



An industry perspective on biomarker-based drug discovery

Advancing Therapeutic Development for Pain and Opioid Use
Disorders through Public-Private Partnerships: A Workshop

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Lilly

Disclosures

- ◆ The speaker is a full-time employee of Eli Lilly and Company
- ◆ The views expressed in this discussion are those of the speaker and do not represent the views of Eli Lilly and Company
- ◆ Galcanezumab (LY2951742) is a CGRP neutralizing antibody currently under clinical development by Eli Lilly and Company for the treatment of migraine and cluster headache

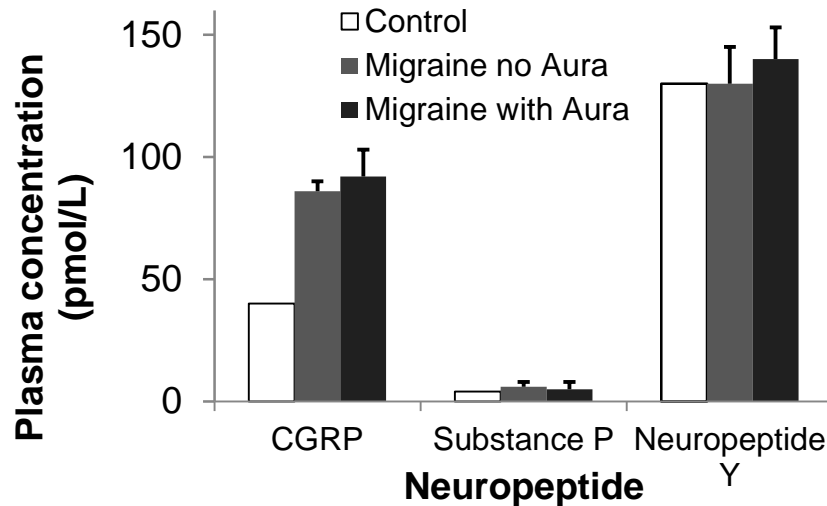
Overview



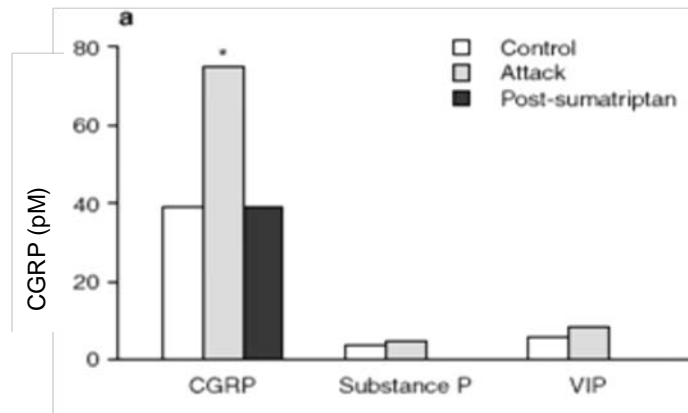
- ◆ A story of biomarker-based development
 - CGRP (calcitonin gene-related peptide) and migraine
 - CGRP antagonists and clinical activity
 - Target engagement and clinical efficacy
- ◆ Key enablers of biomarker-based discovery
 - Biomarker assay development
 - Biomarker association with disease state
 - Biomarkers confirming target engagement

Biomarker Association with Disease

Plasma CGRP associates with migraine attacks and human migraine model



Goadsby et al, *Ann Neurol* 1990;28:183 with permission



Edvinsson, *CNS Drugs* 2001;15:745 with permission

Table 2. MA patients and controls reporting headache and migraine-like attacks after CGRP*

Attack	MA patients	Controls	p value
Migraine-like attacks (post-infusion phase I–13 hours)	8/14	0/11	.003
Headache (infusion phase 0–60 min)	11/14	7/11	.65
Headache (post-infusion phase I–13 hours)	12/14	2/11	.001

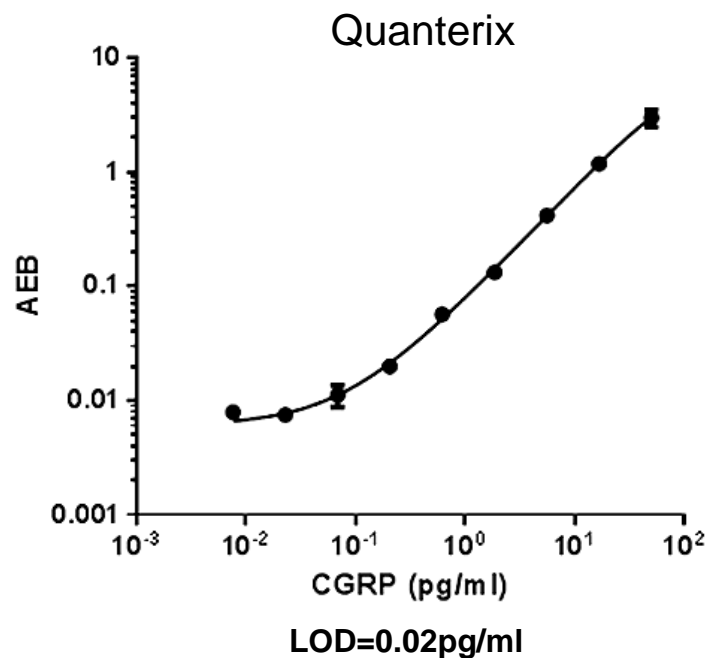
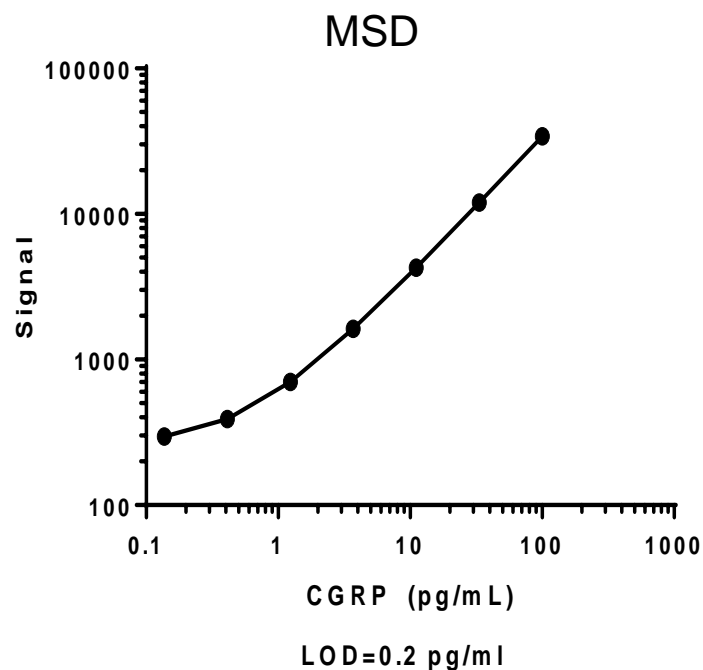
MA = migraine with aura; CGRP = calcitonin gene-related peptide.

*Groups compared with Fisher's exact test.

Hansen et al, *Cephalalgia* 2010;30:1179 with permission

Bioassay Development and Validation

CGRP Assays using Meso Scale Discovery and Quanterix Platforms



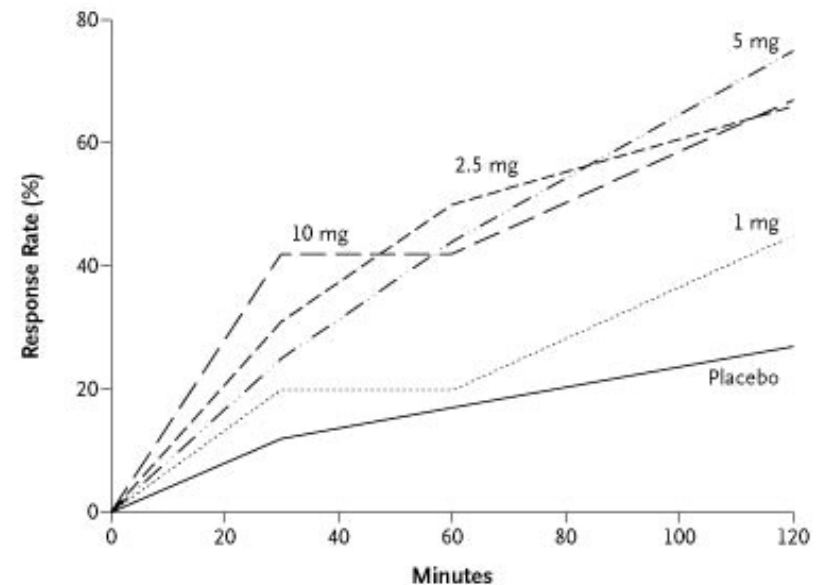
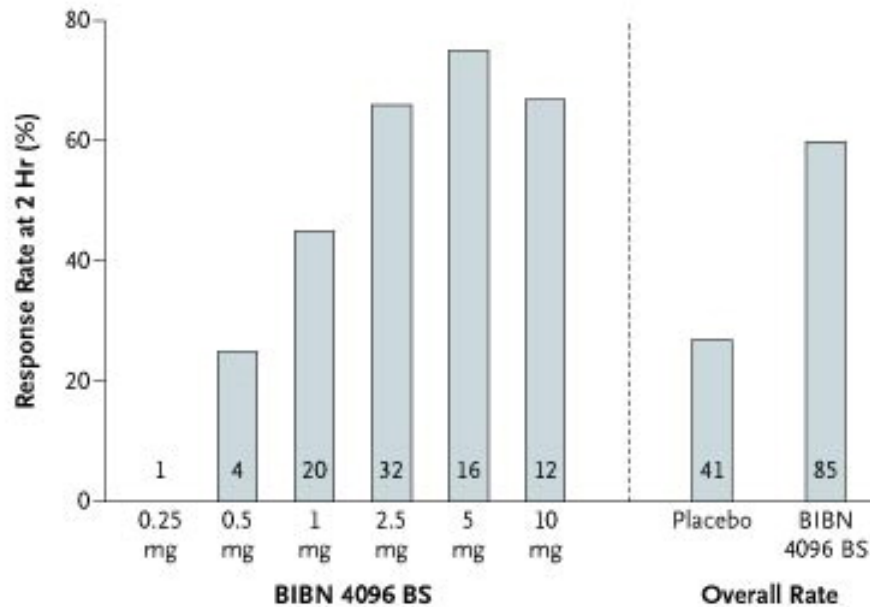
Key validation properties of a CGRP assay

- **Sensitivity** at physiological levels
- Verified in tissues/collection media
- Dilutional linearity
- **Specificity** by immunodepletion
- Spike recovery

Chai et al *American Headache Society* 2016

CGRP antagonist: migraine abortive

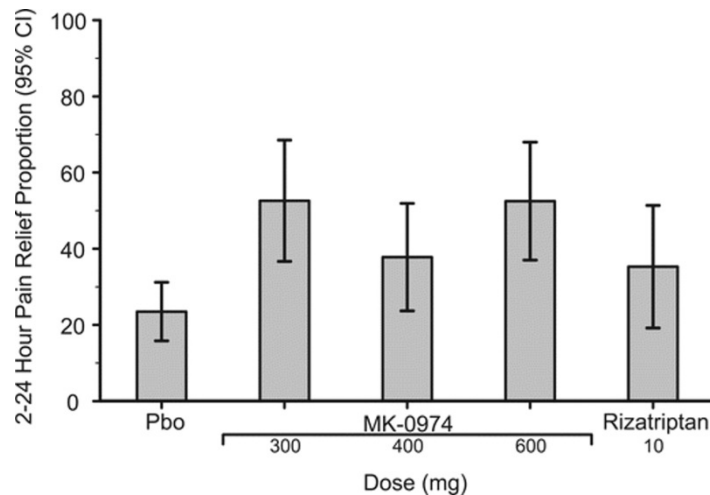
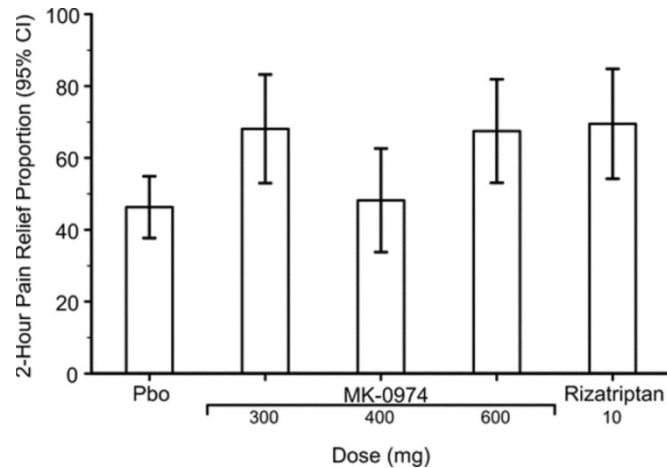
Ocegepant (BIBN4096BS) IV



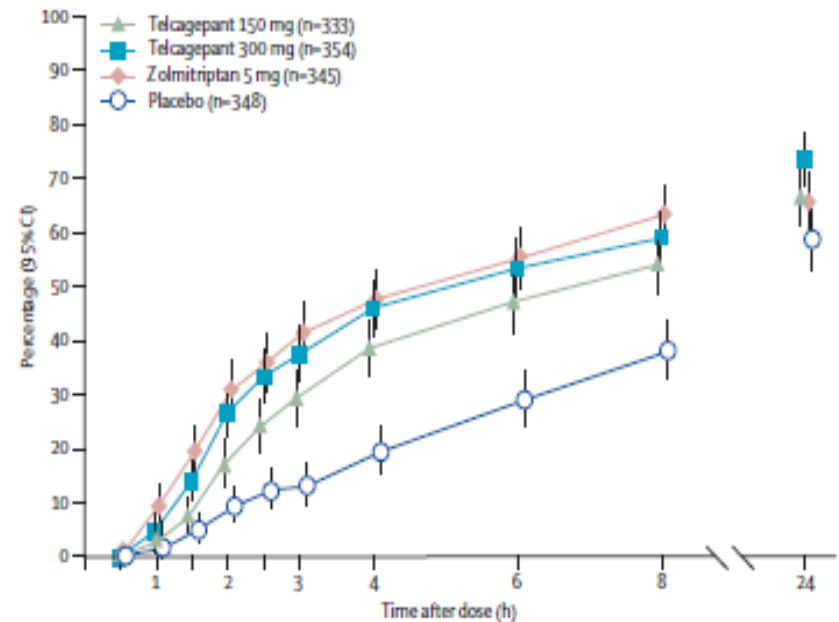
Olesen et al, *NEJM* 2004 with permission

CGRP antagonist: migraine abortive

Telcagepant (MK-0974)

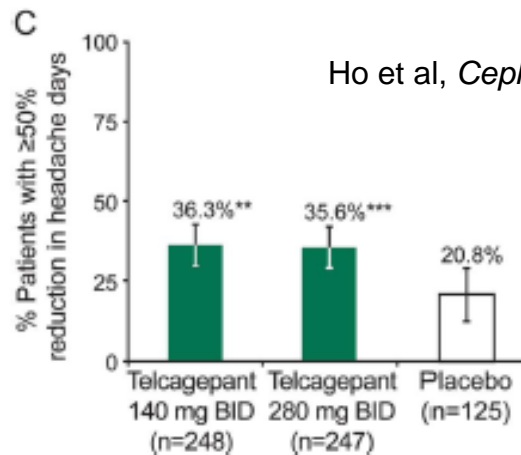
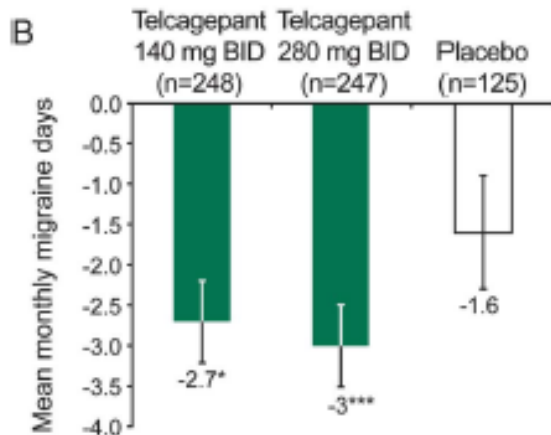
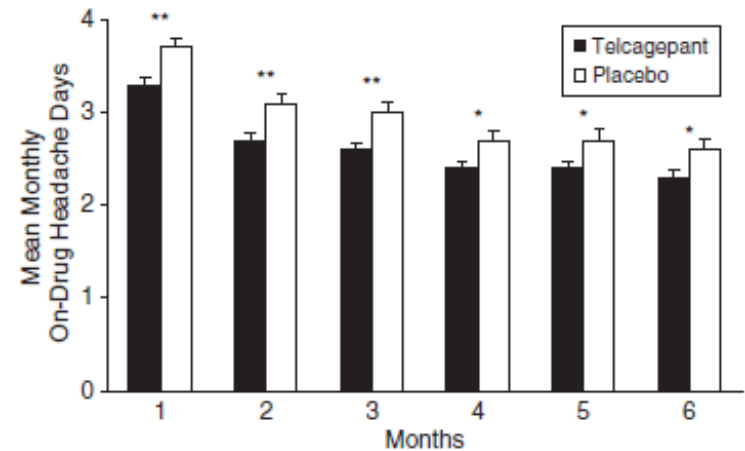
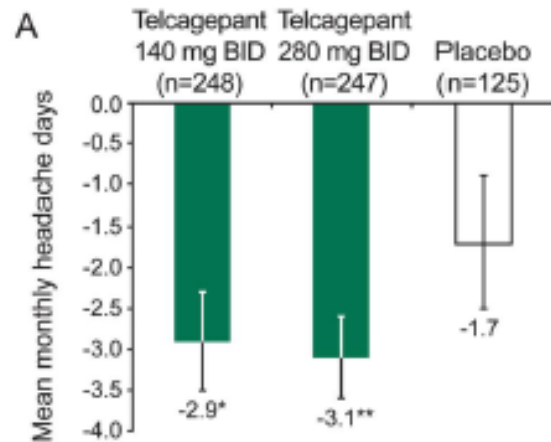


Ho et al, *Neurology* 2008, with permission



Ho et al, *Lancet* 2008, with permission

CGRP antagonist: migraine prevention



(A-C) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

Ho et al, *Neurology* 2014 with permission

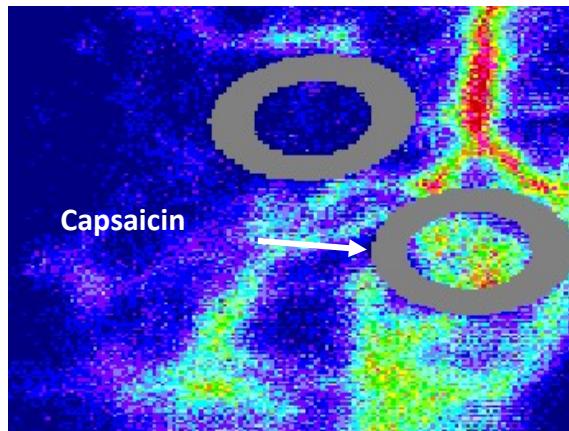
Ho et al, *Cephalalgia* 2016 with permission

Biomarker of peripheral target engagement

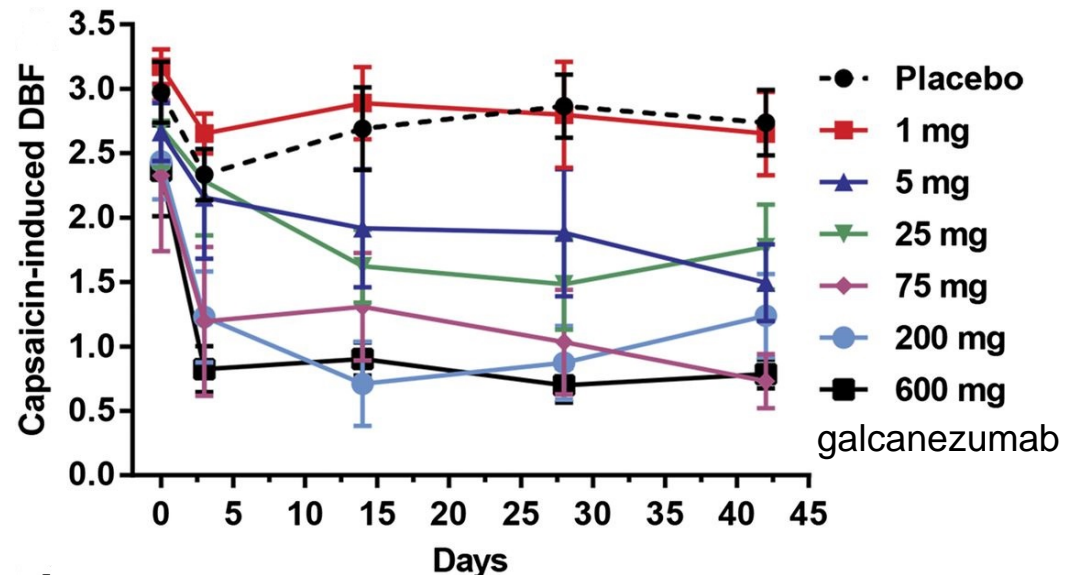
CGRP blockade inhibits capsaicin-induced dermal blood flow,
Sets nominal CGRP-inhibitory activity required for peripheral activity



Sinclair et al, *BJCP* 2010;69:15 with permission



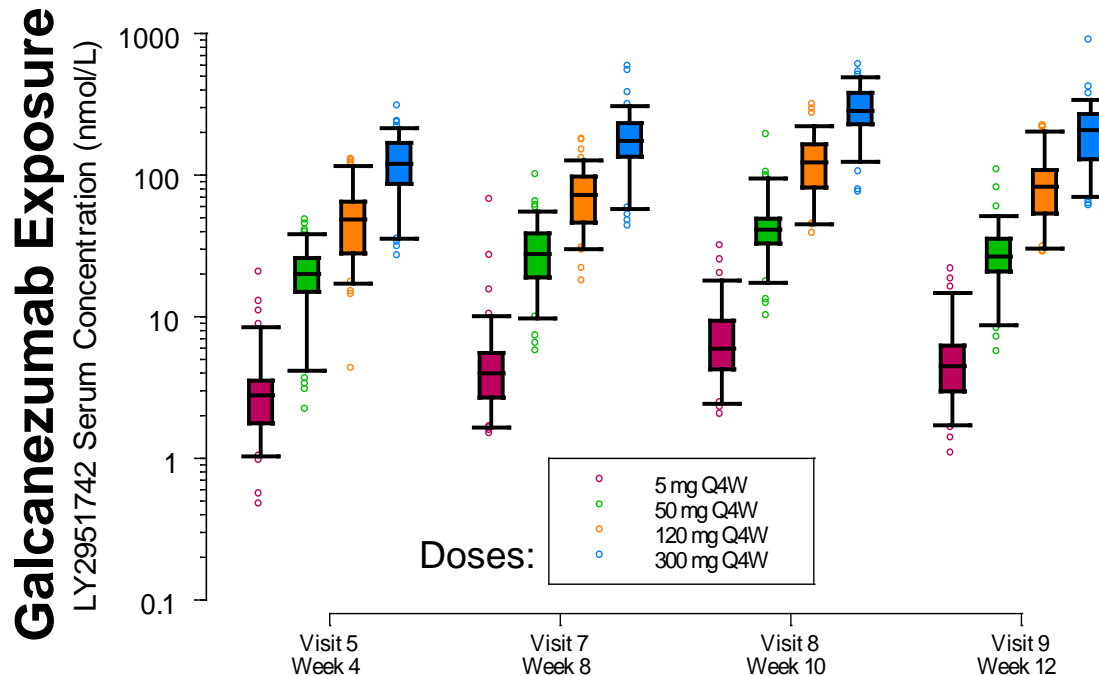
Eli Lilly and Company, data on file



Vermeersch et al, *JPET* 2015 with permission

Dose-Exposure Relationship

Monthly doses of galcanezumab 5, 50, 120 and 300 mg SC

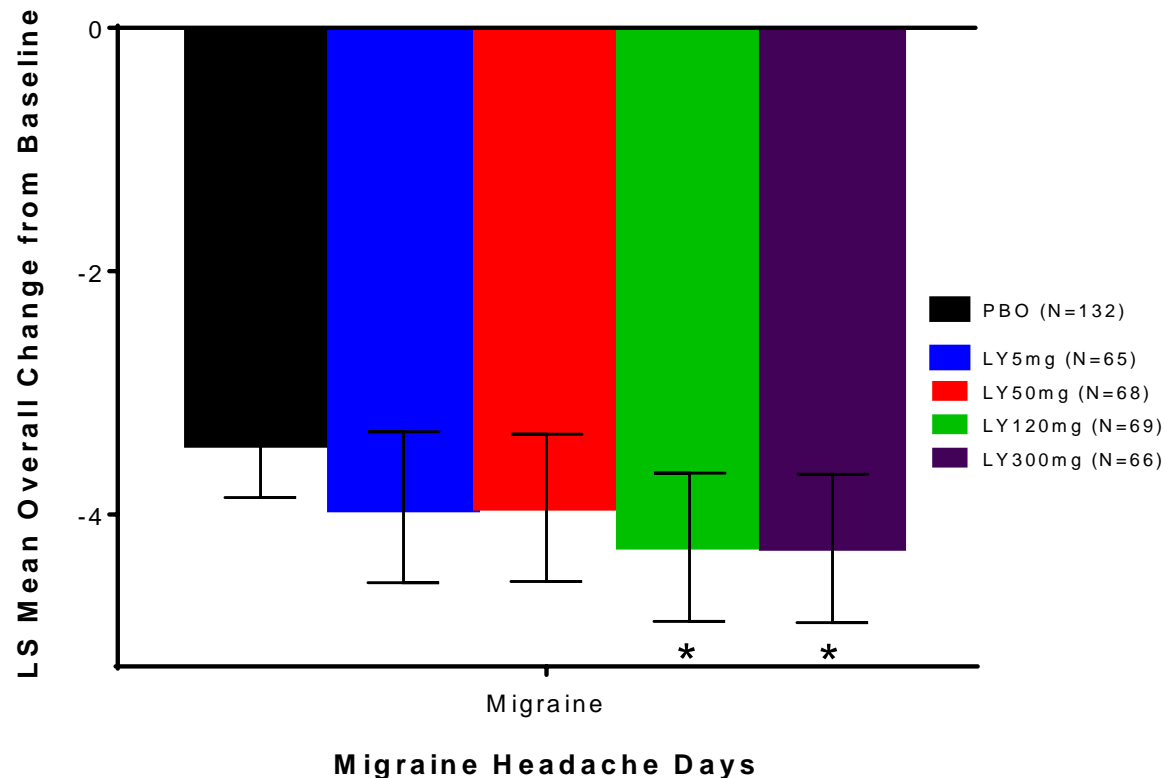


Note: The middle line in each box plot represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; data points outside the whiskers represent the points beyond the percentiles.

*Weeks 4, 8, and 12 collected at 4 weeks post-dose (trough level).
Week 10 collected at mid-point of the dosing interval, at 2 weeks after the last dose (peak level)*

CGRP antibodies: migraine prevention

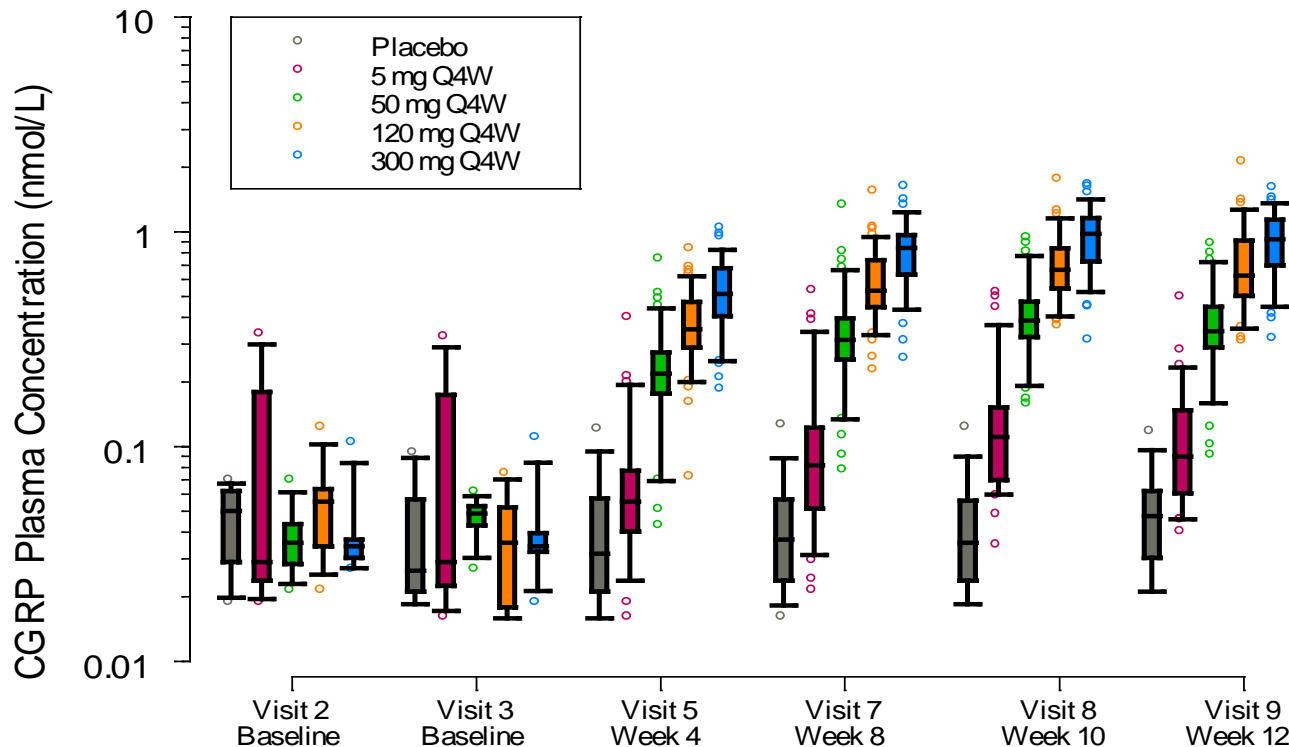
Galcanezumab reduces monthly migraine headache days



Skjarevski et al, *Japanese Headache Society* 2015

CGRP Bioassay Demonstrates Target Engagement

CGRP concentrations rise after 5, 50, 120, and 300 mg SC

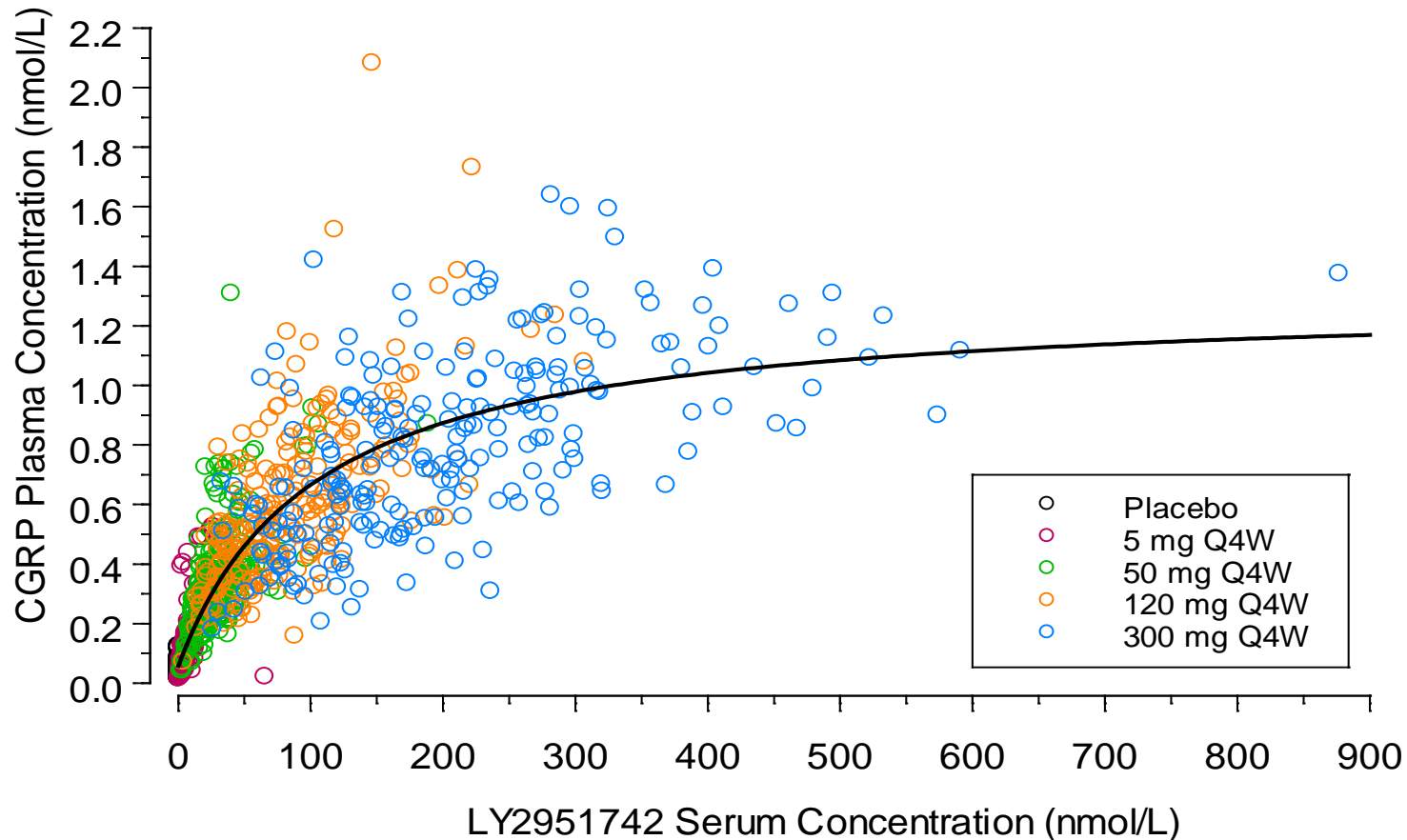


Note: The middle line in each box plot represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; data points outside the whiskers represent the points beyond the percentiles.

Using a **drug-tolerant assay**, baseline (pre-dose) CGRP concentrations were assessed at Visit 2 and Visit 3. Weeks 4, 8, and 12 collected at 4 weeks post-dose. Week 10 collected at mid-point of the dosing interval, at 2 weeks after the last dose. (Excludes measures below limit of assay quantification)

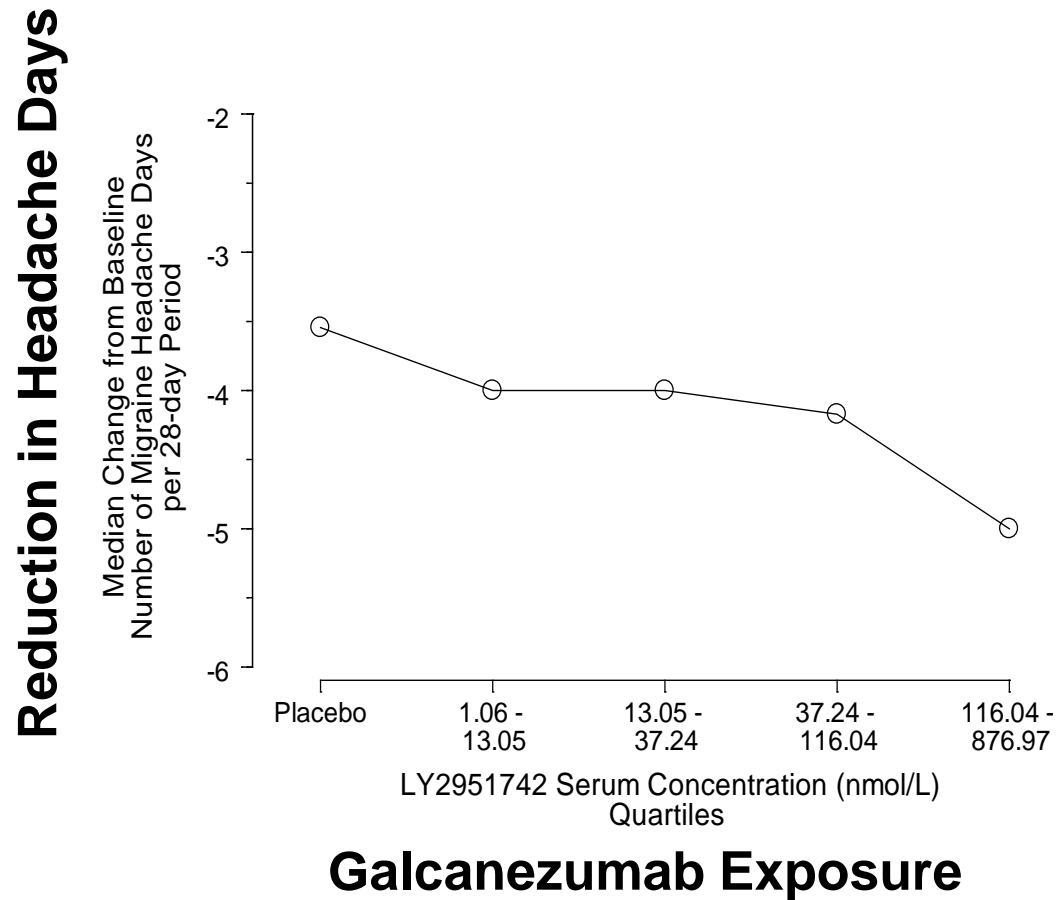
Drug Exposure-Biomarker Relationships

Plasma CGRP levels plateau under an excess of galcanezumab



Exposure-Efficacy Relationships

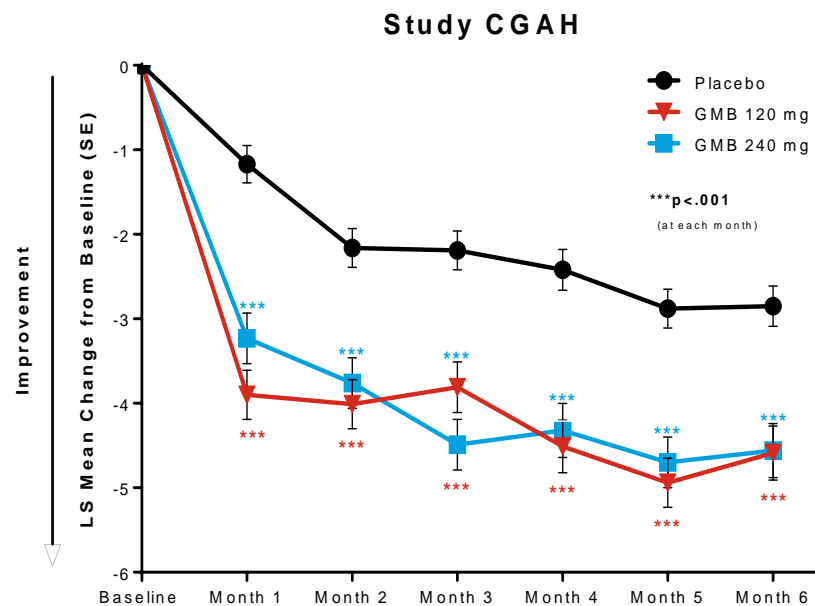
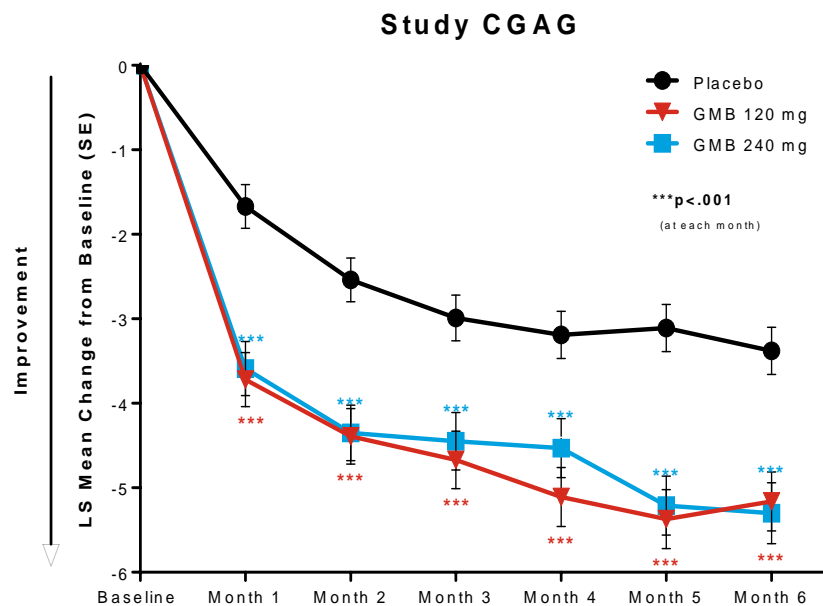
Galcanezumab exposure vs reduction in migraine headache days



Kielbasa et al, *Amer Acad Neurol* 2016

Study CGAG vs. CGAH

Mean Change in Monthly MHD

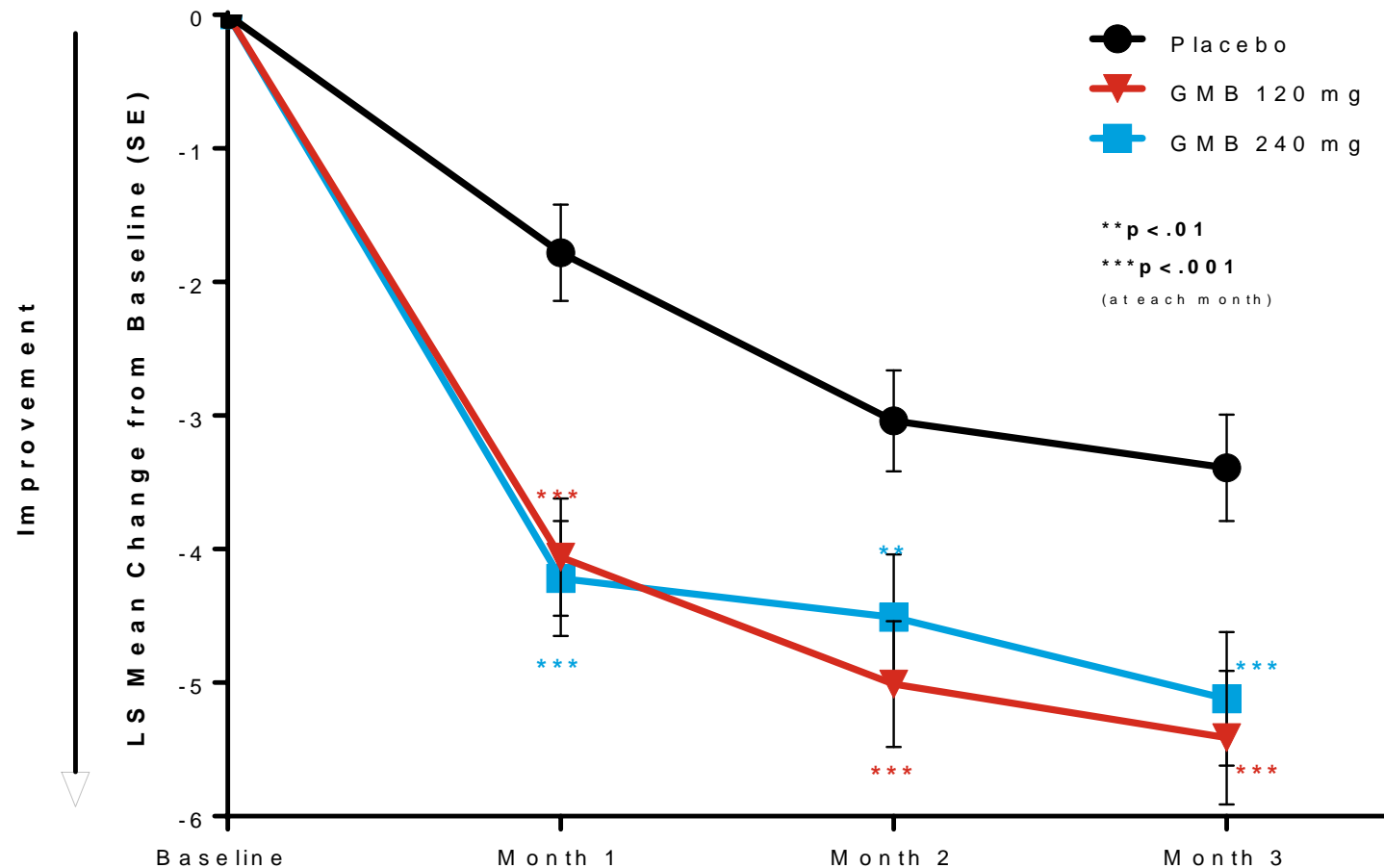


Abbreviations: GMB=galcanezumab; LS=least square; MHD=migraine headache days; SE=standard error
Note: not statistically significant between GMB doses at any month

Skjarevski et al, *American Headache Society* 2017
Stauffer et al, *American Headache Society* 2017

Study CGAI

Mean Change in Monthly MHD



Note: not statistically significant between GMB doses at any month

Detke et al, *American Headache Society* 2017

Questions and Next Steps



- ◆ Specific questions for CGRP biomarkers
 - Tailoring and prediction of individual response
 - Therapeutic hypothesis for other clinical conditions
 - CGRP receptor availability in clinical conditions
- ◆ Key enablers of biomarker-based pain therapies
 - Biomarker assay development/validation
 - Biomarker association with clinical conditions
 - Relationship between biomarker and disease state (ictal/interictal, acute/chronic, clinical subtypes)
 - Biomarkers of target engagement