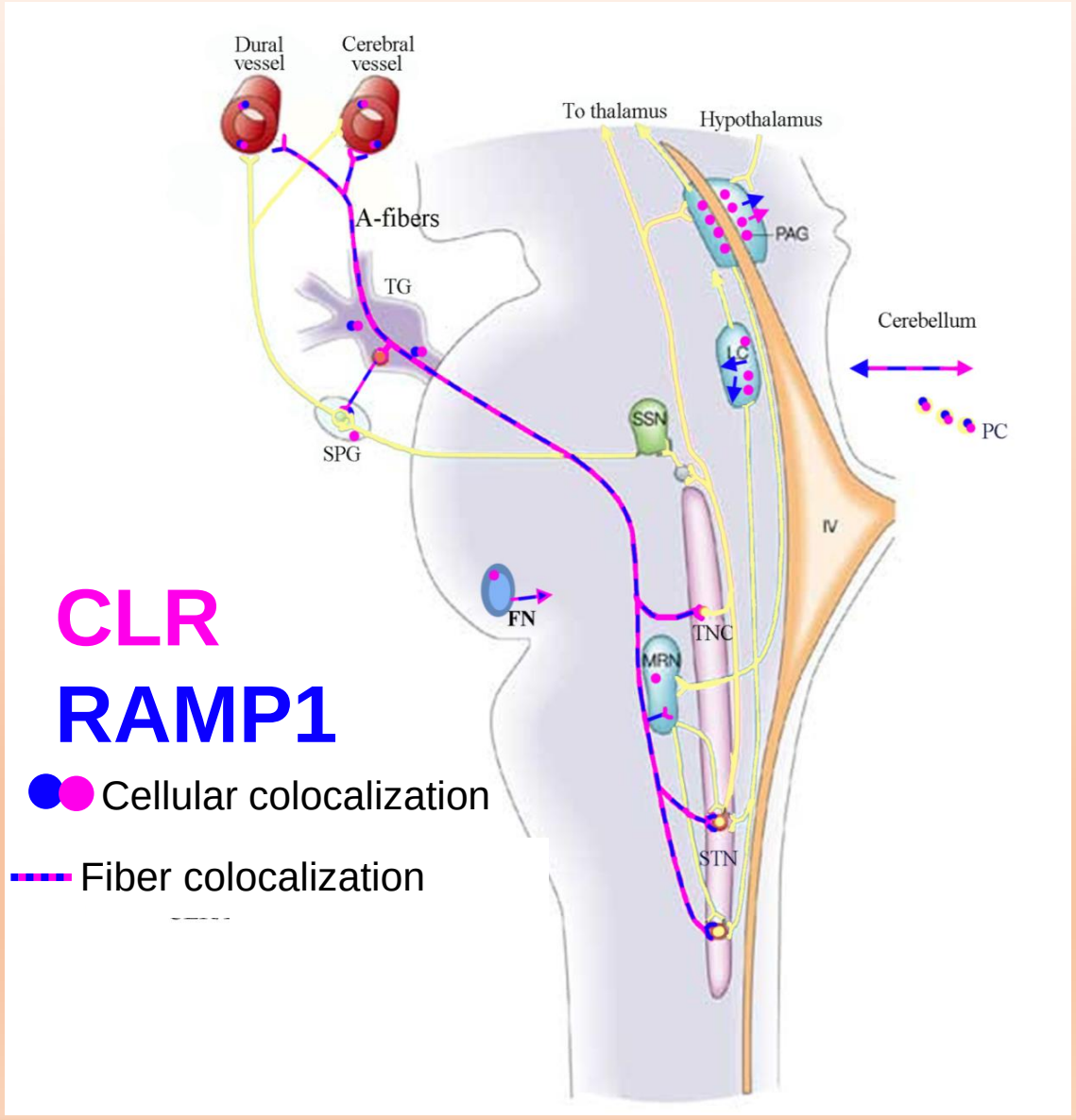
- The trigeminal ganglion may be a key site of action for CGRP receptor antagonists, and antibodies



Edvinsson L. Br J Clin Pharmacol 2015;80:193–199.

CGRP and receptor distribution – cell bodies and fibers

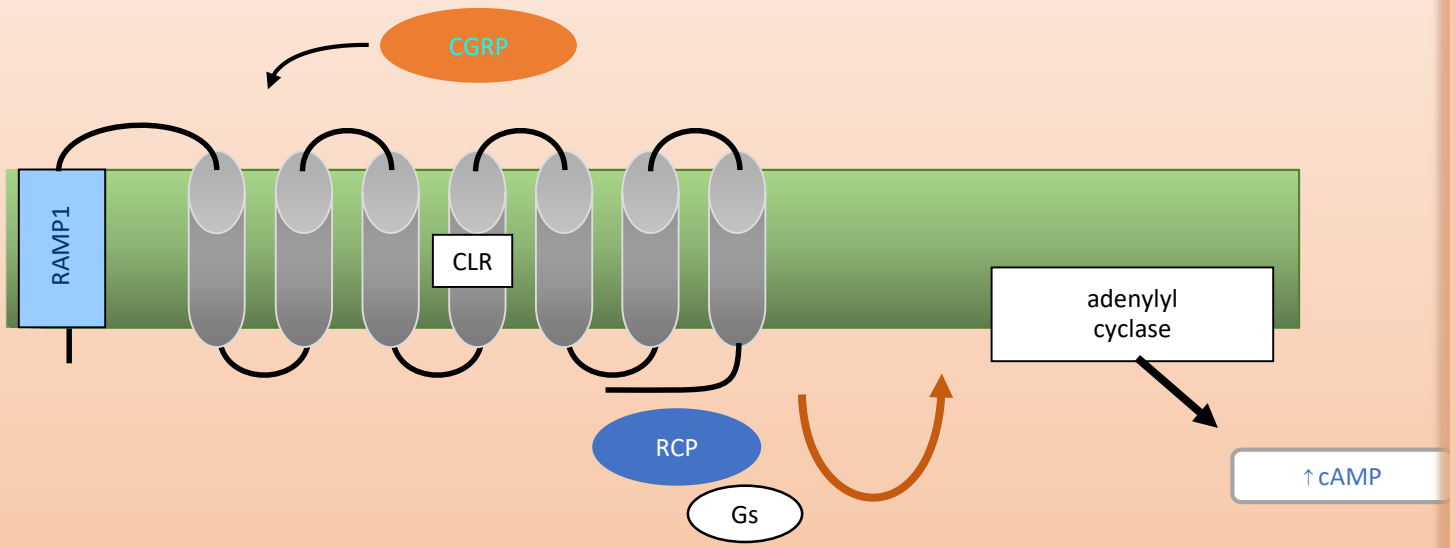




Edvinsson L, Warfvinge K. Cephalalgia 2017; 0(0):1-8 Epub ahead of print. DOI: 10.1177/0333102417726909

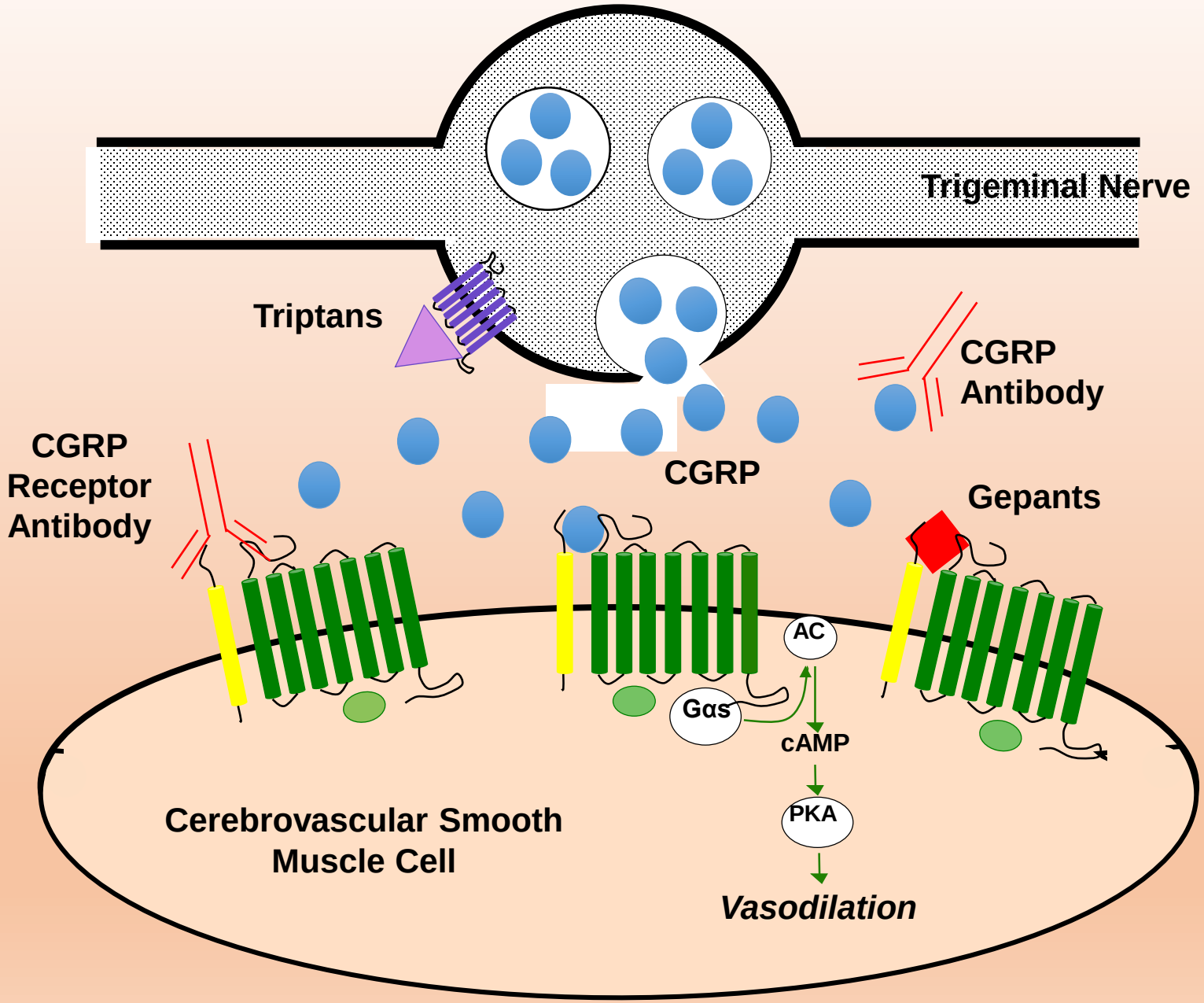
Calcitonin Gene-Related Peptide (CGRP)

- Neuropeptide belonging to calcitonin family
  - CGRP
  - Calcitonin
  - Amylin
  - Adrenomedullin
  - Intermedin
- In humans two forms
  - α-CGRP: 37-amino acid peptide
  - β-CGRP: main isoform of enteric NS; differs in 3 amino acids



CLR, calcitonin receptor-like receptor; NS, nervous system; RAMP, receptor activity modifying protein; RCP, receptor component protein

Sites of effects of specific anti-migraine drugs



Rationale for CGRP modulation

- Released from trigeminovascular afferents
- Potent vasodilator
- Causes perivascular plasma protein extravasation and nociceptive pain
- CGRP levels elevated in migraineurs
  - Migraine-specific triptans block CGRP release
- CGRP induces migraine-like headache in susceptible individuals
- CGRP enhances transmission of pain signals in the CNS

Buchanan T, et al. *Expert Rev Neurotherapeutics* 2004; Edvinsson L. *Expet Opin Ther Targets* 2003; Buzzi MG, et al. *Cephalalgia* 1995; Goadsby PJ, et al. *Ann Neurol* 1988; Edvinsson L, et al. *J Auton Nerv Syst*, 1998; Ashina M, et al. *Pain* 2000.

1st Clinical Paper on CGRP-R Blocker

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

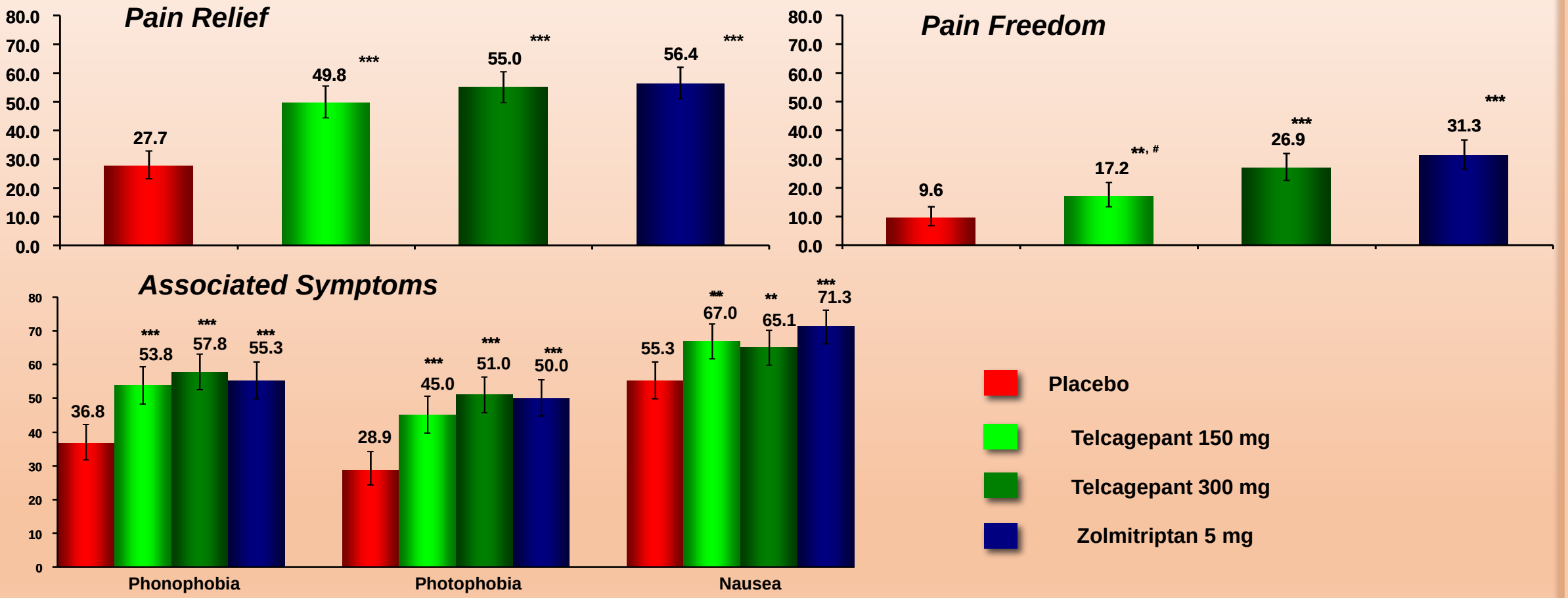
Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D.,
Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D.,
Stephane Pollentier, M.D., and Lynna M. Lesko, M.D.,
for the BIBN 4096 BS Clinical Proof of Concept Study Group

BIBN4096BS (Olcegepant) Phase II Trial

- One phase-II trial (iv preparation)
- Effective in acute migraine vs. placebo
  - 2.5 mg iv
  - 66% 2 hour headache response vs 27% Pl
- AEs: mild paresthesia
- Does not constrict blood vessels

Olesen J, *Cephalalgia* 2003. also *NEJM 2004*
Buchanan T, et al. *Expert Rev Neurotherapeutics* 2004.

MK-0974 (telcagepant) phase 3 clinical data
Primary outcomes @ 2h



$^{**}p<0.010$, $^{***}p<0.001$ for telcagepant-placebo pairwise comparison
$^{\#}p<0.001$ for telcagepant 150 mg-zolmitriptan pairwise comparison

Source. Ho TW et al. *Lancet*. 2008

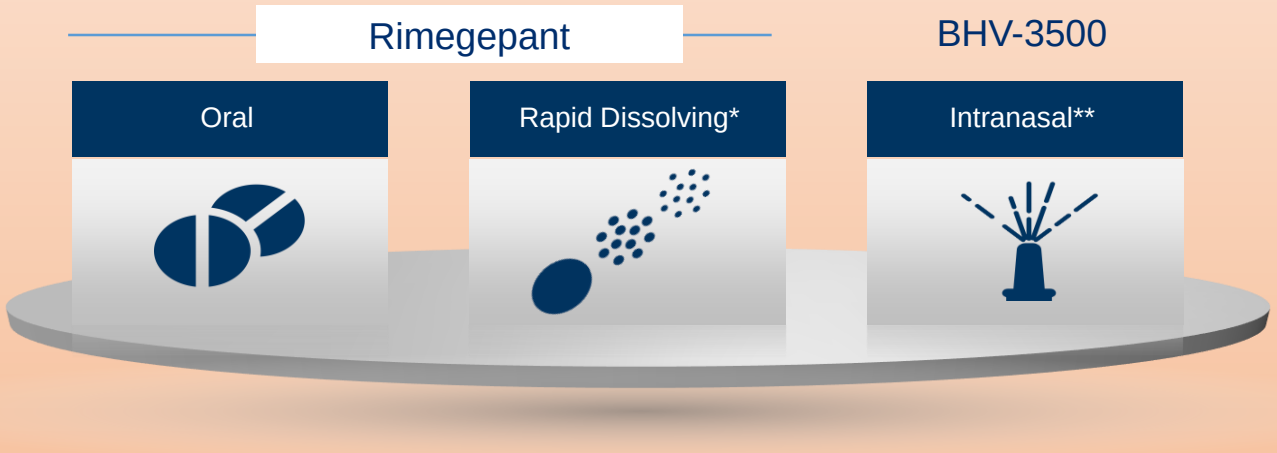
Gepants – Small molecule CGRP Receptor Antagonists

- Olcegepant
- Telcagepant
- Allergan: bought Merck's ubrogepant (formerly MK-1602) for acute care and atogepant (MK-8031) for prevention;
- Biohaven: has rights to BMS's rimegepant for acute care, prevention and via nasal spray

Rimegepant: Multiple Treatments and Formulations **Acute and Preventive Treatment of Migraine**

Rimegepant and BHV-3500 are small molecule CGRP receptor antagonists in development for the acute and preventive treatment of migraine

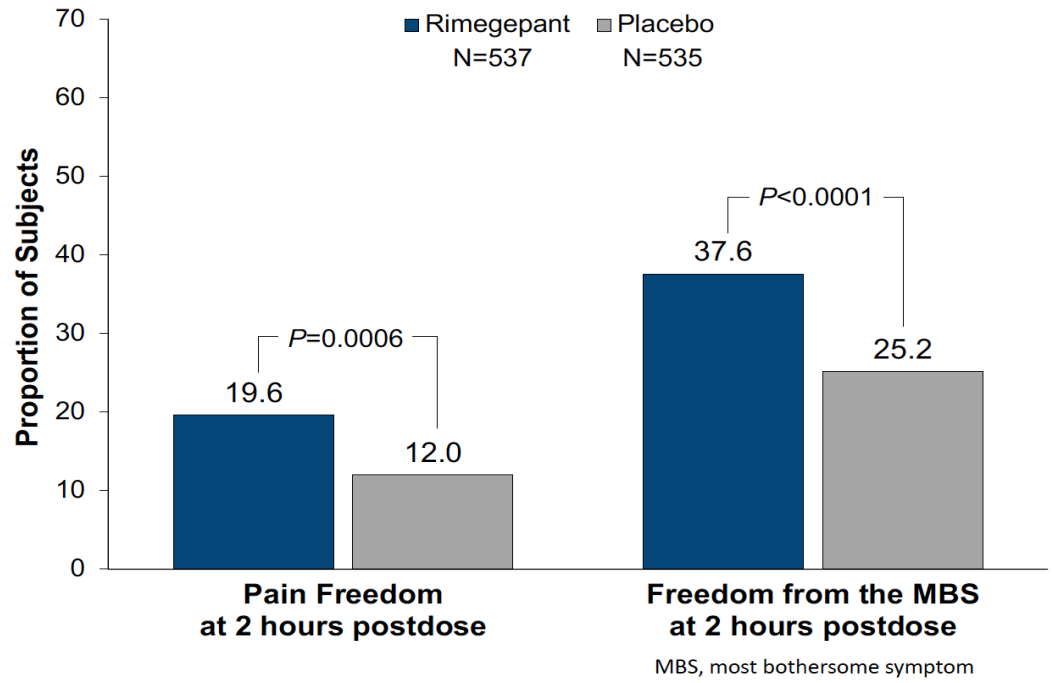
NOJECTION™ Drug Delivery Platform



* Exclusive World-Wide License with Catalent for use of Zydis® Fast Dissolve Technology in our migraine product candidates
** Aptar Pharma Unit-Dose System (UDS) single shot nasal technology

Rimegepant Phase III

Superior to Placebo on Both Coprimary Efficacy Endpoints



MBS, most bothersome symptom

Pooled Adverse Event (AE) Safety Data: Rimegepant was Well Tolerated and Similar to Placebo Across Studies

RIMEGEPANT PHASE 3 – **301**, **302** (75 MG TABLET) & **303** (75 MG ZYDIS ODT)

AEs from Studies 301, 302, and 303 with an incidence ≥ 1%		
Adverse Event	**Rimegepant** n=1771	**Placebo** n=1785
≥ 1 On-Study AE[1]	252 (14.2%)	209 (13.2%)
Nausea	26 (1.5%)	15 (0.8%)
UTI	21 (1.2%)	12 (0.7%)
SAEs[2]	3 (0.2%)	3 (0.2%)

1. No other individual AEs ≥ 1% in rimegepant treated subjects than those listed in table. Includes all AEs without attribution to drug relatedness.
2. No drug-related Serious Adverse Events (SAEs). Two of the subjects with SAE in rimegepant group and one in placebo group had not been dosed before onset of SAE.

BHV-3500: Third Generation CGRP Receptor Antagonist

BHV-3500 HIGHLIGHTS

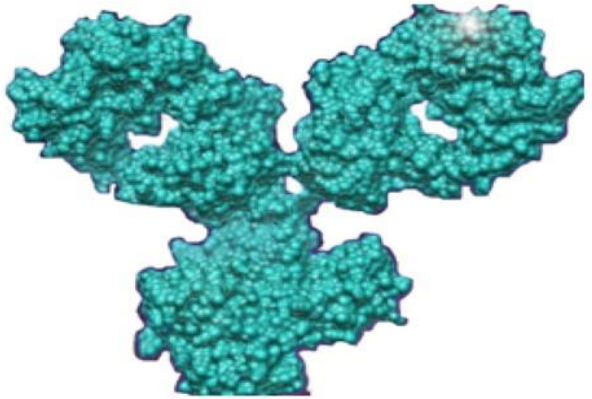
- First intranasal formulation of a small molecule CGRP receptor antagonist
  - Initial development for the acute treatment of migraine
- Favorable safety profile in preclinical studies even at very high doses
- Pursuing development for the acute and preventive treatment of migraine
  - IND submitted 3Q2018 for intranasal
  - Phase 1 study cohorts enrolling and administered BHV-3500

Aptar Pharma Unit-Dose System (UDS) single sho
nasal technology

CGRP
Monoclonal Antibodies

Four mAbs are being actively developed for the preventive treatment of episodic or chronic migraine

mAbs vs Small Molecules



mAbs	Small Molecules
Size ~150 kD	Size <1 kD
Must be injected	Orally administered
Do not enter cells or cross BBB	Many enter cells and cross BBB
Half-life of 1-4 weeks	Half-life of minutes to hours
Manufactured in tissue culture	Chemically synthesized

Carden CP, et al. In: Hidalgo ME, et al. eds. *Cancer Drug Discovery and Development*. 2011.

Key Properties of Antibodies Relevant to Therapy

- Exquisite specificity

  High avidity from two binding sites

- No liver toxicity (broken down in the RE system)
- Long half life (weeks to over one month)
- Large size

  Unique biological activities

  Restricted tissue distribution (does not cross the BBB)

New therapies: Preventive Drugs for Migraine
Four injectable monoclonal antibodies to CGRP

	Amgen erenumab	Alder ALD403 eptinezumab	Lilly/Arteaus galcanezumb	Teva/Labrys fremanezumab
Episodic vs Chronic Migraine	Migraine	Ep Migraine	Mig & CH	Mig & CH
Phase 2 Dosing	Multidose, dose-ranging with OLE	Single dose l level	Single dose level	Multi-dose, Dose-ranging
Phase 2 Administration	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous Prefilled syringe
Phase 2 Dosing Frequency	Monthly	Quarterly	Monthly	Monthly or Quarterly
Target (peripheral)	CGRP receptor	CGRP peptide	CGRP peptide	CGRP peptide

State of the mAbs

- Erenumab-aooe (Aimovig) 70 or 140 mg, monthly in autoinjectors launched May 17th, 2018
    - Supply-chain issues, unanticipated demand, and poor preparation by manufacturers, payors and providers led to major challenges.
- Fremanezumab-vfrm (Ajovy) 225 mg monthly or 675 mg quarterly in prefilled syringes, launched September 16, 2018
- Galcanezumab-gnlm (Emgality) 120 or 240 mg monthly in autoinjectors, launched September 27, 2018

- By Deccember, an estimated 250,000 patients had tried the mAbs
    - 500,000 prescriptions had been written, almost all of which were for free samples

- In December, new scripts distributed as about 50% Aimovig, 30% Ajovy, and 20% Emgality per industry watchers
- In SWEDEN; on prescription since summer 2018, TLV approved “högkostnads rabbatt” 1/1 2019 for CM and by Neurologist/Headache specialist.

mAb Adverse Events

- Erenumab: Injection site reactions, constipation and cramping
- Fremanezumab: Injection site reactions, hypersensitivity reactions
- Galcanezumab: Injection site reactions, dizziness

Theoretical Concerns About Blocking CGRP

- Involved with skin blushing, flushing, cold sensitivity, itch, edema, and thermoregulation. After surgery, or serious burn, healing may be impaired mAbs
- Involved in bone metabolism and bone healing
- Involved in GI motility, and in protecting the gastric mucosa. Constipation and diarrhea may occur with CGRP antagonism
- Severe fatigue reported with CGRP mAbs. CGRP inhibits platelet aggregation. Blocking may impede or diminish recovery after ischemia.

Two Early Concerns on Safety

1. Will there be liver toxicity? Was the problem with gepants mechanism based?

- **So far, LFT abnormalities have not been seen in excess of placebo for Gepants or mAb to CGRP or receptor**

2. Will losing CGRP or its receptor result in loss of compensatory vasodilation/homeostatic cardioprotective mechanisms necessary to prevent stroke or infarction in the setting of ischemia?

MaassenVanDenBrink et al. *Trends Pharmacol Sci*. 2016;37:779-88.

Bigger, more rigorous study: Intravenous erenumab did not make angina worse

- Double-blind, placebo-controlled study in patients with stable angina due to documented coronary artery disease
- Study designed to test whether erenumab would worsen stress-induced myocardial ischemia in patients with stable angina and ≥ one angina episodes per month

Mikol et al. Presented at IHC Vancouver 2017.
Depre et al. IHC Abstract, Vancouver 2017.

Erenumab angina study

- Then, they were randomized 1:1 (44 patients in each arm, N=88) to *intravenous* erenumab 140 mg or placebo
- In practice, erenumab is administered subcut, but IV gives an instant Cmax
- A ***third***, post-administration ETT was then conducted
- No difference in:
  - Change from baseline in exercise duration as measured by TET
  - Time to onset of ≥ 1 mm ST-segment depression
  - Time to onset of exercise-induced angina during the ETT
- No infarctions, no evidence for failure of compensatory mechanisms

Mikol et al. Presented at IHC Vancouver 2017.
Depre et al. IHC Abstract, Vancouver 2017.

Will the mAbs be an improvement?

Significant problems with older prevention

- On the optimal dose of preventive medication (beta blockers, AEDs or antidepressants) for at least 2-3 months, the likelihood of having ≥50% reduction in headache days/month is ≈45%

- The problems currently include poor efficacy, lack of specificity, significant adverse events, very poor adherence and 2-3 months to achieve benefit

- When we start a patient on older preventive, 83% are off of it in one year

Hepp et al. *Cephalalgia*. 2015;35:478-488.

Efficacy of the 4 MABs

- All data announced to date for EM and CM have shown a reduction in mean monthly migraine days (MMDs) with a magnitude of 1-3 days drop over placebo, similar to the registration studies for onabotulinumtoxinA
- Using MMDs is necessary from a regulatory standpoint
- However, MMDs are not a useful clinical endpoint for estimating value, as the clinical effect is underestimated due to inclusion of placebo
- More useful is the decrease from baseline and the secondary endpoints, such as 50 and 75% responder rates

Clinical Utility of the 4 MABs

- Erenumab in CM prevention, a 6.7 day reduction in MMDs found in the pivotal trial, which would represent 79 fewer migraine days per year[1]
- The *≥50% responder rates* (secondary endpoint) for erenumab in the EM registration studies were ≥50%, and *the 75% responder rates for fremanezumab are about 21%*
- All 4 mAbs work in CM prevention with medication overuse (pre-specified secondary analysis)[3]
- Erenumab worked better in patients who had failed ≥2 preventive meds vs none, odds ratio 4.18 vs 1.33 (pre-specified secondary analysis)[4]

1. Tepper et al. *Lancet Neurol* 2017;16:425–434.
2. Skljarevski et al. AHS meeting June 2017.
3. Tepper et al EP-01-013, E-poster presentation, Sept 8, 2017.
4. Ashina et al. PO-01-180. IHC, Sept 2017.

Clinical Utility of the 4 MABs

- Fremanezumab showed improvements in all migraine associated symptoms of nausea, photophobia, and phonophobia in <1 week (post hoc analysis)[1]
- Eptinezumab IV given quarterly showed a very significant and clinically meaningful reduction of the number of patients with migraine attacks in the first day of treatment of EM prevention (post hoc analysis)[2,3]
- Fremanezumab was equally effective in preventing EM and CM whether administered subcutaneously monthly or quarterly (primary endpoints)[4]
- Erenumab was equally effective in preventing chronic migraine with and without aura (post hoc analysis)[5]

1. Aycardi et al. PO-01-082, IHC, Sept 2017.
2. Goadsby et al. EP-01-019, IHC Sept 2017.
3. Cady et al. PO-01-199, IHC Sept 2017.
4. Dodick et al. PO-01-201, IHC, Sept 2017.
5. Ashina et al. EP-01-014, E-poster presentation, IHC, Sept 2017.

What about switching between mAbs and using 2 different antibodies?

- No data available regarding the safety and efficacy of switching among CGRP mAbs
- Experience shows that most of those who stopped erenumab due to lack of efficacy or AEs, did respond to fremaneumab, without AEs
- In rheumatoid arthritis where mAbs have been available for an extended period of time, the safety and efficacy of switching due to tolerability or efficacy among biologics in the same class is well-established
- Trials in patients with rheumatoid arthritis ranging from 6-24 months in length suggest similar safety profile when switching occurs with or without a washout
- Patients on an antibody for RA can be started on an anti CGRP mAb
- Patients on onabotulinumtoxinA can be started on an anti CGRP mAb and often show improvement

How could this change the future?

Current situation

Current preventive medications:

- were designed for other therapeutic areas
- have numerous adverse events
- takes 2-4 months to be effective
- have ≥50% responder rates of <50%
- may lose effectiveness in MOH
- sometimes don't even lower acute medication use

Future potential for MABs

- Specificity: designed for primary migraine prevention
- wide therapeutic targets: EM, CM, MOH, ?TACs
- Speed: time to onset is <1 week to one month
- Tolerability: similar to placebo
- Safety: no safety signals
- Improved responder rates, even at ≥ 75% or more
- Lower acute med use

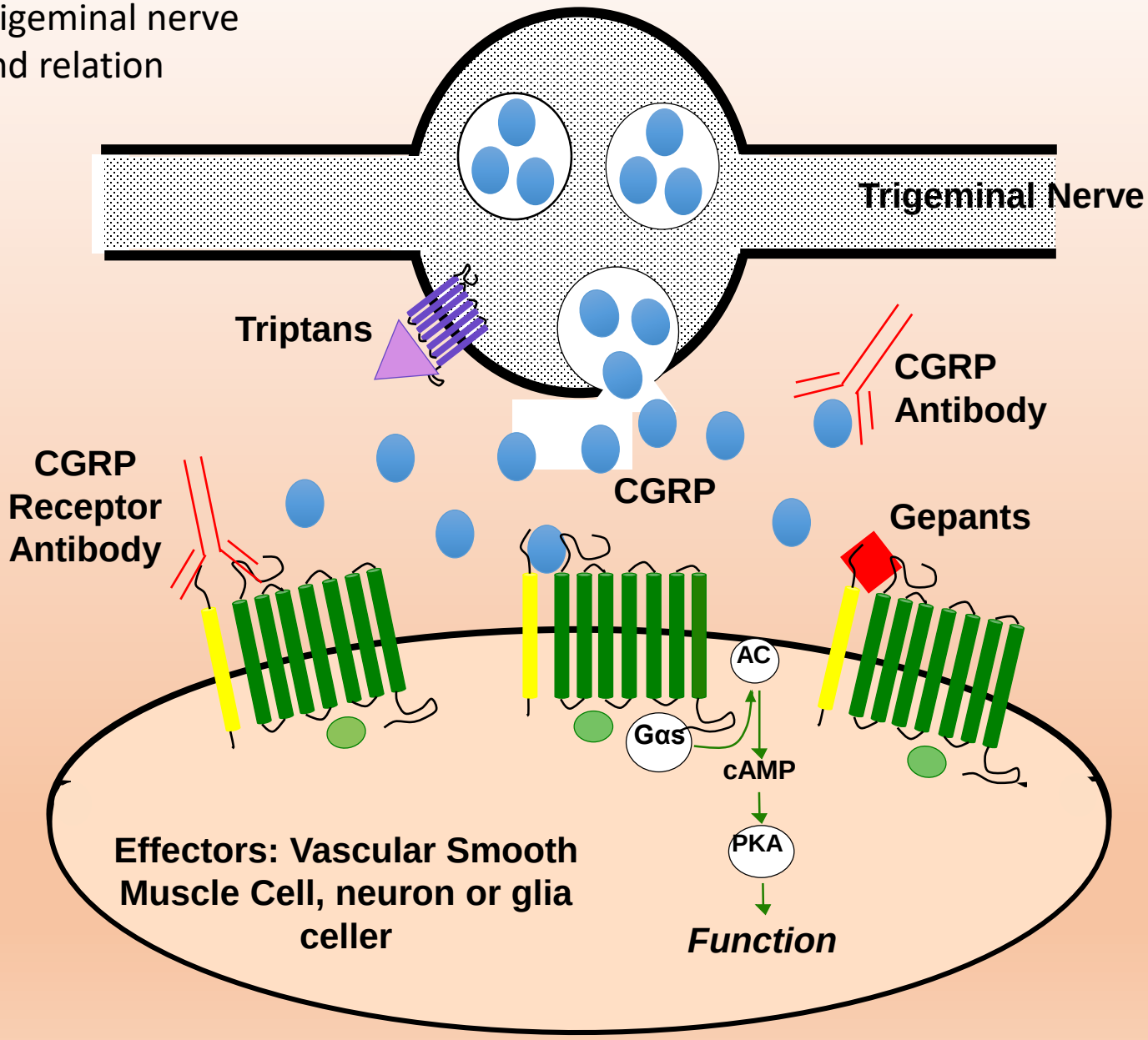
If current safety is confirmed, one could potentially use these specific preventive biologics first line

The potential for this paradigm shift will depend on cost and access!

Conclusions

- *CGRP small molecule receptor antagonists (gepants) +*
- *mAbs to CGRP or its receptor appear to be promising new treatments with few AEs and rapid action*
- *The gepants are tablets, some for acute care and/or prevention*
- *The monoclonal antibodies are SC injections given monthly or quarterly for prevention. One is given IV*
- *They have few adverse events, no contraindications and work when other medications have failed*
- *The 50 % responder rates are about 50% or more*

Trigeminal nerve and relation



Small molecule CGRP-r antagonists:

Ubro-, Rimegepant, Atogepant,

mAbs binding to CGRP:

Galcanezumab (LY2951742)

Eptinezumab (ALD403)

Fremanezumab (TEV-48125)

mAbs binding to the CGRP receptor:

Erenumab (AMG334)

Thanks for your attention!

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