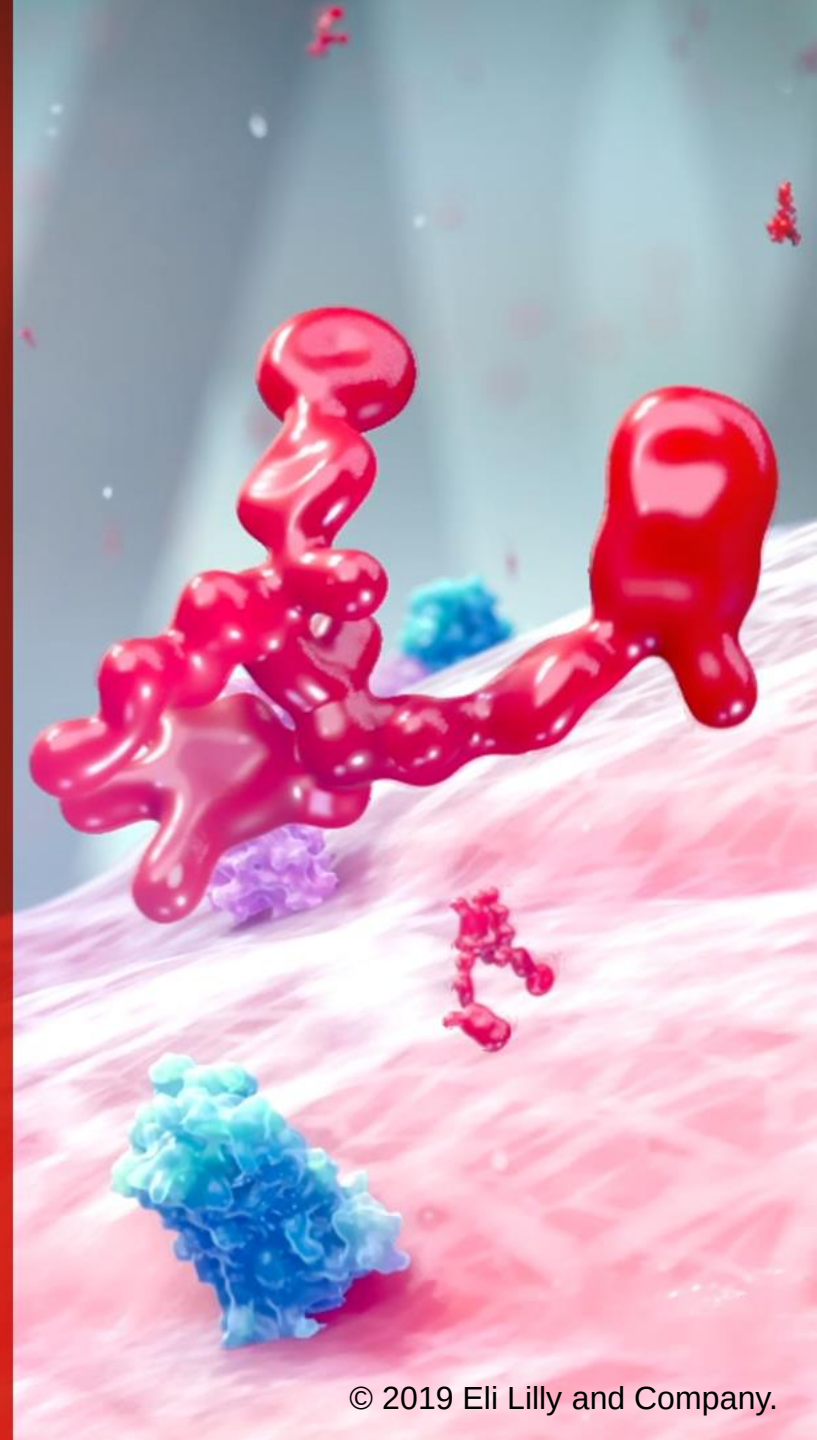
Preventing Migraine: The Mechanism of Action of Galcanezumab



Objectives

1. Migraine: Burden of Disease
2. CGRP and Migraine
3. Understanding Galcanezumab

Migraine: Burden of Disease

What Is Migraine?

A common debilitating neurological disease that affects ~12% (over 1 billion) of the world population[1-3]

Women are affected 3x more than men

- It is associated with recurrent headaches that can range in severity[4,5]
- Patients with migraine can exhibit other neurological symptoms, including visual aura, nausea, phonophobia, and photophobia[5,6]

References: 1. GBD 2016. *Lancet*. 2017;390(10100):1211-1259. 2. Steiner TJ, Stovner LJ, Birbeck GL. *J Headache Pain*. 2013;14:1. 3. Woldeamanuel YW, Cowan RP. *J Neurol Sci*. 2017;372:307-315. 4. World Health Organization. http://www.who.int/mental_health/management/who_atlas_headache_disorders.pdf. Accessed May 21, 2017. 5. Goadsby PJ, Holland PR, Martins-Oliveira M, et al. *Physiol Rev*. 2017;97(2):553-622. 6. Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38(1):1-211.

ICHD-3 Diagnostic Criteria: Migraine

Without Aura

A. At least five attacks fulfilling criteria B–D

B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

With Aura

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least three of the following six characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5–60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis

Reference: Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018; 38(1):1-211.

Migraine:
A Tremendous Burden

- Migraine has a complex clinical presentation that can vary widely from person to person[1]
  - Variable headache frequency and severity
  - Variable symptoms and severity of symptoms

- Migraine prevalence peaks during the most productive working years and can have substantial burden on the individual and workforce[2]
  - Indirect costs due to increased absenteeism and reduced productivity at work

References: 1. D'Amico D, Solari A, Usai S, et al. *Cephalalgia*. 2006;26(6):691-696. 2. Landy SH, Runken MC, Bell CF, et al. *J Occup Environ Med.* 2011;53(1):74-81.

Migraine:
An Unmet Need

~40% **of patients with migraine worldwide are professionally diagnosed[1]**

Only 12.4% **of respondents in the 2004 AMPP survey who were diagnosed with migraine were on preventive medication[2]**

- Despite almost 40% of patients being eligible for preventive medication[3]

<50% **of patients will remain on their prescribed preventive treatment[4]**

- Decreased efficacy and adverse reactions were the main reasons for discontinuation[5]

References: 1. World Health Organization. http://www.who.int/mental_health/management/who_atlas_headache_disorders.pdf. Accessed May 21, 2017. 2. Diamond S, Bigal ME, Silberstein S, et al. *Headache*. 2007;47(3):355-363. 3. Lipton RB, Bigal ME, Diamond M, et al; AMPP Advisory Group. *Neurology*. 2007;68(5):343-349. 4. Pike J, Mutebi A, Shah N, et al. *Value Health*. 2016;19:(3)A1-A23. 5. Blumenfeld AM, Bloudek LM, Becker WJ. *Headache*. 2013;53(4):644-655.

Calcitonin Gene-Related Peptide (CGRP) and Migraine

What Is CGRP?

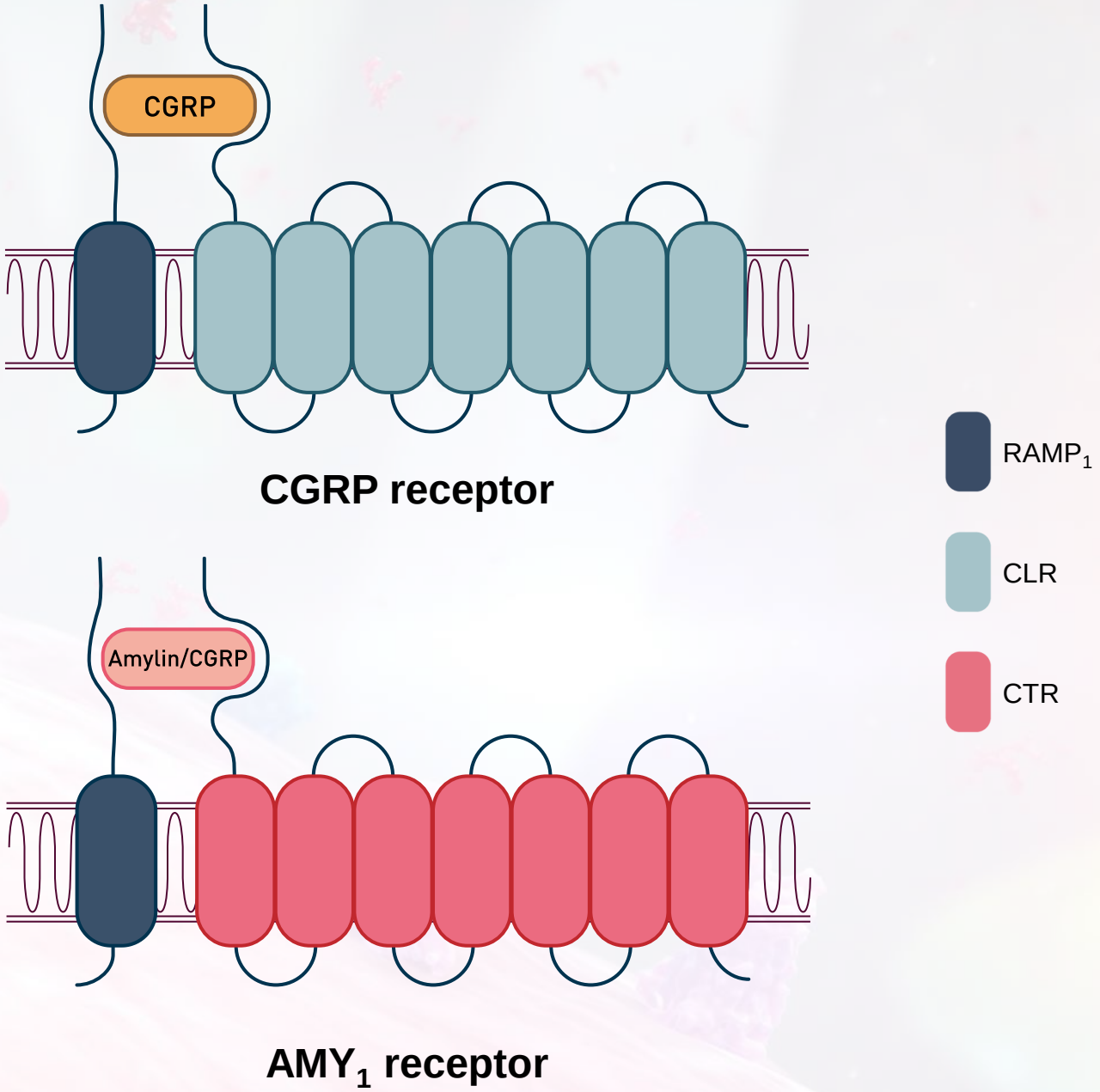
- Calcitonin gene-related peptide, or CGRP, is a small (~37 amino acid) neuropeptide with a wide distribution in both peripheral and central nervous systems[1-3]
- CGRP is one of the most abundant neuropeptides in the trigeminovascular system[1]
  - CGRP is expressed in approximately 50% of neurons in the trigeminal ganglia[4]
- Along with other neuropeptides and neurotransmitters, CGRP is released during a migraine attack and leads to:[1,2]
  - Activation of meningeal nociceptors
  - Vasodilation
  - Neurogenic inflammation

References: 1. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533-552. 2. Durham PL. *Headache*. 2006;46(suppl 1):S3-8. 3. Arulmani U, Maassenvandenbrink A, Villalon CM, et al. *Eur J Pharmacol*. 2004;500(1-3):315-330. 4. Eftekhari S, Salvatore CA, Calamari A, et al. *Neuroscience*. 2010;169(2):683-696.

CGRP Can Activate CGRP and AMY_1 Receptors[1,2]

- The CGRP receptor is made up of CLR and $RAMP_1$ subunits
- It binds with high affinity to CGRP and has important roles in migraine
- CGRP can also activate the amylin 1 (AMY_1) receptor with an affinity that is similar to amylin
  - AMY_1 is made up of $RAMP_1$ and CTR subunits
  - The role of the AMY_1 receptor in migraine is not completely understood

CLR=calcitonin receptor-like receptor; CTR=calcitonin receptor; $RAMP_1$=receptor activity modifying protein 1.



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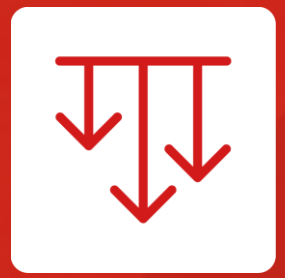
CGRP in Migraine

- Increased CGRP levels correlate with onset and pain intensity in migraine attacks[1,2]
- Infusion of CGRP has been shown to induce migraine-like attacks in susceptible patients[1,3,4]



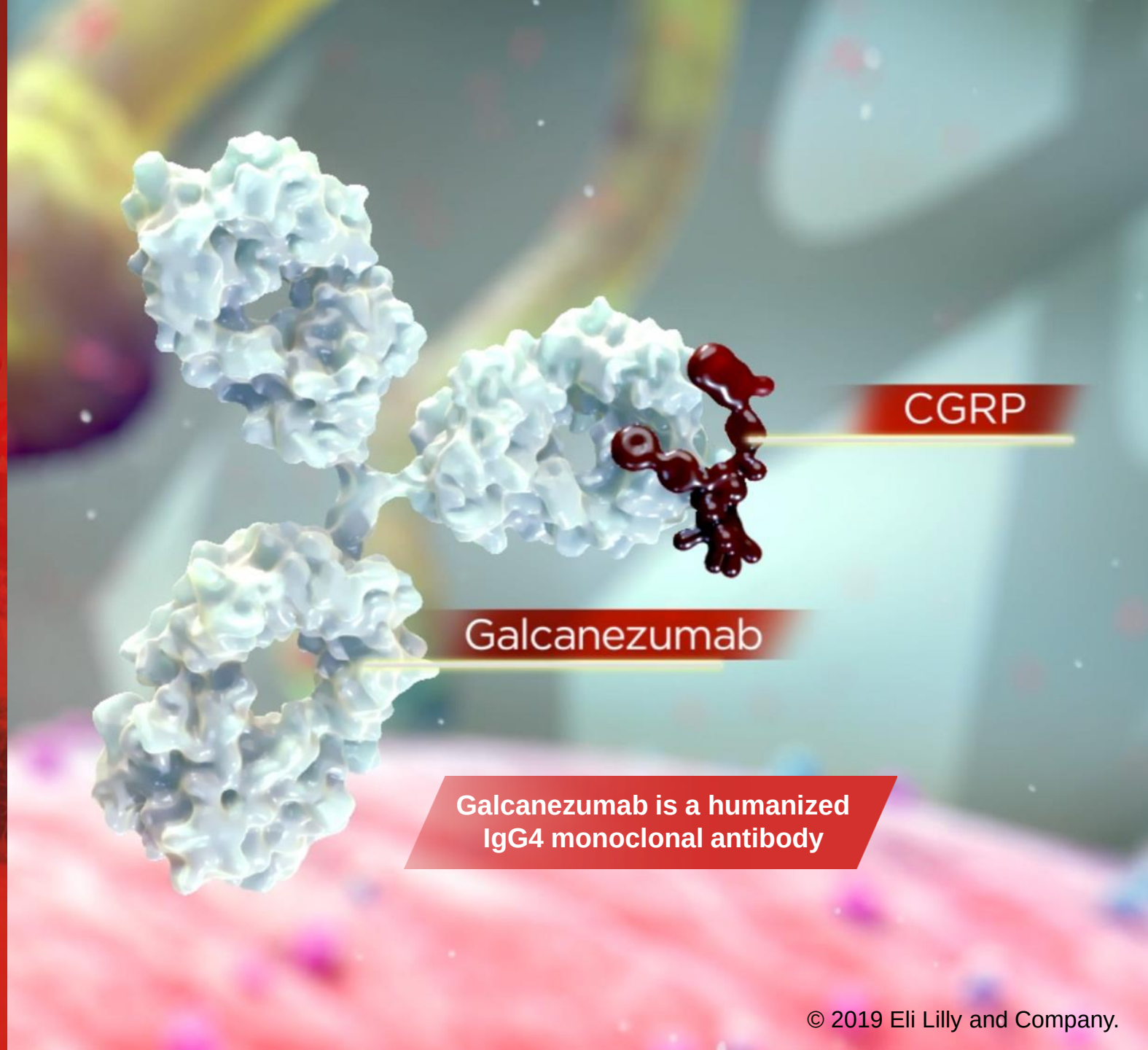
- Triptans, medications commonly used for the acute treatment of migraine, reduce CGRP levels[1,5]
- Blocking the CGRP ligand or receptor reduces migraine symptoms[6,7]

References: 1. Arulmani U, Maassenvandenbrink A, Villalon CM, et al. *Eur J Pharmacol*. 2004;500(1-3):315-330. 2. Juhasz G, Zsombok T, Modos EA, et al. *Pain*. 2003;106(3):461-470. 3. Hansen JM, Hauge AW, Olesen J, et al. *Cephalalgia*. 2010;30(10):1179-1186. 4. Lassen LH, Haderslev PA, Jacobsen VB, et al. *Cephalalgia*. 2002;22(1):54-61. 5. Goadsby PJ, Edvinsson L. *Brain*. 1994;117(pt 3):427-434. 6. Edvinsson L. *Br J Clin Pharmacol*. 2015:80(2):193-199. 7. Peroutka SJ. *BioDrugs*. 2014;28(3):237-244.

Understanding Galcanezumab

What Is Galcanezumab?

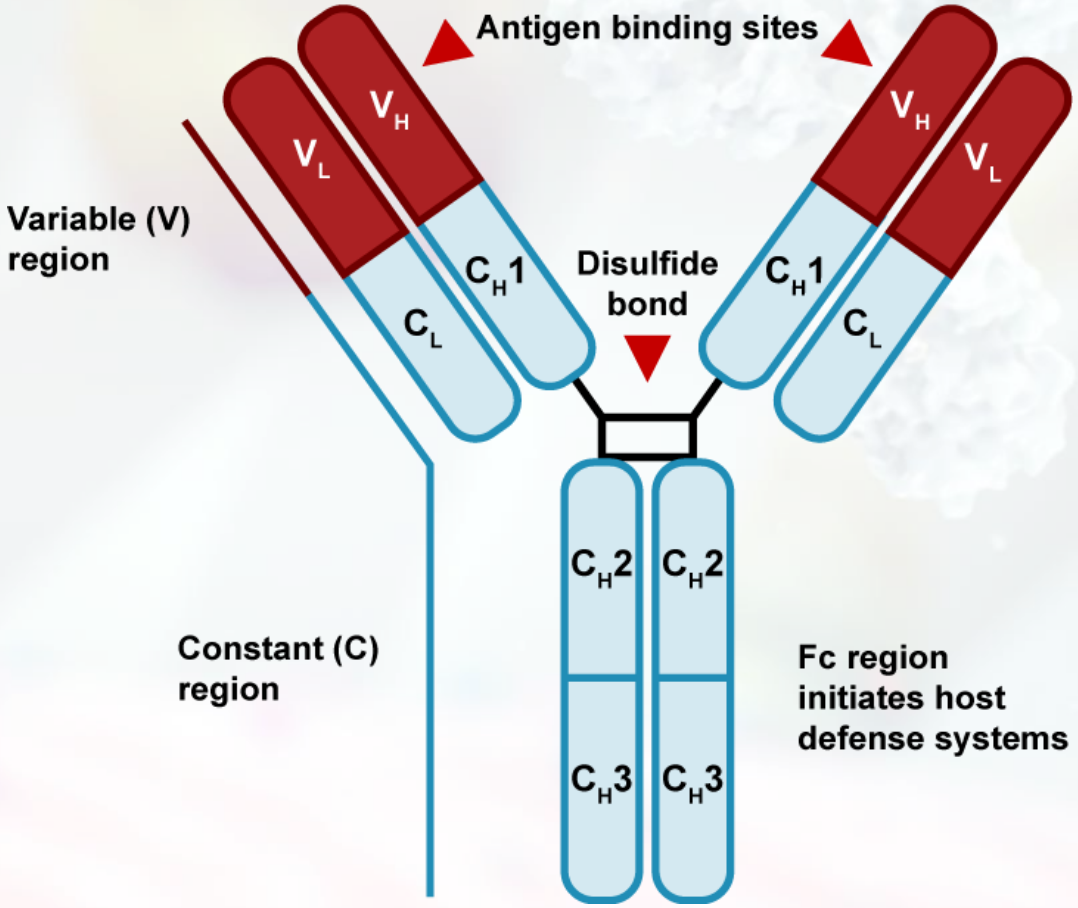
- Galcanezumab is an IgG4 monoclonal antibody
- Galcanezumab is indicated for the preventive treatment of migraine in adults



Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Understanding Monoclonal Antibodies

- Monoclonal antibodies (immunoglobulins) are large proteins produced by the immune system to counteract foreign substances (antigens) in the body[1-3]
- Like galcanezumab, antibodies can be developed to target specific antigens for therapeutic purposes[4,5]
- There are approximately 5 classes of immunoglobulins (IgA, IgD, IgE, IgG, IgM)[6]

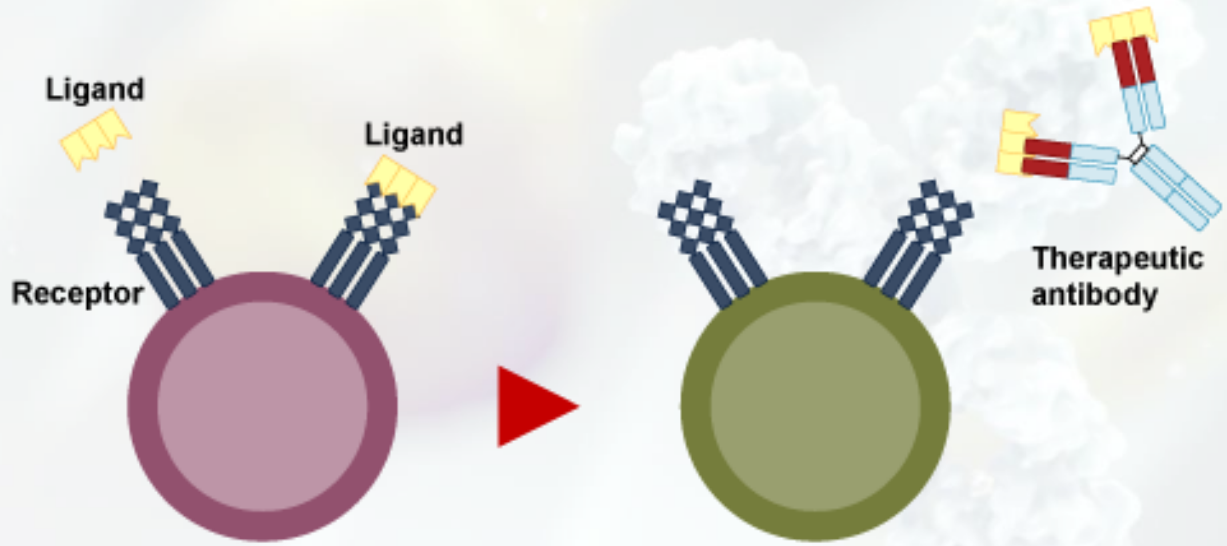


References: 1. Voynov V, Chennamsetty N, Kayser V, et al. *MAbs*. 2009;1(6):580-582. 2. Hansel TT, Kropshofer H, Singer T, et al. *Nat Rev Drug Discov*. 2010;9(4):325-338. 3. Llewelyn MB, Hawkins RE, Russell SJ. *BMJ*. 1992;305(6864):1269-1272. 4. Data on File. Eli Lilly and Company and/or its subsidiaries. 5. Chames P, Van Regenmortel M, Weiss E, et al. *Br J Pharmacol*. 2009;157(2):220-233. 6. Brekke OH, Sandlie I. *Nat Rev Drug Discov*. 2003;2(1):52-62. Erratum in 2(3):240.

Mechanisms of Action for Therapeutic Monoclonal Antibodies

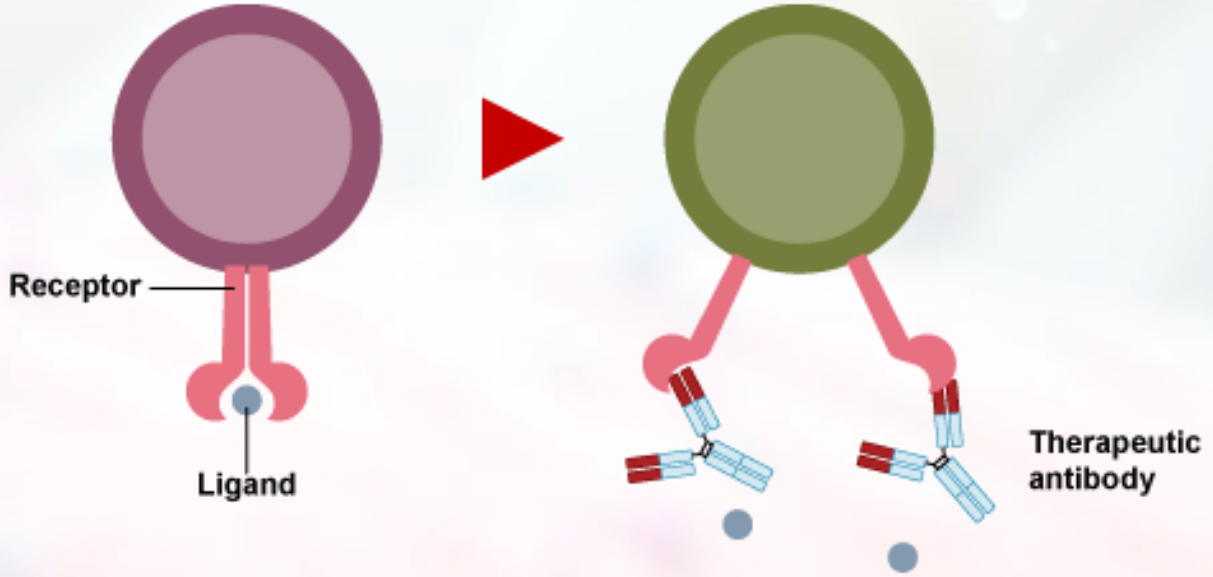
Ligand Blockade:

Antibodies or antibody fragments can prevent ligands from activating all of their receptors



Receptor Blockade:

Antibodies bind the receptor and block binding of the ligand to the receptor

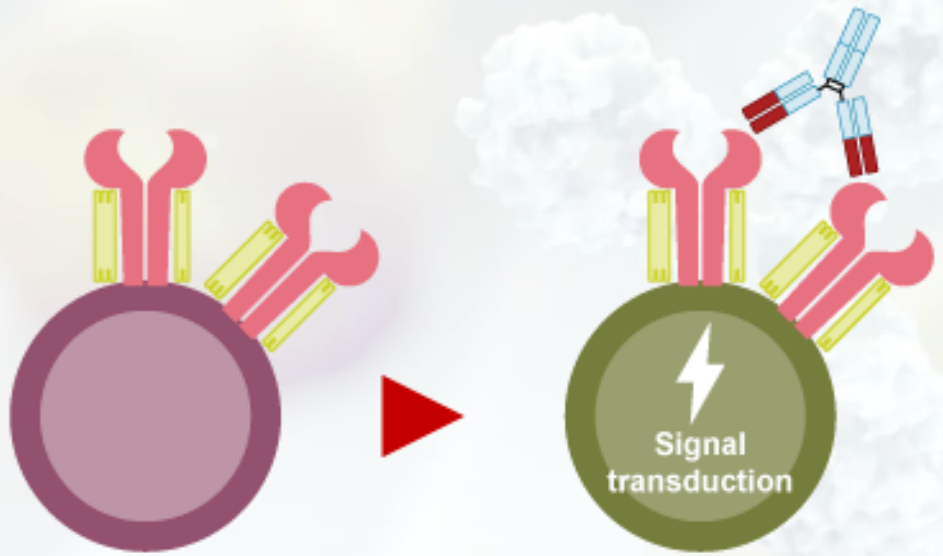


Reference: Chan AC, Carter PJ. *Nat Rev Immunol*. 2010;10(5):301-316.

Mechanisms of Action for Therapeutic Monoclonal Antibodies (Cont'd)

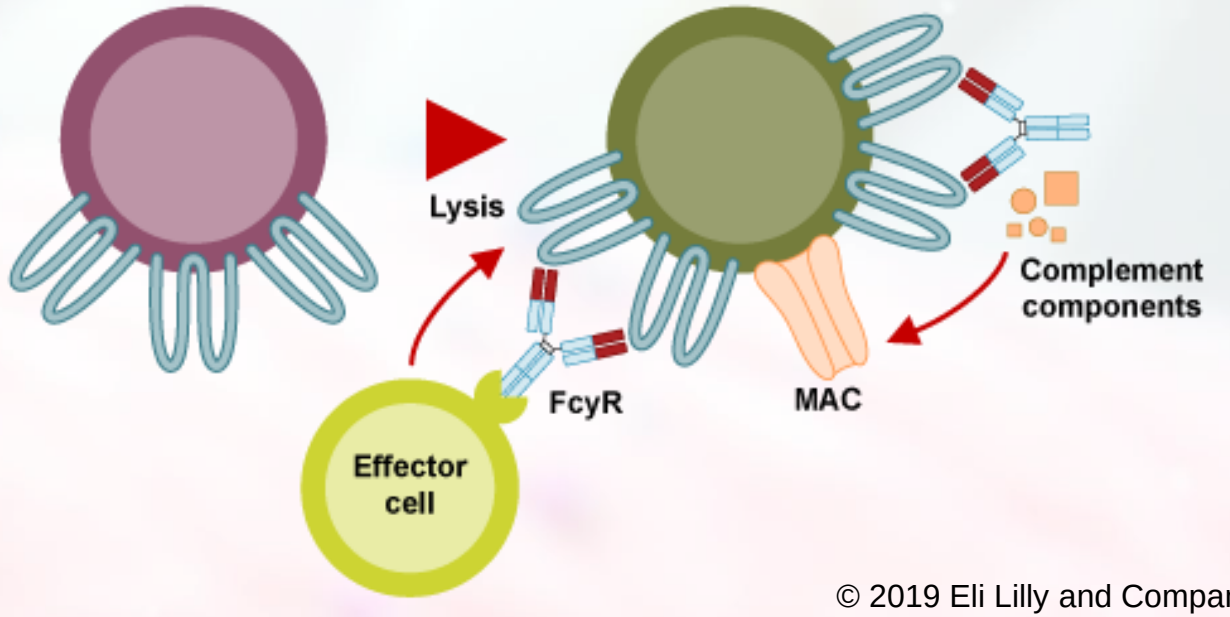
Signaling Induction:

Antibodies bind receptor complexes and induce receptor-mediated signaling, altering cell functions and differentiation



Depletion:

Antibodies binding to cell surface receptors can result in depletion of antigen-bearing cells through complement-mediated or FcγR-mediated lysis



Reference: Chan AC, Carter PJ. *Nat Rev Immunol*. 2010;10(5):301-316.

IgG Immunoglobulins

- IgG is the most common Ig class used as the basis for therapeutic antibodies and is subdivided into 4 subclasses[1-3]
- Galcanezumab is an IgG4 monoclonal antibody, and it is expected that it will not induce an innate immune complement reaction[4-6]

Property	IgG1	IgG2	IgG3	IgG4
Total IgG,[6-8] %	60	40	4	4
Serum half-life, days	21	21	21-7	21
Classical complement fixation[a]	+++	+	+++	-
Binding affinity for Fc receptors (ADCC)[b]	+++	+	+++	+
Anti-protein antibodies[c]	++	+	++	+
Anti-polysaccharide antibodies (encapsulated bacterial pathogens)[c]	+	+++	+	+
Age when adult concentrations acquired, years	≥5	Adolescence		

[a]Binding affinity for C1q: +++ (highest), - (no binding).

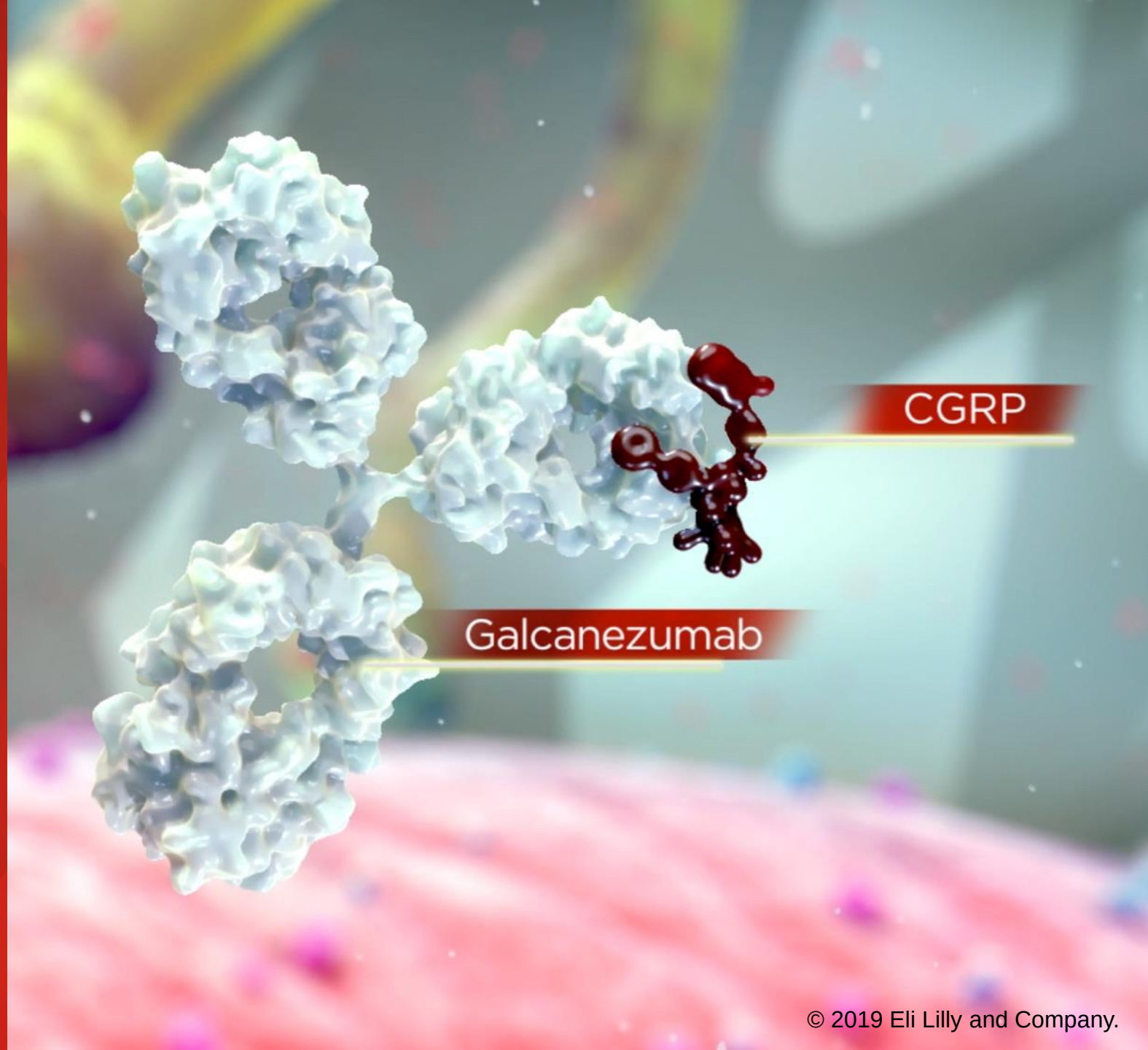
[b]++ (higher), + (lower).

[c]Antibodies to polysaccharide antigens are largely but not exclusively of the IgG2 subclass, whereas antibodies to protein and viral antigens occur dominantly in the IgG1 and IgG3 subclasses.

References: 1. Buckley RH. *Curr Allergy Asthma Rep*. 2002;2(5):356-360. 2. Foltz IN, Karow M, Wasserman SM. *Circulation*. 2013;127(22):2222-2230. 3. Brekke OH, Sandlie I. *Nat Rev Drug Discov*. 2003;2(1):52-62. Erratum in 2(3):240. 4. Kielbasa W, Helton DL. *Cephalalgia*. [published online ahead of print, March 27, 2019]. doi: 10.1177/0333102419840780. 5. Data on File. Eli Lilly and Company and/or its subsidiaries. 6. Vidarsson G, Dekkers G, Rispens T. *Front Immunol*. 2014;5:520. 7. Valenzuela NM, Hickey MJ, Reed EF. *Front Immunol*. 2016;7:433. 8. Agarwal S, Cunningham-Rundles C. *Ann Allergy Asthma Immunol*. 2007;99(3):281-283.

Mechanism of Action of Galcanezumab

- Designed to target CGRP with
  - High affinity (K_D = 31 pM)
  - High specificity (>10,000-fold versus related peptides)
- Binds CGRP and prevents its biological activity without blocking the CGRP receptor
- Thought to act peripherally in structures involved in migraine headache pathogenesis, including the trigeminal ganglia



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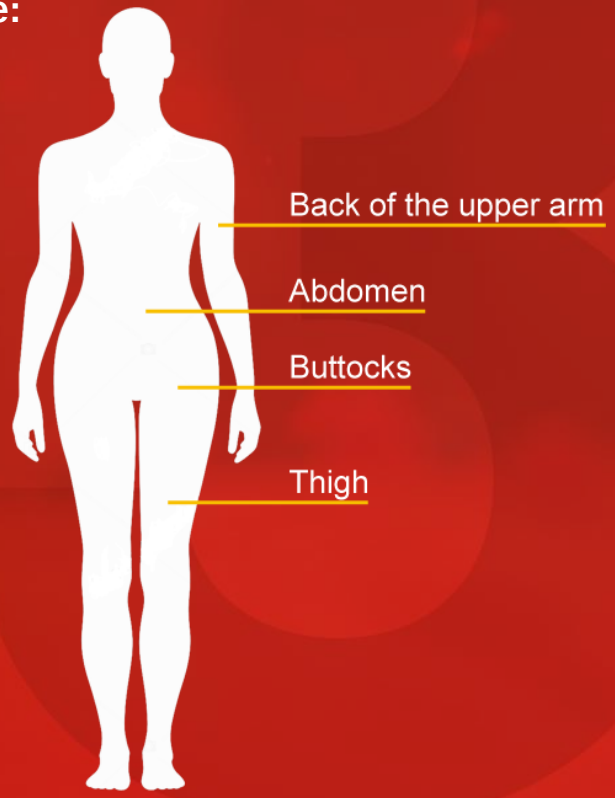
Dosing and Administration of Galcanezumab for Migraine

Galcanezumab injection
Subcutaneous injection sites can include:



- After a loading dose, therapeutic steady-state concentrations of galcanezumab are achieved

Approved dosing

Initial loading dose:	Recommended dose:
240 mg subcutaneous injection	120 mg/monthly subcutaneous injection

- Galcanezumab can be self-administered once monthly by subcutaneous injection

Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Pharmacokinetics (PK) of Galcanezumab

Absorption*	Following a 240 mg loading dose, the maximum serum concentration (C_{max}) was ~30 µg/mL (27% coefficient of variation [CV]).[1] Monthly doses of 120 mg or 240 mg achieved a steady-state C_{max} ($C_{max,ss}$) of approximately 28 µg/mL (35% CV) or 54 µg/mL (31% CV), respectively.[1] Injection site location did not significantly influence the absorption of galcanezumab.[1]
Distribution*	The apparent volume of distribution (V/F) of galcanezumab was 7.3 L.[1]
Metabolism	As a humanized IgG4 monoclonal antibody, galcanezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.[1] Liver enzymes (CYP450 isozymes) are not involved in IgG metabolism.[2]
Elimination*	The apparent clearance (CL/F) of galcanezumab was approximately 0.008 L/h, and the half-life of galcanezumab was 27 days.[1]

*Based on population PK analysis.

References: 1. Data on File. Eli Lilly and Company and/or its subsidiaries. 2. Lobo ED, Hansen RJ, Balthasar JP. *J Pharm Sci*. 2004;93(11):2645-2668.

Pharmacodynamics of Galcanezumab

- CGRP is a key mediator of capsaicin-induced dermal blood flow
- Single doses of galcanezumab (75, 200, or 600 mg) resulted in attenuation of capsaicin-induced dermal blood flow by Day 3
- Galcanezumab at 150 mg every 2 weeks for 6 weeks (4 total doses) resulted in an inhibition of capsaicin-induced dermal blood flow for at least 134 days after the last dose was given

Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Summary

- **Galcanezumab is indicated for the preventive treatment of migraine in adults**
- As an IgG4 antibody, it is expected that it will
  - Not induce an innate immune complement reaction
  - Degrade into small peptides in the same manner as endogenous IgG, without inducing an immune response
- By targeting and sequestering CGRP, a key neuropeptide in migraine, galcanezumab may prevent underlying pathological processes associated with migraine and prevent migraine attacks

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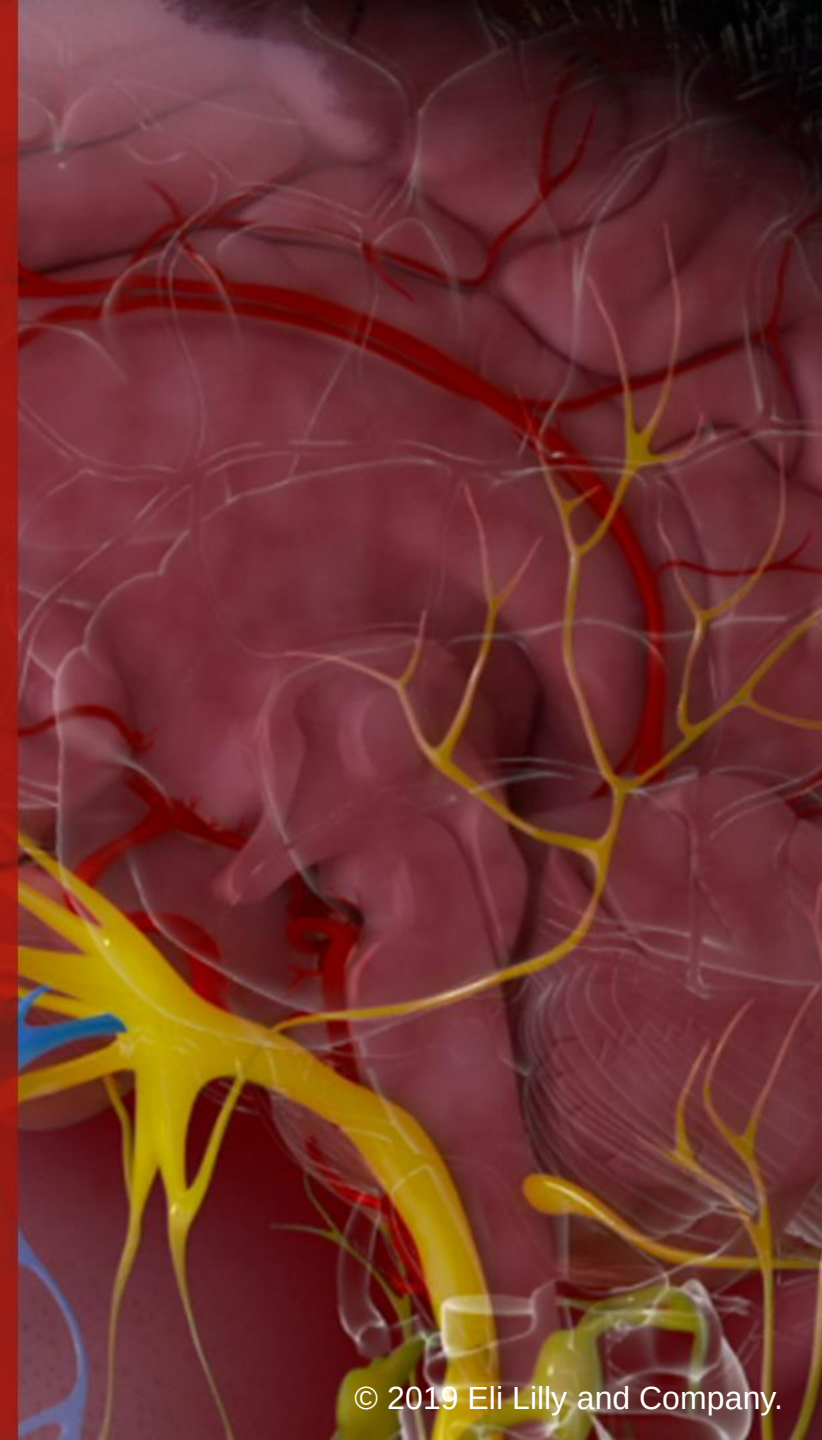
Exploring **Cluster Headache**

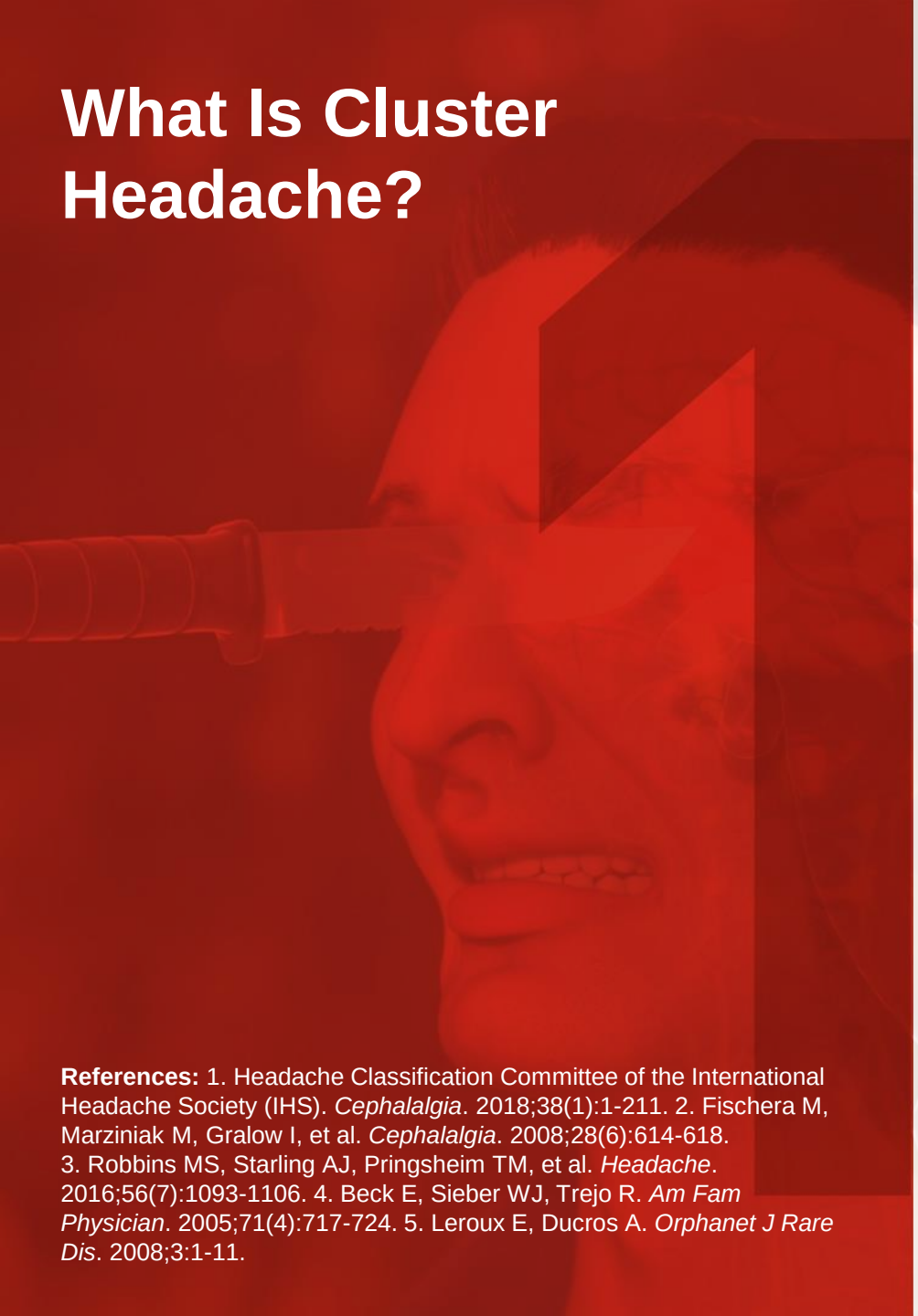


Objectives

1. Cluster Headache: Burden of Disease
2. CGRP and Episodic Cluster Headache
3. Understanding Galcanezumab

Cluster Headache:
Burden of Disease

What Is Cluster Headache?



- Cluster headache is a primary headache disorder[1]
  - Occurs more commonly in men than women
  - Most common age at onset is between **20** to **40** years
- Lifetime prevalence of approximately **0.12** percent [2,3]
  - Approximately **85** to **90** percent of patients have episodic cluster headache[1]
  - Variation in these numbers is not expected worldwide [2,3]
- Often described as excruciatingly painful[4,5]

> *The pain is like having a red-hot knife stabbing you behind the eye*

References: 1. Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38(1):1-211. 2. Fischera M, Marziniak M, Gralow I, et al. *Cephalalgia*. 2008;28(6):614-618. 3. Robbins MS, Starling AJ, Pringsheim TM, et al. *Headache*. 2016;56(7):1093-1106. 4. Beck E, Sieber WJ, Trejo R. *Am Fam Physician*. 2005;71(4):717-724. 5. Leroux E, Ducros A. *Orphanet J Rare Dis*. 2008;3:1-11.

ICHD-3 Diagnostic Criteria:
Cluster Headache

A. At least five attacks fulfilling criteria B–D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)

C. Either or both of the following:

1. at least one of the following symptoms or signs, ipsilateral to the headache:
   - conjunctival injection and/or lacrimation
   - nasal congestion and/or rhinorrhea
   - eyelid edema
   - forehead and facial sweating
   - miosis and/or ptosis
2. a sense of restlessness or agitation

D. Occurring with a frequency between one every other day and eight per day

E. Not better accounted for by another ICHD-3 diagnosis

Reference: Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38(1):1-211.

Defining Episodic Cluster Headache

- Attacks fulfill ICHD-3 criteria for cluster headache
- At least two cluster headache periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of 3 months or more
- Cluster headache periods usually last between 2 weeks to 3 months

Reference: Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38(1):1-211.

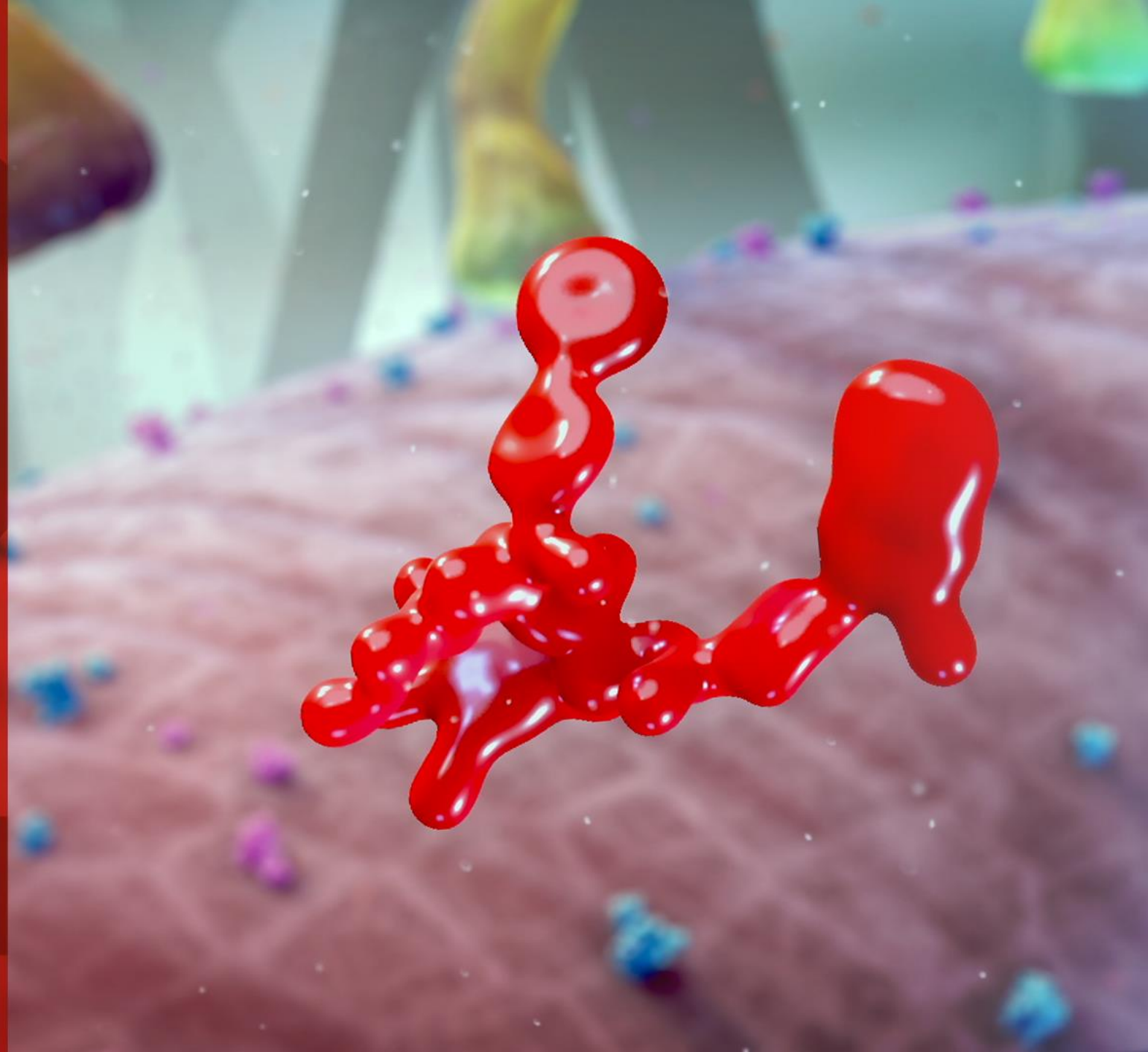
Commonly Underdiagnosed and Undertreated

- Worldwide, the average delay in diagnosis of cluster headache can be years[1-3]
- Patients with cluster headache reported visiting different clinicians and receiving multiple incorrect diagnoses prior to being correctly diagnosed[1,2]
- Clinically, cluster headache can resemble migraine, trigeminal neuralgia, and sinusitis, among other diseases[1,4,5]
- Based on a 2014 European survey, following a cluster headache diagnosis:[3]
  - Approximately **25%** of patients received either no or non-recommended acute treatment options
  - Approximately **26%** of patients received either no or non-recommended preventive treatments

References: 1. Buture A, Ahmed F, Dikomitis L, et al. *Neurol Sci*. 2018;40(1):25-39. 2. Rozen TD, Fishman RS. *Headache*. 2012;52:99-113. 3. Voiticovschi-Iosob C, Allena M, De Cillis I, et al. *J Headache Pain*. 2014;15(1):56. 4. Vollesen AL, Benemei S, Cortese F, et al. *J Headache Pain*. 2018;19:2-15. 5. Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38(1):1-211.

2

CGRP and Episodic Cluster Headache



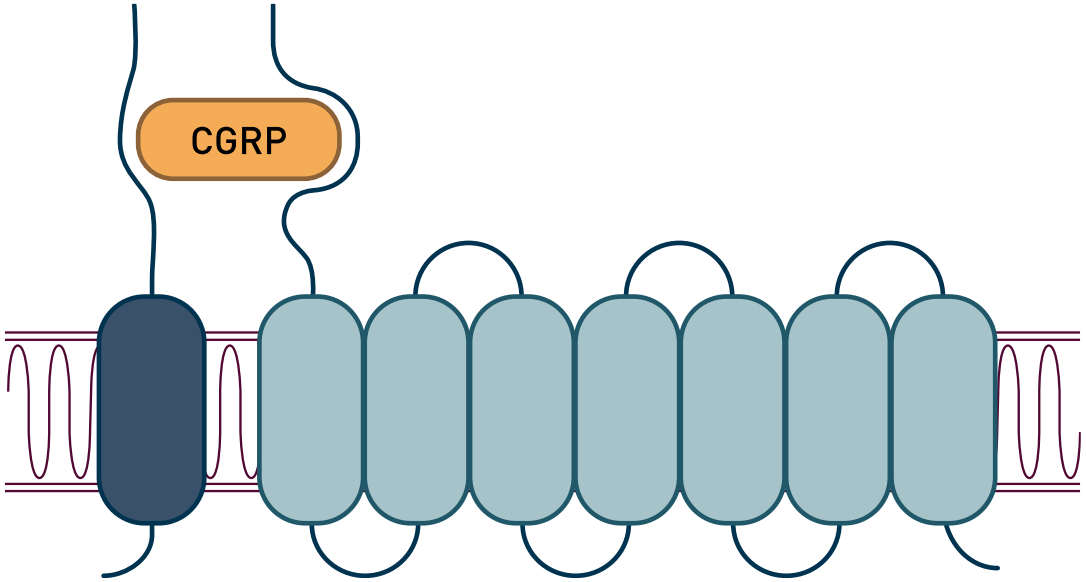
What Is CGRP?

- Calcitonin gene-related peptide, or CGRP, is a small (~37 amino acid) neuropeptide with a wide distribution in both peripheral and central nervous systems[1]
- CGRP is one of the most abundant neuropeptides in the trigeminovascular system[1]
  - CGRP is expressed in approximately 50% of neurons in the trigeminal ganglia[2]
- Activation of the trigeminovascular system occurs during cluster attacks, causing the release of neuropeptides including CGRP and leads to:[3,4]
  - Activation of meningeal nociceptors
  - Vasodilation
  - Neurogenic inflammation

References: 1. Tfelt-Hansen P, Le H. *J Headache Pain*. 2009;10(3):137-143. 2. Eftekhari S, Salvatore CA, Calamari A, et al. *Neuroscience*. 2010;169(2):683-696. 3. Buture A, Gooriah R, Nimeri R, et al. *Anesth Pain Med*. 2016;6(3):e35190. 4. Alstadhaug KB, Ofte HK. *Tidsskr Nor Laegeforen*. 2015;135(15):1361-1364.

CGRP Activates the CGRP Receptor

- CGRP binds and activates the CGRP receptor with a high affinity
- The CGRP receptor is found on nerves and blood vessels throughout the trigeminovascular system



CGRP receptor

$RAMP_1$ CLR

Reference: Walker CS, Hay DL. *Br J Pharmacol*. 2013;170(7):1293-1307.

CGRP and Cluster Headache

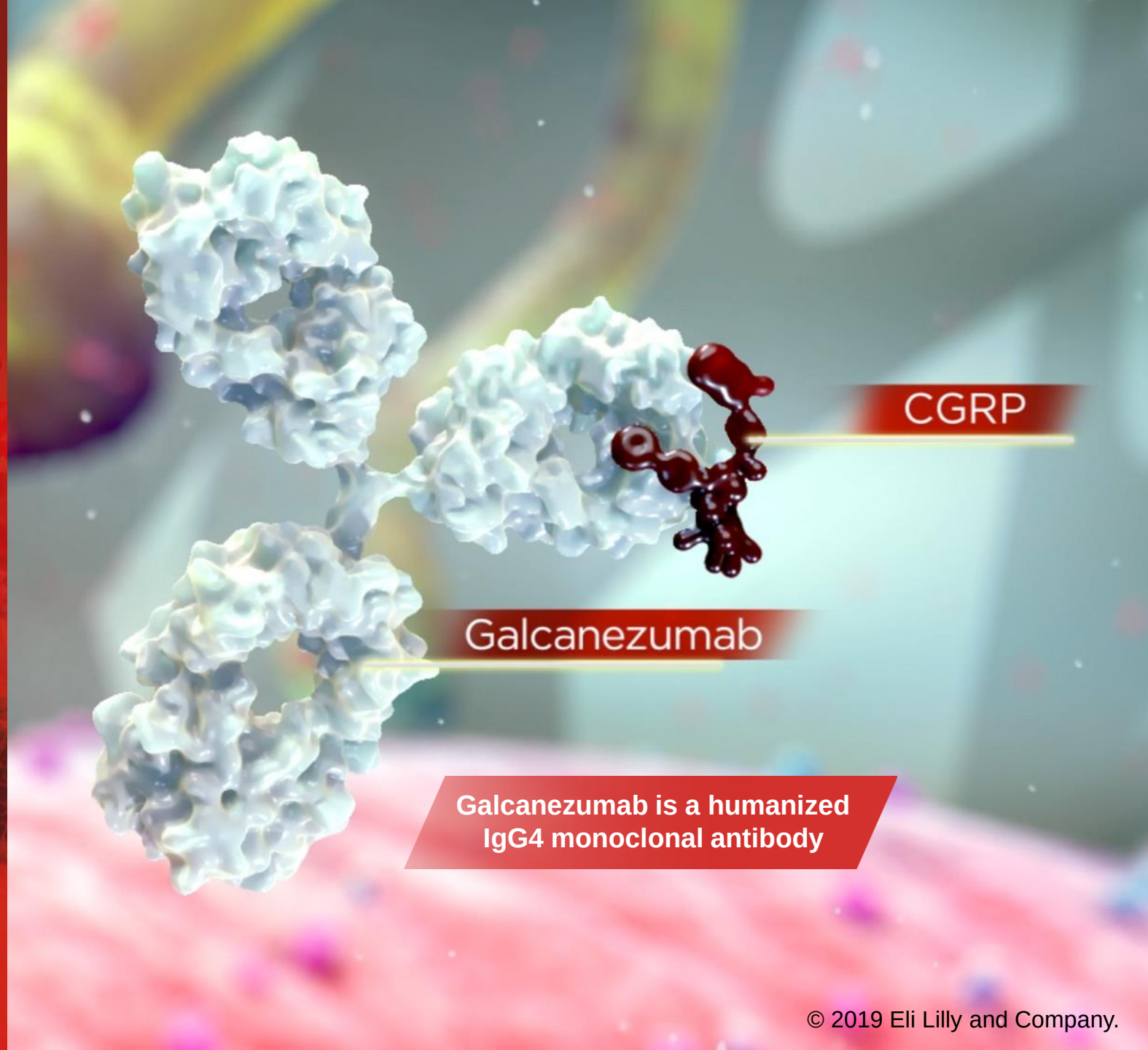
- CGRP has been shown to be increased during cluster headache attacks in patients with episodic cluster headache[1,2]
  - CGRP levels return to normal following the cessation of an attack
- In a recent study, infusion of CGRP precipitated attacks in 8 out of 9 individuals during their active period of episodic cluster headache[3]
- Triptans, medications demonstrated effective for the acute treatment of cluster headache, were shown to reduce CGRP levels[1,2]

References: 1. Fanciullacci M, Alessandri M, Figini M, et al. *Pain*. 1995;60(2):119-123. 2. Goadsby PJ, Edvinsson L. *Brain*. 1994;117:427-434. 3. Vollesen ALH, Snoer A, Beske RP, et al. *JAMA Neurol*. 2018;75(10):1187-1197.

Understanding Galcanezumab

What Is Galcanezumab?

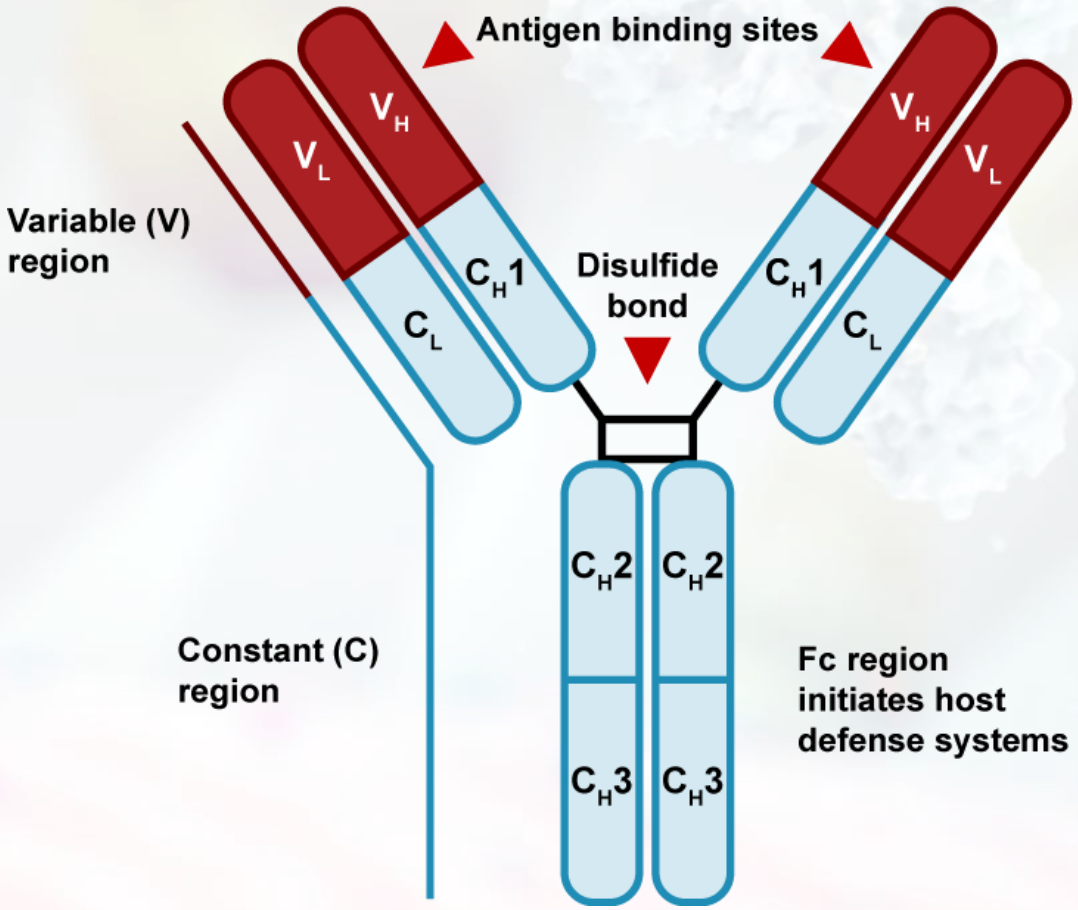
- Galcanezumab is indicated in adults for the treatment of episodic cluster headache



Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Understanding Monoclonal Antibodies

- Monoclonal antibodies (immunoglobulins) are large proteins produced by the immune system to counteract foreign substances (antigens) in the body[1-3]
- Like galcanezumab, antibodies can be developed to target specific antigens for therapeutic purposes[4,5]
- There are approximately 5 classes of immunoglobulins (IgA, IgD, IgE, IgG, IgM)[6]



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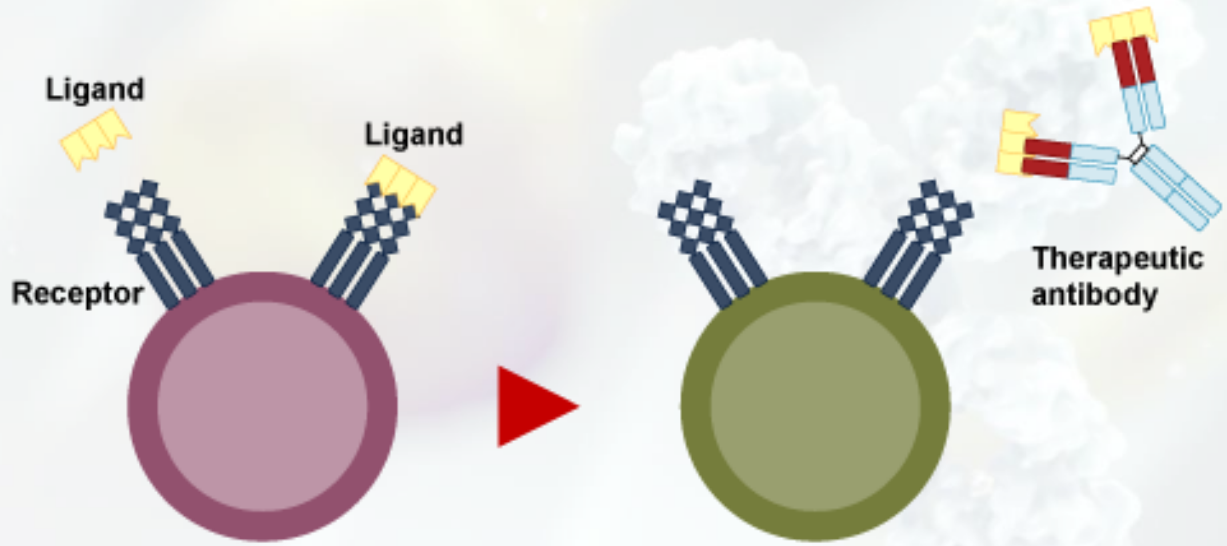
Mechanisms of Action for Therapeutic Monoclonal Antibodies

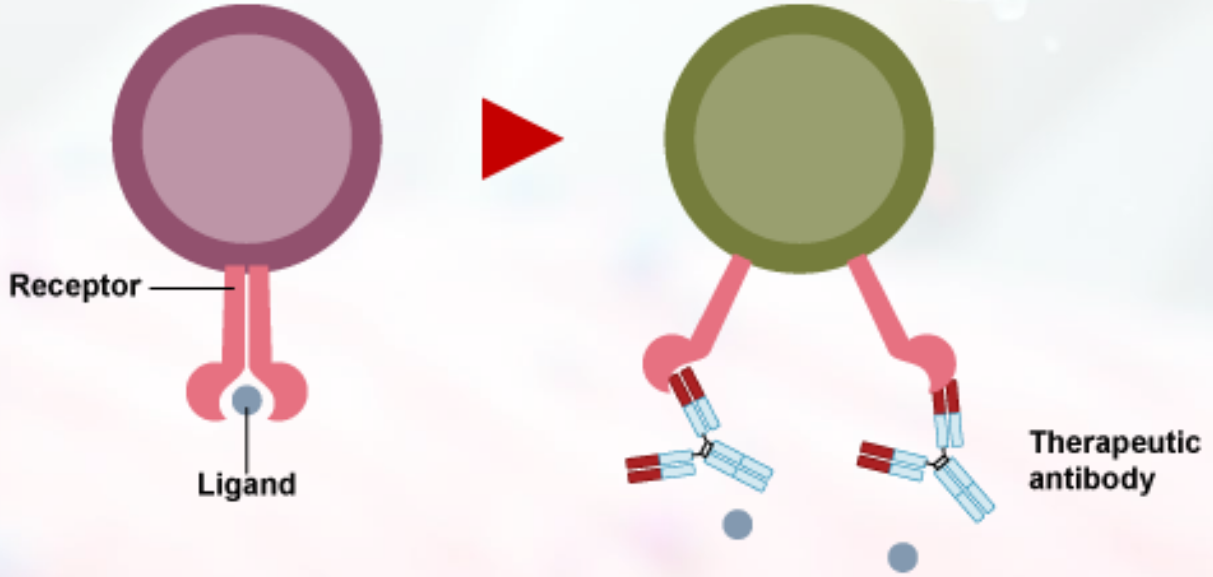
Ligand Blockade:

Antibodies or antibody fragments can prevent ligands from activating all of their receptors



Receptor Blockade:

Antibodies bind the receptor and block binding of the ligand to the receptor

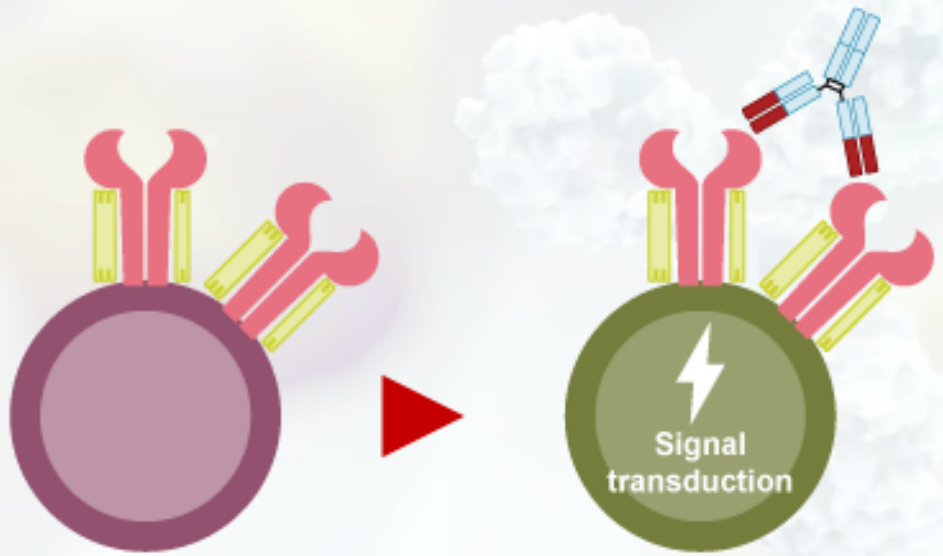


Reference: Chan AC, Carter PJ. *Nat Rev Immunol*. 2010;10(5):301-316.

Mechanisms of Action for Therapeutic Monoclonal Antibodies (Cont'd)

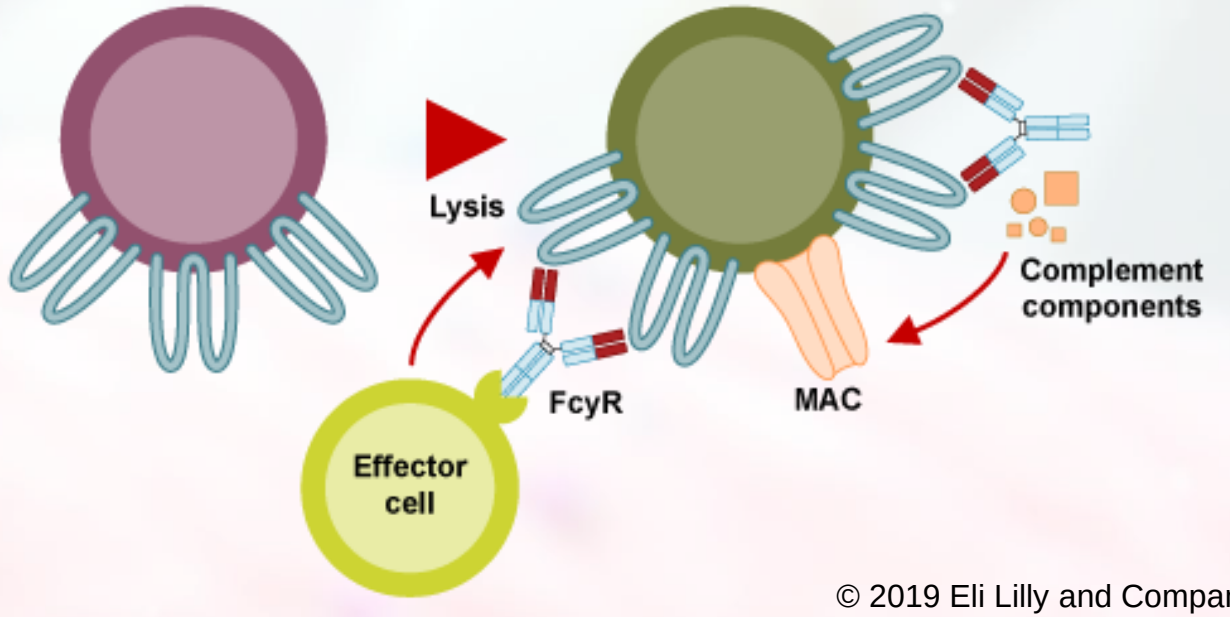
Signaling Induction:

Antibodies bind receptor complexes and induce receptor-mediated signaling, altering cell functions and differentiation



Depletion:

Antibodies binding to cell surface receptors can result in depletion of antigen-bearing cells through complement-mediated or FcγR-mediated lysis



Reference: Chan AC, Carter PJ. *Nat Rev Immunol*. 2010;10(5):301-316.

IgG Immunoglobulins

- IgG is the most common Ig class used as the basis for therapeutic antibodies and is subdivided into 4 subclasses[1-3]
- Galcanezumab is an IgG4 monoclonal antibody, and it is expected that it will not induce an innate immune complement reaction[4-6]

Property	IgG1	IgG2	IgG3	IgG4
Total IgG,[6-8] %	60	40	4	4
Serum half-life, days	21	21	21-7	21
Classical complement fixation[a]	+++	+	+++	-
Binding affinity for Fc receptors (ADCC)[b]	+++	+	+++	+
Anti-protein antibodies[c]	++	+	++	+
Anti-polysaccharide antibodies (encapsulated bacterial pathogens)[c]	+	+++	+	+
Age when adult concentrations acquired, years	≥5	Adolescence		

[a]Binding affinity for C1q: +++ (highest), - (no binding).

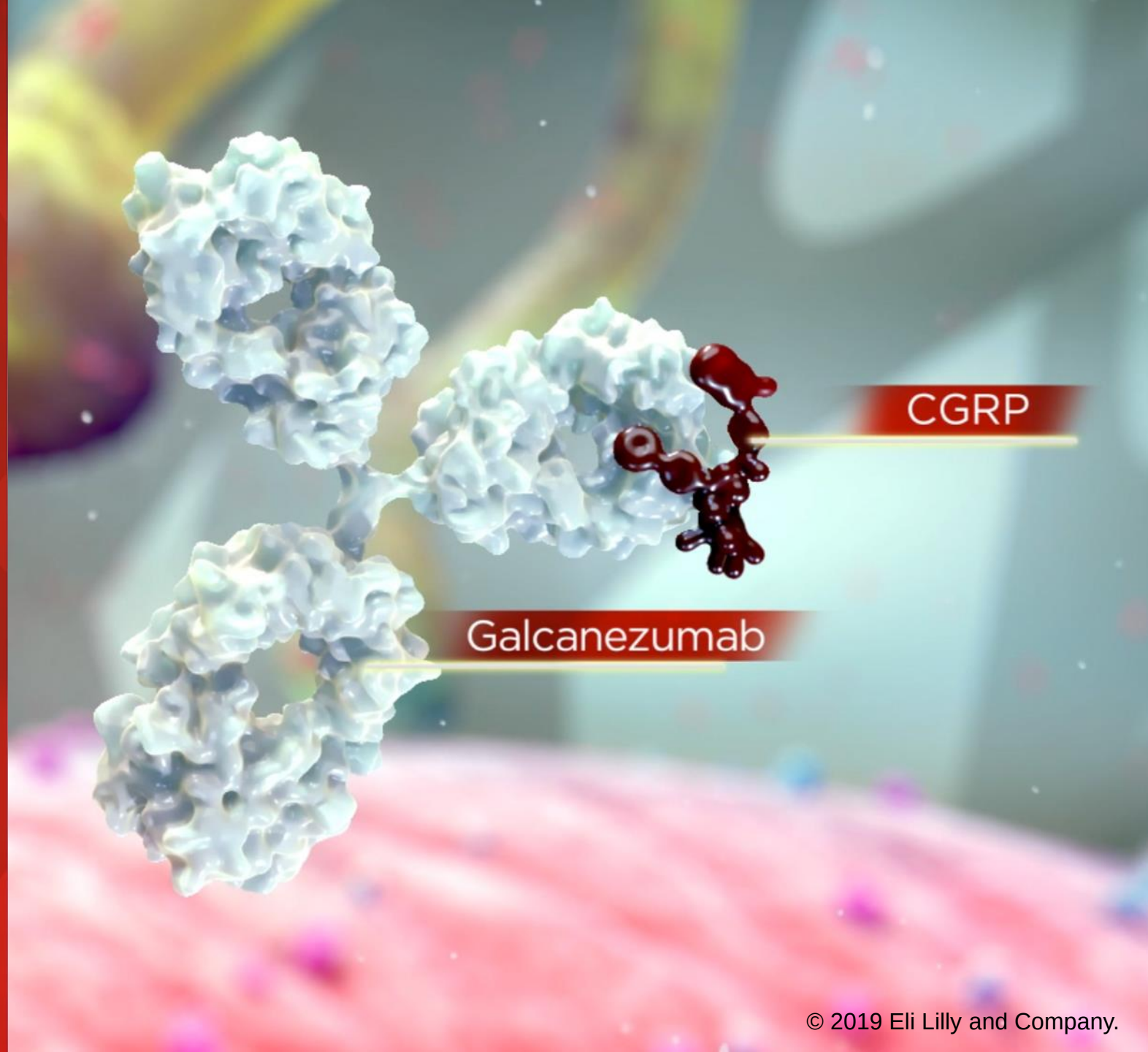
[b]++ (higher), + (lower).

[c]Antibodies to polysaccharide antigens are largely but not exclusively of the IgG2 subclass, whereas antibodies to protein and viral antigens occur dominantly in the IgG1 and IgG3 subclasses.

References: 1. Buckley RH. *Curr Allergy Asthma Rep*. 2002;2(5):356-360. 2. Foltz IN, Karow M, Wasserman SM. *Circulation*. 2013;127(22):2222-2230. 3. Brekke OH, Sandlie I. *Nat Rev Drug Discov*. 2003;2(1):52-62. Erratum in 2(3):240. 4. Kielbasa W, Helton DL. *Cephalalgia*. [published online ahead of print, March 27, 2019]. doi: 10.1177/0333102419840780. 5. Data on File. Eli Lilly and Company and/or its subsidiaries. 6. Vidarsson G, Dekkers G, Rispens T. *Front Immunol*. 2014;5:520. 7. Valenzuela NM, Hickey MJ, Reed EF. *Front Immunol*. 2016;7:433. 8. Agarwal S, Cunningham-Rundles C. *Ann Allergy Asthma Immunol*. 2007;99(3):281-283.

Mechanism of Action of Galcanezumab

- Designed to target CGRP with
  - High affinity (K_D = 31 pM)
  - High specificity (>10,000-fold versus related peptides)
- Binds CGRP and prevents its biological activity without blocking the CGRP receptor
- Thought to act peripherally in structures involved in cluster headache pathogenesis, including the trigeminal ganglia



Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

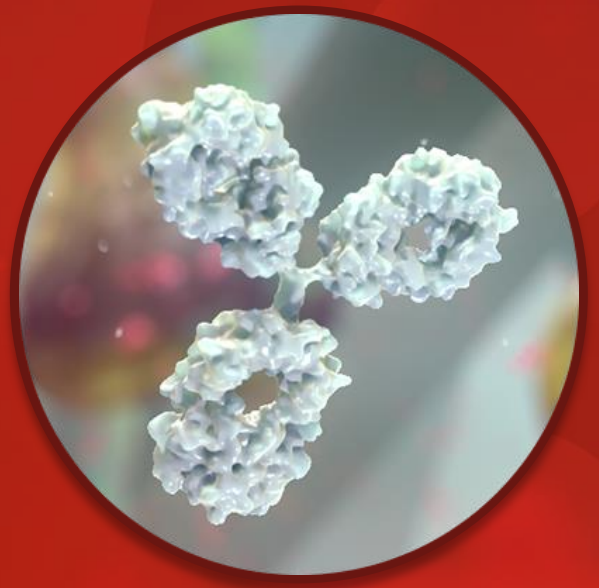
Pharmacokinetics (PK) of Galcanezumab

Absorption*	Following a 240 mg loading dose, the maximum serum concentration (C_{max}) was ~30 µg/mL (27% coefficient of variation [CV]).[1] Monthly doses of 120 mg or 240 mg achieved a steady-state C_{max} ($C_{max,ss}$) of approximately 28 µg/mL (35% CV) or 54 µg/mL (31% CV), respectively.[1] Injection site location did not significantly influence the absorption of galcanezumab.[1]
Distribution*	The apparent volume of distribution (V/F) of galcanezumab was 7.3 L.[1]
Metabolism	As a humanized IgG4 monoclonal antibody, galcanezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.[1] Liver enzymes (CYP450 isozymes) are not involved in IgG metabolism.[2]
Elimination*	The apparent clearance (CL/F) of galcanezumab was approximately 0.008 L/h, and the half-life of galcanezumab was 27 days.[1]

*Based on population PK analysis.

References: 1. Data on File. Eli Lilly and Company and/or its subsidiaries. 2. Lobo ED, Hansen RJ, Balthasar JP. *J Pharm Sci*. 2004;93(11):2645-2668.

Galcanezumab Metabolism



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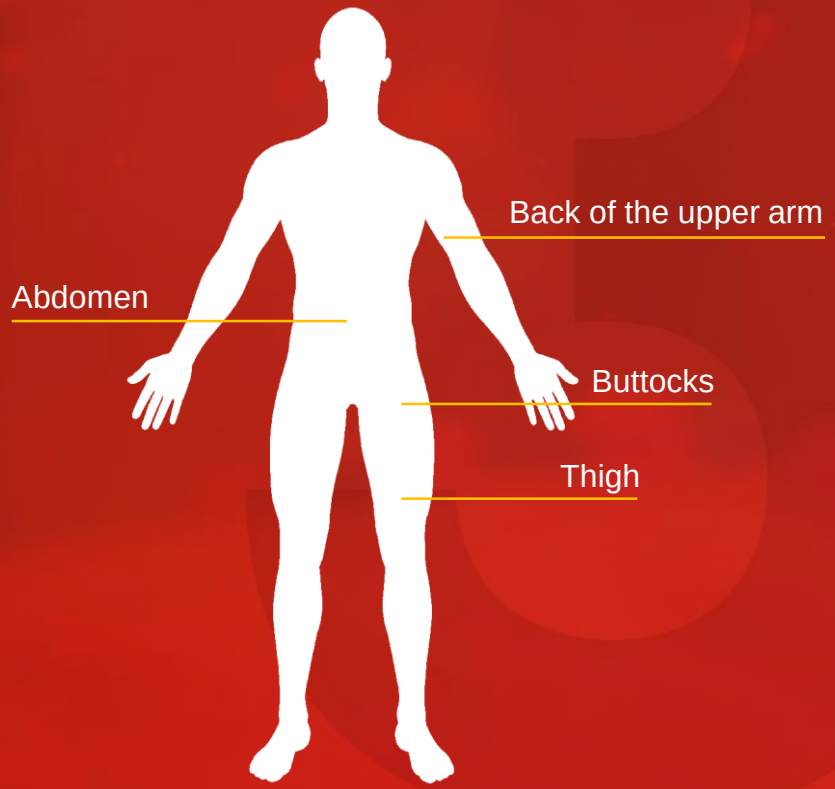
References: 1. Data on File. Eli Lilly and Company and/or its subsidiaries. 2. Lobo ED, Hansen RJ, Balthasar JP. *J Pharm Sci*. 2004;93(11):2645-2668.

Dosing and Administration of Galcanezumab for Episodic Cluster Headache

Injection sites



- The recommended dosage of galcanezumab is 300 mg at the onset of the cluster period, and then monthly until the end of the cluster period
- The 300 mg dose is administered by three consecutive subcutaneous injections of 100 mg prefilled syringes
- Galcanezumab may be self-injected

Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Dosing Rationale for Galcanezumab: Episodic Cluster Headache

- The 300 mg total monthly dose was selected because it demonstrated efficacy in a prior phase 2 study where galcanezumab was administered subcutaneously as 150 mg every 2 weeks[1]
  - This was the only efficacy study conducted prior to initiating the cluster headache phase 3 study[1]

- Galcanezumab 300 mg once monthly was predicted to provide the same monthly galcanezumab exposure and target engagement as 150 mg every 2 weeks based on:[2]
  - Area under the galcanezumab concentration time curve
  - Plasma CGRP concentrations as a marker of indicating galcanezumab target engagement

References: 1. Dodick DW, Goadsby PJ, Spierings EL, et al. *Lancet Neurol*. 2014;13(9):885-892. 2. Data on File. Eli Lilly and Company and/or its subsidiaries.

Formulation Rationale: 300 mg Dose of Galcanezumab for Episodic Cluster Headache

- Delivering a 300 mg dose via subcutaneous administration at an injection volume of 1 mL would require a 300 mg/mL galcanezumab formulation, which is currently not available[1]
- Based on the characteristics of monoclonal antibodies, solubility of the drug product can pose a technical challenge. Therefore, the 100 mg/mL galcanezumab formulation was developed, which ensures the required stability of the formulation at the recommended storage temperature over the shelf life of the product[1]
- The 120 mg/mL solution was developed after the initiation of the cluster studies and was subsequently carried forward for the migraine studies[1]

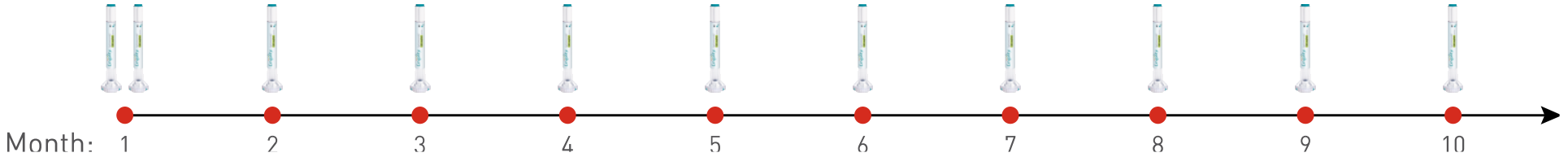
References: 1. Data on file. Eli Lilly and Company and/or its subsidiaries.

Galcanezumab Dosing:
Migraine

This represents a hypothetical patient.

Recommended dosing for migraine

240 mg as loading dose; **120 mg** monthly as maintenance dose



Two consecutive SC 120 mg injections

Subsequent months: One SC 120 mg injection per month

Loading dose of **240 mg**	=	Two **120 mg** autoinjectors		One dose of **120 mg**	=	One **120 mg** autoinjector	

mg=milligram; SC=subcutaneous.

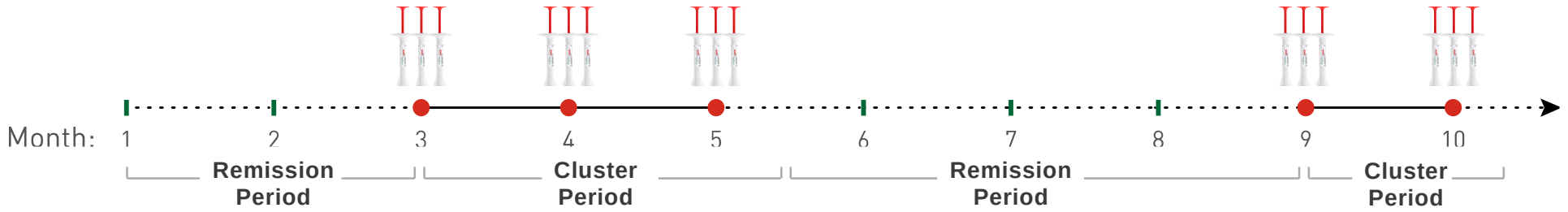
Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Galcanezumab Dosing:
Episodic Cluster Headache

This represents a hypothetical patient.

Recommended dosing for episodic cluster headache

300 mg monthly during a cluster period



Three consecutive SC 100 mg injections at the onset of the cluster period, and then monthly **until the end of the cluster period**

One dose of **300 mg** = Three **100 mg** prefilled syringes

mg=milligram; SC=subcutaneous.

Cluster headache periods usually last between 2 weeks to 3 months. Remission periods typically last at least three months.

Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Galcanezumab Dosing:

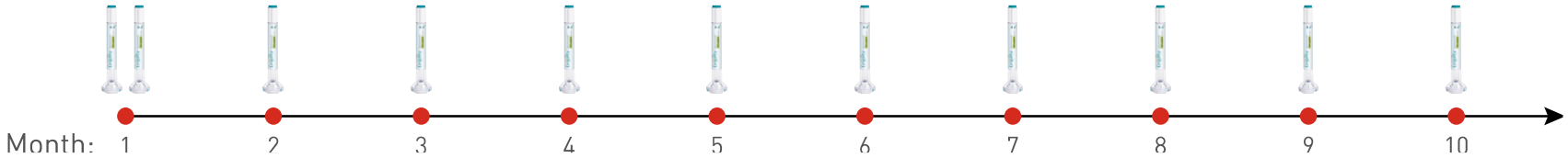
Migraine vs Episodic Cluster Headache

This represents a hypothetical patient.

Recommended dosing for migraine

Loading dose of **240 mg**	=	Two **120 mg** autoinjectors
One dose of **120 mg**	=	One **120 mg** autoinjector

240 mg as loading dose; **120 mg** monthly as maintenance dose



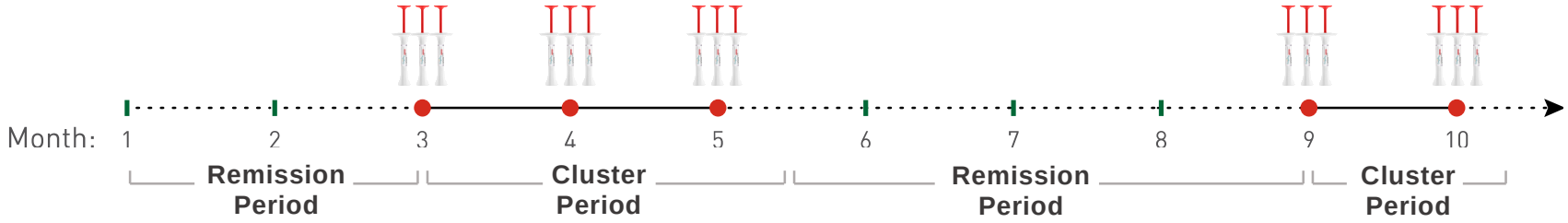
Two consecutive SC 120 mg injections

Subsequent months: One SC 120 mg injection per month

Recommended dosing for episodic cluster headache

One dose of **300 mg**	=	Three **100 mg** prefilled syringes

300 mg monthly during a cluster period



Three consecutive SC 100 mg injections at the onset of the cluster period, and then monthly **until the end of the cluster period**

Cluster headache periods usually last between 2 weeks to 3 months. Remission periods typically last at least three months.

mg=milligram; SC=subcutaneous.

Reference: Data on File. Eli Lilly and Company and/or its subsidiaries.

Summary

- **Galcanezumab is indicated in adults for the treatment of episodic cluster headache**
- As an IgG4 antibody, it is expected that it will
  - Not induce an innate immune complement reaction
  - Degrade into small peptides in the same manner as endogenous IgG, without inducing an immune response
- By targeting and sequestering CGRP, a key neuropeptide in episodic cluster headache, galcanezumab may prevent underlying pathological processes associated with cluster headache and prevent cluster headache attacks

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