

# Galcanezumab modulates Capsaicin-induced C-fiber reactivity

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## Abstract

**Background:** The vasodilatory calcitonin-gene related peptide (CGRP) is understood as pivotal mediator in migraine pathophysiology. Blocking CGRP with small molecules or monoclonal antibodies (CGRP-mAb) reduces migraine frequency. However, prescription of CGRP-mAbs is still regulated and possible predictive measures of therapeutic success would be useful.

**Methods:** Using standardized capsaicin-induced dermal blood flow model, 29 migraine patients underwent a laser speckle imaging measurement before and after administration of galcanezumab. At both sessions dermal blood flow before and after capsaicin stimulation as well as flare size were analyzed over all three trigeminal branches and the volar forearm for extracranial control. Long-term measures were repeated in 14 patients after continuous treatment ranging from 6 to 12 months.

**Results:** Resting dermal blood flow remained unchanged after administration of galcanezumab. Capsaicin-induced dermal blood flow decreased significantly after CGRP-mAb in all tested areas compared to baseline and this was consistent even after 12 months of treatment. However, following galcanezumab administration, the flare size decreased only in the three trigeminal dermatomes, not the arm and was therefore specific for the trigemino-vascular system. None of these two markers distinguished between responders and non-responders.

**Conclusion:** CGRP-mAb changed blood flow response to capsaicin stimulation profoundly and this effect did not change over a 12-month application. Neither capsaicin-induced flare nor dermal blood flow can be used as a predictor for treatment efficacy. These data suggest that the mechanism of headache development in migraine is not entirely CGRP-mediated.

## Keywords

Migraine, trigeminal physiology, facial nociception, vascular capacities, skin physiology, axon-flare reflex, TRPV, CGRP antibodies

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## Introduction

Calcitonin gene-related peptide (CGRP) is a neuropeptide considered to exert a pivotal role in mediating migraine pain. Studies have shown that CGRP itself is not nociceptive (1), whereas infusion of CGRP triggers migraine headaches (2). Clinical trials of small molecular antagonists of CGRP (gepants) (3,4) or monoclonal antibodies (mAbs) (5,6), which neutralise CGRP or block its receptor, have shown that targeting the CGRP signalling pathway can be clinically beneficial to migraine patients.

Topical application of capsaicin to human skin leads to an activation of the transient receptor potential of

the vanilloid receptor type 1 (TRPV1) on nociceptive nerve terminals mediating a local release of CGRP prompting an increase in dermal blood flow (DBF) and flare (7). This response to local application of

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capsaicin can be objectified by laser Doppler or laser speckle imaging (7,8). The non-invasive capsaicin-induced DBF (CIDBF) model is well established for this purpose (7). As this model has already been shown to be reliable and repeated measurements are possible, it is also suitable for longitudinal assessment before and after drug intervention.

Galcanezumab is a mAb that binds to the ligand CGRP and thus inhibits CGRP binding to the receptor (9). In animal studies with rats as well as with non-human primates, galcanezumab was shown to prevent the CGRP-dependent capsaicin induced increase in DBF (10). This was also demonstrated in phase 1 clinical trial in humans using laser Doppler measurement (11). However, these studies were aimed exclusively at investigating pharmacodynamics including different dosing regimens. For this purpose the measurements of DBF were performed exclusively on the arm and not the trigeminal system, which may well behave differently (12,13).

We focused on this question and also whether capsaicin induced CGRP-response can be used as a treatment predictor and compared the galcanezumab-induced reduction in CIDBF and flare expansion between patients with good (>50%) and poor (<50%) clinical response as measured by monthly headache days before and after galcanezumab.

## Material and methods

### Participants

Twenty-nine migraine patients (28 f, 1 m) were recruited by headache specialists in the headache and facial pain outpatient clinic of University Medical Centre Hamburg-Eppendorf (UKE). The participants sample size was estimated from previous behavioral studies without a power calculation due to missing comparable references. All patients fulfilled the diagnosis of migraine (chronic and episodic) according to the ICHD-3 criteria (14). Drug-naïve participants to any CGRP-antibody treatment were eligible when a therapy with galcanezumab 240 mg (loading dose) was planned following national treatment guidelines (15). All participants were free from severe psychiatric, neurological, or dermatological diseases and neither were they taking any regular medication that are assumed to alter DBF, nor had they taken any pain medication in the last 48 hours.

The study was approved by the local ethics committee in Hamburg, Germany (2020-10101.BO-ff) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained before initiation and after explanation of the purpose of the study.

### Experimental design

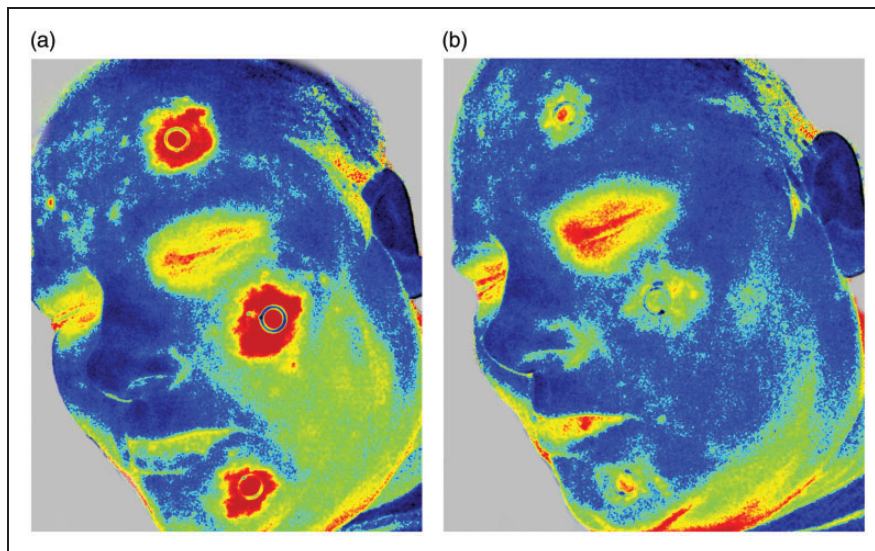
All measurements were carried out in the same temperature-controlled behavioral lab ( $20 \pm 1^\circ$  Celsius). Participants attended to two study sessions before and after the first administration of galcanezumab. Both study sessions took place three weeks apart (pharmacokinetic drug peak blood level) and followed the same protocol. After the completed first study visit (T0), the loading dose of galcanezumab 240 mg was administered subcutaneously by the patient HB under the prior instruction of a headache specialist (T1). Additionally, 14 patients attended a long-term follow-up session after 6 to 12 months of continuous galcanezumab treatment (T2).

At each study sessions the participants were instructed to maintain a supine position on a bed with their heads fixed onto an inflatable cushion to avoid movement (tilted towards the right). Adhesive patches with metal O-rings (8 mm diameter) were applied to the corresponding dermatomes of the left trigeminal branches (V1 [2 cm above the eyebrow along the mid-pupillary line], V2 [above the infraorbital foramen], V3 [2 cm lateral and inferior to the mouth angle] (Figure 1) and one on the left ventral forearm [10 cm distal from the antecubital fossa, midline] as a non-trigeminal, peripheral control.

Subsequently, resting DBF measurements ( $t_0$ ) of the face and the forearm was taken using laser speckle imaging (16,17) (Pericam PSI HR, Perimed AB, Järfälla, Schweden) by sequential image acquisition of one minute each. Afterwards, 0.1 ml of the stimulation agent (0.6% capsaicin/propylene glycol solution, supplied by the hospital pharmacy) was applied to each of the O-rings using a pipette in a pseudorandomized order over the three different branches in the face and five minutes later onto the forearm. DBF was repeatedly measured 15 minutes ( $t_{15}$ ) and 30 minutes after the capsaicin application ( $t_{30}$ ) on the face as well as on the forearm. The five minutes difference between the trigeminal areas and the arm were chosen to allow enough time between measurements of two different sites.

### Data processing

The recorded DBF images were analyzed in randomized order by one of the authors (EGS), who remained blinded to the primary outcome. The measurement of the DBF (perfusion unit (PU) – arbitrary unit) were determined for each test area (V1, V2, V3, forearm) at three timepoints (resting blood flow,  $t_{15}$  and  $t_{30}$ ), as well as the dimension of the flare ( $\text{mm}^2$ ) for each timepoint ( $t_{15}$  and  $t_{30}$ ) before and after the administration of galcanezumab (T0, T1 and T2).



**Figure 1.** Sample Image of patient visualized by Laser-Speckle Imaging device. O-rings with capsaicin application (V1, V2, V3) with corresponding flare reaction and measurement of dermal blood flow (arbitrary perfusion units [PU]). (a) The image on the left shows participant's face 30 minutes after capsaicin application and (b) The same participant three weeks later after administration of the galcanezumab loading dose (240 mg) and also after 30 minutes of capsaicin application.

### Clinical response

Only patients with pre-existing documentation of headache frequency (e.g. headache calendar) were included in the study. Study participants were instructed to continue this calendar for a period of minimum three months (length of galcanezumab therapy in this study). Subsequently, the headache calendars were collected by email or in person at the follow-up appointment. Based on these headache diaries, the participants were divided into good responders (>50%) and poor responders (<50%) based on the reduction in monthly headache days attributable to galcanezumab. As the patients can be assigned to an appropriately difficult-to-treat migraine cohort, the less conservative response rates of 30% were also calculated.

### Analysis and statistics

The statistical analyses were performed using SPSS Statistics 27 (IBM, Armonk, New York, USA). The assumption of a normal distribution was violated for both variables: DBF and flare size and could not be achieved by any transformation. Wilcoxon signed-Rank test was applied to compare between the sessions before and after the administration of galcanezumab (T0 vs. T1 [vs. T2]). Mann-Whitney U test was used for the comparison responders vs. non-responders. A two-sided p-value of <0.05 (not corrected for multiple comparisons) was considered significant.

## Results

### Participant characteristics and behavioral data

A total of 29 patients (28 women, 1 man) with ICHD-3 diagnosis of migraine were enrolled in this study. Twelve of the 29 patients fulfilled the criteria for chronic migraine ( $\geq 15$  headache days/month) and 17 patients for episodic migraine, based on their baseline headache diaries. Twenty patients had migraine without aura, nine with aura. Overall, 13 patients out of 29 (44.8%) were classified as responders (>50% reduction of monthly headache days) to galcanezumab treatment after three months. The less conservative response rate of 30% equaled 20 out of 29 patients (69%) as responders. Patient characteristics are shown in Table 1.

### Dermal blood flow (Capsaicin-induced dermal blood flow)

Resting DBF was unchanged for all tested regions (V1, V2, V3, forearm,  $p > 0.5$ ) in all patients after the administration of galcanezumab (T1). The reduction in CIDBF induced by galcanezumab was significant ( $p < 0.001$ ) for the trigeminal regions 15 as well as 30 minutes after capsaicin (Figure 2). The reduction in CIDBF for the arm induced by galcanezumab was significantly decreased after 30 minutes ( $t_{15}$ :  $p = 0.41$ ,  $t_{30}$ :  $p < 0.001$ ). These results were not associated with migraine diagnosis (episodic vs. chronic), monthly migraine days, any intake of medication or female

**Table 1.** Patient characteristics.

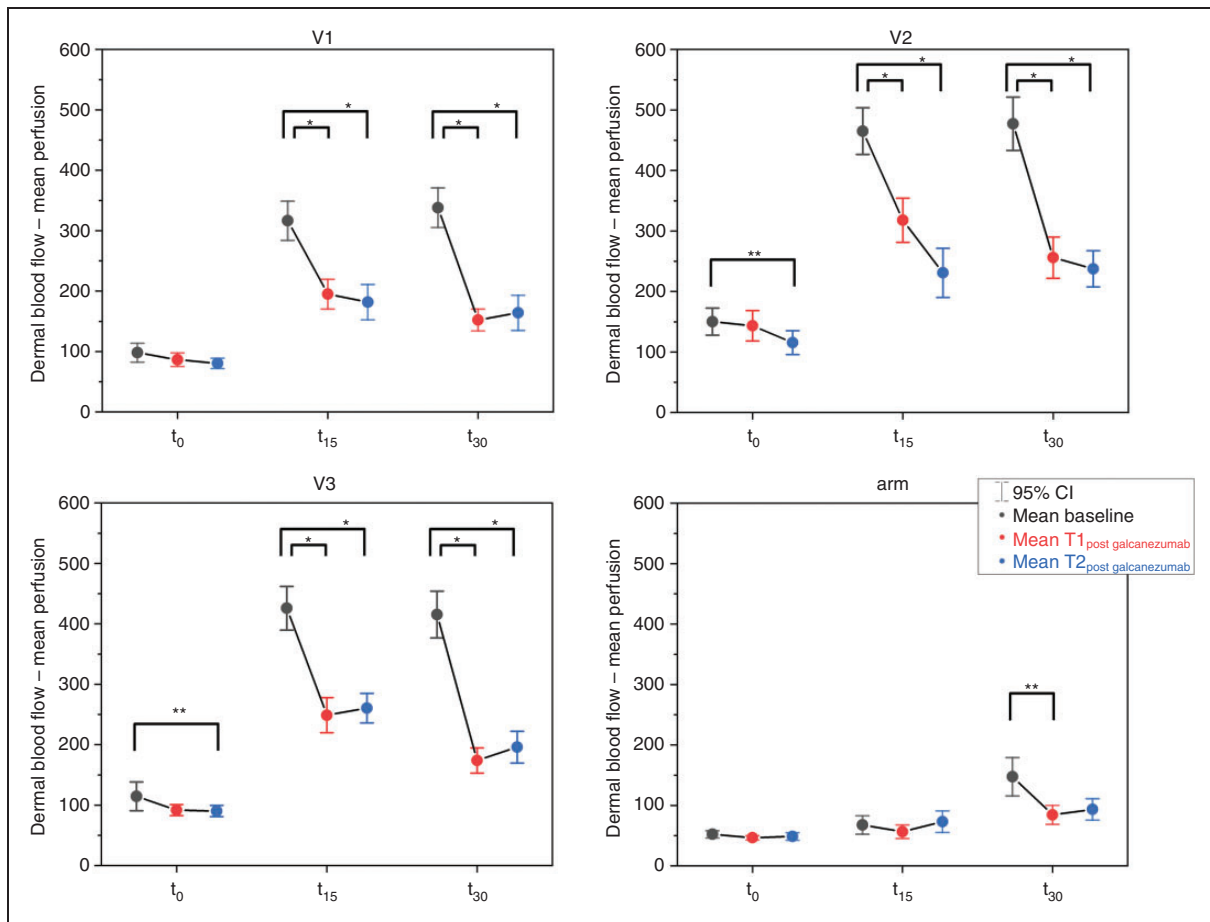
Number	29
Female, n (%)	28 (93.3)
Age, mean ± SD (range), in years	39.5 ± 12.38 (21–60)
Disease duration, mean ± SD (range), in years	20.14 ± 12.91 (2–50)
Headache frequency, mean ± SD (range), days/month	15.86 ± 8.88 (4–30)
Migraine with and without aura, n (%)	5 (17.2)
Migraine without aura, n (%)	20 (69)
Chronic migraine (ICHD-3), n (%)	12 (41.4)
Episodic migraine (ICHD-3), n (%)	17 (58.6)
Responder (>50% reduction of MHD), n (%)	13 (44.8%)

ICHD-3: International Classification of Headache Disorders, 3rd edition; MHD: Monthly Headache Days.

menstrual cycle. The migraine state (ictal vs. inter-ictal) was correlated with the  $V1t_0$  dermal blood flow (Pearson-Correlation:  $\rho = -0.37$   $p = 0.022$ , two-sided) in the migraine subgroup analysis, showing ictal migraine patients have less  $V1t_0$  blood flow than inter-ictal migraine patients ( $77.5 \pm 17.83$  ( $n = 12$ ) vs.  $105.79 \pm 41.88$  ( $n = 17$ ),  $p = 0.022$ , two-sided).

The Mann-Whitney U test for the resting DBF as well as the CIDBF revealed no significant difference between responders and non-responders before versus after administration of galcanezumab and therefore did not allow any kind of predication.

The additional long-term measurement of 14 patients showed that the CIDBF did not change compared to the initial post-galcanezumab session over all tested areas (V1, V2, V3, forearm,  $p > 0.5$ ). Instead, the



**Figure 2.** Dermal blood flow – mean microvascular perfusion. The absolute dermal blood flow values (arbitrary perfusion units [PU]) are plotted for all test areas (V1, V2, V3, arm) and for each timepoint before and after capsaicin application ( $t_0$  = resting phase without Capsaicin,  $t_{15}$ ,  $t_{30}$  (both after Capsaicin), black: baseline = before administration of galcanezumab, red: T1 = after three weeks following galcanezumab loading dosage, blue: T2 = 6–12 months after continuous treatment with galcanezumab. Whiskers indicate the 95% confidence interval.

Significant differences with  $p < 0.001$  are marked with lines\* and  $p < 0.05$  is indicated as\*\*.

resting DBF of V2 ( $p=0.015$ ) and V3 ( $p=0.004$ ) showed a decrease compared to resting DBF before initiation of galcanezumab therapy.

### Flare size

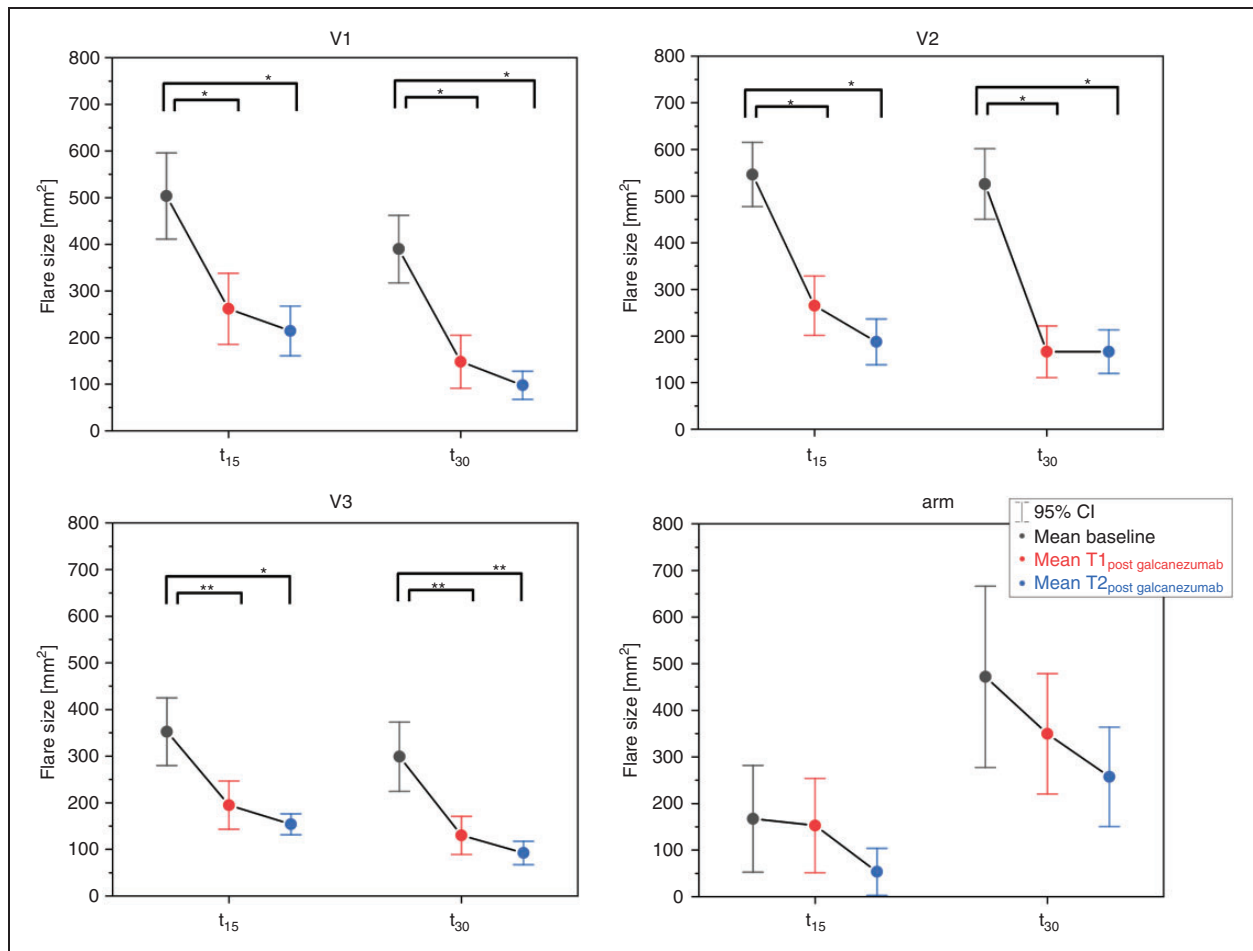
After administration of galcanezumab, the extent of the flare size was significantly decreased in all three trigeminal dermatomes (V1, V2, V3,  $p < 0.001$ ) but not on the forearm ( $t_{15}$ :  $p=0.41$ ,  $t_{30}$ :  $p=0.17$ ). Flare size showed no significant difference between responders and non-responders, neither before nor after administration of galcanezumab.

The long-term evaluation showed the same result, i.e. a decreased flare size (V1, V2, V3,  $p < 0.001$ ) compared to pre-treatment session and no further change compared to the initial post-galcanezumab session size

(V1, V2, V3,  $p > 0.05$ ). The trigeminal specific change of galcanezumab (i.e. not seen in the arm) in flare size was also persistent in the long-term evaluation (Figure 3).

### Discussion

Our data demonstrate that galcanezumab significantly reduced the capsaicin-mediated increase in dermal blood flow and flare response in migraine patients and that this effect persists as long as the medication is given, or, following our data, for at least 12 months. The short-term effect has previously been shown in pharmacological-clinical studies in healthy volunteers (10,11). The change in DBF and CIBDF caused by galcanezumab was not different between the somatic and trigeminal system, although the arm showed



**Figure 3.** Flare size following topical capsaicin application. The absolute dimensions of flare size [in mm<sup>2</sup>] are plotted across all test areas (V1, V2, V3, arm) and for each timepoint after capsaicin application (t<sub>15</sub>, t<sub>30</sub>), black: baseline = before administration of galcanezumab, red: T1 = after three weeks following galcanezumab loading dosage, blue: T2 = 6–12 months after continuous treatment with galcanezumab. Whiskers indicate the 95% confidence interval. Significant differences with  $p < 0.001$  are marked with lines\* and  $p < 0.05$  is indicated as\*\*.

a certain slower latency for the capsaicin-induced increase in dermal blood flow. However, the dimensions of the flare after administration of galcanezumab were consistently reduced in the trigeminal system compared to T0, while the arm showed no significant change. This suggests that the trigeminal system is more susceptible to capsaicin-mediated activation cascades of vasodilatory active peptides than the periphery (18). This may be due to higher receptor densities in the trigeminal areas, while in the periphery other vasoactive peptides such as substance P, VIP or histamine may play a more predominant role and thus the vessels may react less to CGRP antibodies (19–21). Another possibility is that there is a generally higher susceptibility to capsaicin and more widely interconnected free nerve endings in the trigeminal system, compared to the rest of the body (22). Our data thus suggest, that the CIDBF and the extent of the flare is not directly correlated. Using the area under the curve of dermal blood flow as the primary outcome variable to understand CIDBF, as recently published (23), may thus not give the whole picture.

The assumption of a possible prediction by the CIDBF model in term of response to galcanezumab was proved wrong in our study. Recently, Lentsch and colleagues (23) suggested that responders to the CGRP receptor mAb erenumab may have lower CIDBF compared to non-responders before and after the administration. This discrepancy may be due to a slightly different mechanism of action of the receptor mAb, with its strong specificity, while the ligand CGRP also has other receptor affinities, for example to the amylin type 1 receptor (24). Another, more likely explanation is migraine diagnosis. Our data indicate that chronic migraine patients show considerably higher flare extension and at the same time more often fail to achieve a 50% reduction in headache frequency. However, our group calculation is too small to allow firm conclusions.

In addition to the rejection of our primary hypothesis that the extent of the reduction of capsaicin provoked dermal blood flow may allow distinction between responders and non-responders, this study also offers quantitative interpretations and clinical

implications. Already after three weeks, the loading dose of galcanezumab led to a significant reduction (Figure 1) in capsaicin-induced blood flow (38–41%) as well as flare size decrease (48–51%). This effect was also persistent over the entire period of the study under galcanezumab therapy (up to 12 months) and the continuous administration of galcanezumab to lower the resting dermal blood flow above V2 and V3 (Figure 2). Together with the observation that after discontinuation of anti-CGRP antibodies, the migraine prophylactic effect seems to disappear quite soon (25–27), this raises the question of whether long-term blocking of CGRP (release) also has certain functions on homeostasis from a physiological point of view. So far, clinical studies show that the side effect rate of CGRP antibodies is low (28–30), but there are already implications in animal models (31,32) or case series (33–35) that show that a disturbance of this CGRP homeostasis can indeed have serious side effects in vulnerable constellations such as hypertension (36), other vascular events (31,33,35), osteopenia (32), wound healing (34) or gastrointestinal complications (37,38). The robust and nearly complete suppression of CGRP-mediated blood flow changes should be discussed in the clinical field and therapeutic guideline preparation, given that the fact that, unlike other preventatives, many patients seem to need a continuous and seemingly uninterrupted treatment with CGRP mAbs (25).

Taken together, our study confirms the results from previous pre-clinical animal models as well as clinical studies in healthy controls. Furthermore, we could show that dermal blood flow does not necessarily correlate with the extension of the flare. The flare showed no significant effect on capsaicin stimulation in our extra-trigeminal, peripherally controlled study design. Our data do not allow us to differentiate between responders and non-responders, not by CIDBF nor by flare size.

However, possible limitations of this study need to be addressed. Due to the lack of directly comparable references, no reliable power calculation could be carried out, so the results should be considered exploratory. For the same reason, no correction was made for multiple comparisons.

### Clinical implications

- Galcanezumab significantly reduced the capsaicin-mediated increase in dermal blood flow and flare response in migraine patients and this effect persists as long as the medication is given. Certain functions on CGRP homeostasis from a physiological point of view should be further addressed clinically.
- The assumption of a possible prediction by the CIDBF model in term of response to galcanezumab proved wrong. The discrepancy between CGRP receptor and ligand blockade should be further explored.

## Declaration of conflicting interests


The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Hauke Basedau received fees from Novartis and Teva. Kuan Po Peng received speaker honoraria from Teva. Arne May is editor of *Cephalalgia*.

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