

Hard facts. Clear stories.

Copenhagen
Economics

CE

REAL-WORLD EVIDENCE ON THE ECONOMIC IMPLICATIONS OF CGRP INHIBITORS AS PREVENTIVE TREATMENT OF MIGRAINE IN DENMARK

NOVARTIS HEALTHCARE A/S
AUGUST 2023

AUTHORS

Christian Jervelund, Partner
Nikolaj Siersbæk, Managing Economist, Ph.D.
Lærke Kilsdal, Lead Economist

PREFACE

In this report, we estimate the economic implications of calcitonin gene-related peptide (CGRP) inhibitors as preventive treatment of migraine in Denmark based on new and comprehensive real-world data on Danish patients, supplemented by the existing literature and interviews with patients and healthcare professionals. The report is commissioned by Novartis Healthcare A/S.

Novartis Healthcare A/S has asked Copenhagen Economics (CE) to estimate the economic implications of treating migraine patients with CGRP inhibitors as preventive treatment.

To carry out this analysis, we have generated new and comprehensive real-world evidence through a survey administered to Danish patients with migraine, supplemented by an extensive literature review and a total of eight interviews with patients, the Danish Migraine and Headache Association (*Migræne og Hovedpineforeningen*), one of Denmark's leading professors in health economics, and doctors at the Danish Headache Center (*Dansk Hovedpinecenter*); see Figure 1.

The conclusions of the analysis are exclusively those of Copenhagen Economics and do not necessarily reflect the opinions of the project's interviewees or partners. Copenhagen Economics is responsible for all calculations and data processing in this report.

The main conclusions on the economic implications of CGRP inhibitors in the present report are published in the peer-reviewed journal *BMC Neurology*.¹

Figure 1
Contributors and data sources used in the analysis



Note: We have conducted a total of eight interviews with patients, the Danish Migraine and Headache Association (*Migræne og Hovedpineforeningen*), one of Denmark's leading professors in health economics, and doctors at the Danish Headache Center (*Dansk Hovedpinecenter*). The remaining contributors above are listed due to assistance in sharing the survey with patients with migraine or due to significant use of literature or data from the contributors.

Source: Copenhagen Economics.

¹ Siersbæk, N., Kilsdal, L., Jervelund, C., Antic, S., & Bendtsen, L. (2023). Real-world evidence on the economic implications of CGRP-mAbs as preventive treatment of migraine. *BMC Neurology*, 23(1), 1-11.

TABLE OF CONTENTS

Executive summary	2
1 Migraine is a serious condition	5
2 We estimate that 188,500 adults in Denmark live with chronic or episodic migraine	10
3 We have collected real-world data on Danish patients with chronic or episodic migraine	13
4 CGRP inhibitors improve migraine patients' quality of life	14
5 The potential economic gain of CGRP inhibitors amounts to 4.4bn DKK per year	20
6 The Danish economy is missing out on 685m DKK per year due to long waiting times	27
7 Other qualitative effects of migraine and treatment with CGRP inhibitors	31
References	36
Appendix A	48
Appendix B	67
Appendix C	74
Appendix D	75

EXECUTIVE SUMMARY

Our results suggest that there are substantial economic gains associated with treating severely affected migraine patients with CGRP inhibitors, that CGRP inhibitors improve migraine patients' quality of life, and that society is missing out on potential economic gains due to a bottleneck in patients' access to treatment.

Migraine is a serious condition with large implications for patients. In Denmark, treatment with CGRP inhibitors is recommended by the Danish Medicines Council for patients with chronic migraine who have experienced treatment failure on at least two specific types of preventive treatment. A person has chronic migraine if they have headache occurring on 15 or more days per month, of which at least eight days are characterised by migraine.

We estimate that 8,300 patients in Denmark are eligible or conditionally eligible for treatment with CGRP inhibitors. In addition, we estimate that 6,700 patients with high-frequency episodic migraine (8-14 monthly migraine days but not chronic migraine) and 39,800 patients with low-frequency episodic migraine (4-7 monthly migraine days) are within the indication approved by the European Medicines Agency, have experienced treatment failure of at least two preventive treatments, and thus could be candidates for CGRP inhibitors (54,800 patients in total).

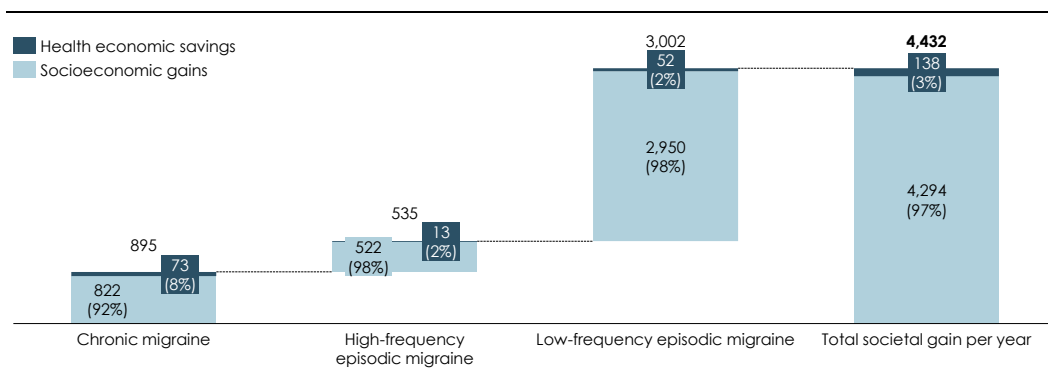
We have **collected real-world data on Danish patients** with at least four monthly migraine days through two Danish patient organisations' patient networks on social media and two informal social media groups for patients with migraine. The final data consists of 362 patients that we use in a tailored economic model to obtain real-world evidence on the economic implications of preventive treatment of migraine with CGRP inhibitors.

Based on the real-world data, we estimate a **total societal gain of 4.4 billion Danish krone (DKK) per year in Denmark from initiating treatment with CGRP inhibitors** in all estimated 54,800 patients with at least four monthly migraine days and two prior treatment failures. The societal gain does not include the cost of CGRP inhibitors, but in Chapter 5 we outline the economic gains relative to the cost of CGRP inhibitors. We estimate that the treatment of patients with chronic migraine currently recommended for treatment in Denmark (8,300 patients) can contribute to economic gains of 895 million DKK per year; see Figure 2.

The societal economic gain from treatment with CGRP inhibitors is **primarily driven by a socio-economic component** of 4,294 million DKK in gross domestic product (GDP) contribution through increased labour supply, and secondly by a health economic component of 138 million DKK due to reduced healthcare spending.² **Assessments of new treatments in Denmark take only health economic savings into account**, which we estimate makes up just 3% of the total economic implications of CGRP inhibitor treatment.

² Health economic savings and socioeconomic gains are theoretically different concepts that in principle should not be directly added together. Throughout this report, we nonetheless allow ourselves this aggregation to make a relative comparison of the two sources of societal gains.

Figure 2
Societal economic gain of CGRP inhibitor treatment in Denmark
 Million DKK per year (% within the group)



Note: The analyses in the health economic and socioeconomic models are based on 362 and 303 respondents, respectively; see Appendix A for an overview of the methodology. We assume that 71.4% of the eligible and conditionally eligible populations from Copenhagen Economics' population mapping will experience at least a 30% response to treatment with CGRP inhibitors based on Cullum et al. (2022); see Appendix B for a sensitivity analysis.

Source: Copenhagen Economics based on Danish Health Authority (2018), Westergaard et al. (2020), sundhed.dk (2020), Katsarava et al. (2011), Naegel and Obermann (2010), Couch for the Amitriptyline Versus Placebo Study Group (2011), Chalmer et al. (2020), Pozo-Rosic et al. (2021), hereinafter called Copenhagen Economics population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), Cullum et al. (2022) and Statistics Denmark (2022a,b).

Patients' access to treatment with CGRP inhibitors has up until the autumn 2022 been restricted to six headache centres³ in Denmark with long waiting lists as a consequence. Today, private neurologists can prescribe treatment with CGRP inhibitors⁴, and an additional five headache centres can now initiate and/or monitor patients that receive treatment with CGRP inhibitors. This has the potential to reduce the waiting lists going forward, however, **waiting time persists and eligible patients can wait up to two years to initiate treatment with CGRP inhibitors.**⁵ Today, approximately 1,950 migraine patients are receiving treatment with CGRP inhibitors at the headache centres.⁶ This is just **23% of the 8,300 patients with chronic migraine** that we estimate are recommended for treatment in Denmark. We find that this bottleneck in access gives rise to **society missing out on 685 million DKK per year or 77% of the total economic gain for this group of patients** with chronic migraine.

³ Migræne & Hovedpineforeningen (2023).

⁴ Pro.medicin.dk (2023).

⁵ Information shared by Novartis.

⁶ Novartis based on patients treated in the secondary sector.

We further find that **CGRP inhibitors improve patients' quality of life** (QoL). Using the generic QoL life instruments EQ-5D-5L and EQ-VAS (Visual Analogue Scale), and the disease-specific QoL instrument HIT-6, we find up to a doubling of patients' QoL after initiating treatment with CGRP inhibitors. In addition, we find that CGRP inhibitors are associated with important improvements in patients' everyday life. For example, subjective sleep quality improves by 21%, fewer patients report adverse effects on relationships with family and friends after initiating treatment with CGRP inhibitors, and patients receiving CGRP inhibitors are less likely to miss social activities due to migraine. Migraine has **large implications for patients both during and between migraine attacks**. We find that uncertainty about the next migraine attack hampers planning and that even between attacks QoL is lower in patients with migraine compared to the general public. In addition, we find that around one-third of all patients with migraine have had an emergency room visit or been hospitalised at least once in their life due to their migraine or migraine symptoms.

CHAPTER 1

MIGRAINE IS A SERIOUS CONDITION

While many people think of a migraine attack as little more than a bad headache, a migraine is a serious condition whose symptoms can be far more debilitating than an ordinary headache.⁷

WHAT IS MIGRAINE?

Migraine is a common disabling primary headache disorder that is divided into two types: migraine without aura and migraine with aura.⁸ Some patients experience early symptoms⁹, occurring hours or days before the migraine, and/or symptoms after the migraine attack.¹⁰ Early symptoms include hyperactivity, hypoactivity, depression, particular food cravings, repetitive yawning, fatigue, and neck stiffness and/or pain. If untreated, a migraine attack usually lasts between four and 72 hours.^{11,12}

Migraine has a hereditary element, meaning that a family history of migraine increases the risk of developing the condition.¹³ Migraines can begin at any age, though the first often occurs during adolescence.¹⁴ Migraines tend to peak during people's 30s and gradually become less severe and less frequent in the following decades. Women are three times as likely as men to suffer from migraines; a large international study has found that migraine is second among the world's causes of disability, and first among young women.¹⁵ Moreover, research has shown that migraine is among the most disabling disorders in terms of its long-term impact on quality of life¹⁶, with attacks peaking during the most productive professional years.¹⁷

DEFINITIONS OF CHRONIC AND EPISODIC MIGRAINE

The literature on migraine distinguishes between chronic migraine and episodic migraine, the former typically being a more serious and debilitating condition than the latter.¹⁸ The definitions of chronic migraine and episodic migraine depend not only on the number of monthly migraine days (MMD) but also on the number of monthly headache days (MHD). A migraine day is by definition a headache day, but a headache day is not necessarily a migraine day. We define an MMD as a day

⁷ Rutberg and Öhrling (2012).

⁸ Headache Classification Committee of the International Headache Society (2018).

⁹ Prodromal symptoms; see Rutberg and Öhrling (2012).

¹⁰ Postdromal symptoms; see Rutberg and Öhrling (2012).

¹¹ Pryse-Phillips et al. (2006).

¹² See Appendix C for an overview of background interviews.

¹³ Russell and Olesen (1995).

¹⁴ Lipton et al. (2007).

¹⁵ James et al. (2018); see also Steiner et al. (2020).

¹⁶ Stovner et al. (2018) and Belam et al. (2005).

¹⁷ Lipton et al. (2007).

¹⁸ Buse et al. (2010) and Lipton and Silberstein (2015).

with at least four continuous hours of migraine, and potentially additional headache. We define an MHD as a day with at least four continuous hours of headache or migraine.^{19,20}

We use the following definitions of chronic, high and low-frequency episodic, and non-episodic migraine in this report:

- **Chronic migraine (CM).** At least 15 MHD, of which at least eight are MMD according to the ICHD-3 definition²¹
- **Episodic migraine (EM).** Fewer than 15 MMD, but at least four MMD.
 - **High-frequency episodic migraine (HFEM)**²². Eight to 14 MMD and potentially additional MHD, adding up to a total of no more than 14 MHD
 - **Low-frequency episodic migraine (LFEM)**²³. Four to seven MMD and any number of MHD
- **Non-episodic migraine**²⁴. Fewer than four MMD, but at least one migraine day per year, and any number of MHD. We do not include this group in our calculations in the present report since CGRP inhibitors are only approved for patients with at least four MMD.²⁵

For an illustration of chronic and episodic migraine, and their relation to the number of associated MMD and MHD, see Figure 3 below. Note that in this figure, we use the label (MHDnm) to indicate a headache day *not* characterised by migraine, i.e., $MHD = MMD + MHDnm$. During a month of 30 days, it is not possible to have more than either 30 MMD or MHDnm, or any combination of MMD and MHDnm adding up to more than 30 days. Depending on the distribution of MMD, MHDnm, and their sum, it is possible to determine whether a person suffers from chronic or episodic migraine, and if so, what subcategory of episodic migraine.

¹⁹ In parts of the migraine literature, a migraine day is defined as a day with at least 30 minutes of migraine; see, e.g., Goadsby et al. (2019), Olesen and Steiner (2004), and the ICHD-2 classification in Headache Classification Subcommittee of the International Headache Society (2004). We apply the more recent ICHD-3 classification; see Headache Classification Committee of the International Headache Society (2018). A headache day is defined as a day with at least four continuous hours of either headache or migraine. This implies that a headache day can be either a day with headache or migraine and that, e.g., ten headache days may be composed of five days with headache only and five days with migraine.

²⁰ Danish Medicines Council (2021a) the ICHD-3 definition of chronic migraine; see Headache Classification Committee of the International Headache Society (2018).

²¹ This definition is the ICHD-3 definition of chronic migraine; see Headache Classification Committee of the International Headache Society (2018). Note that these criteria should be fulfilled for more than three months, and that the chronic migraine can occur with or without medication overuse.

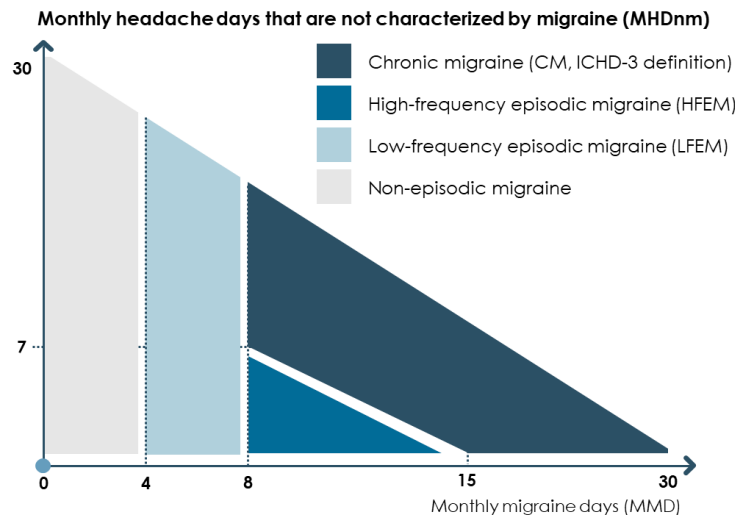
²² See, e.g., terminology in Silberstein et al. (2019) and Chalmer et al. (2020).

²³ See, e.g., terminology in Silberstein et al. (2019).

²⁴ Sometimes referred to as very low-frequency episodic migraine (VLFEM); see, e.g., Jedynek et al. (2021).

²⁵ European Medicines Agency (2018, 2019a-b).

Figure 3
Mapping of chronic and episodic migraine



Source: Copenhagen Economics based on the Danish Medicines Council (2019) and Chalmer et al. (2020).

A peculiarity of the employed definitions of chronic and episodic migraine is the role of MHDnm. Imagine a person with chronic migraine due to eight MMD and seven MHDnm (i.e., 15 MHD in total), and another person with episodic migraine due to 14 MMD and zero MHDnm (i.e., 14 MHD in total). In this scenario, it is not evident that the person with episodic migraine is worse off than the person with chronic migraine, although this is counterintuitive taking the wordings ‘chronic’ and ‘episodic’ into account. It has therefore been proposed in the literature to define chronic migraine as all patients with at least eight MMD and disregard the need for at least 15 MHD.²⁶ However, we do not employ this proposed definition in our analysis but instead, follow the official international definitions in the third version of the International Classification of Headache Disorders (ICHD-3).²⁷

Although low-frequency episodic migraine and non-episodic migraine can appear to be less serious conditions, particularly in light of chronic and high-frequency migraine, the case of Lene explained in Case 1 below underlines that low-frequency episodic migraine is also a greatly debilitating condition.

²⁶ Chalmer et al. (2020).

²⁷ Headache Classification Committee of the International Headache Society (2018).

Case 1: “It is frustrating to know that I am not eligible for a treatment that may help me regain a quarter of my life”, Lene**Lene suffers from low-frequency episodic migraine with six to seven monthly migraine days**

Lene, aged 53, has suffered from migraine for more than three decades. Lene currently experiences six to seven MMD and an additional two to three MHD not characterised by migraine. According to the Danish Medicines Council's current recommendation, Lene is not eligible for treatment with CGRP inhibitors because her monthly migraine and headache days do not place her in the category of chronic migraine, but in low-frequency episodic migraine.

Lene has experienced treatment failure on conventional, preventive migraine medicines

Lene has been treated with many conventional, preventive medicines, but all have led to treatment failure or serious side effects. For a period, Lene responded positively to an antiepileptic medicine that reduced her monthly migraine days. However, Lene eventually developed depression as a side effect of the antiepileptic medicine. Her neurologist therefore decided to discontinue the treatment. Since then, Lene has tried several other preventive treatments, including antihypertensive medicine, but all have led to treatment failure. Against this background, Lene would like to try a treatment that has been developed specifically for migraine patients, e.g., a CGRP inhibitor.

Migraine negatively impacts Lene's life and her ability to perform at work

Lene describes her migraine as a condition that costs her a quarter of her life. Having six to seven monthly migraine days, Lene is on average losing one week per month due to her condition. Lene's migraine affects her not only physically but also mentally, including on days without migraine, as she needs to plan her life according to her condition, e.g., by making sure to get sufficient sleep, eat at roughly the same time every day, and not strain herself. Despite her migraine, Lene is active in the labour market. However, Lene is working fewer hours than she ideally would like to, and she has had to compromise on her career, e.g., by limiting herself to taking jobs with a high degree of flexibility that allows her not to work on migraine days.

Note: The interviewee has approved the case and provided informed consent for its use in this report. See Appendix D for an outline of our methodology regarding patient interviews.

Source: Copenhagen Economics' interview with Lene, who has opted to participate anonymously, on 26 October 2021.

PREVENTIVE MEDICINE AND ATTACK MEDICATION

Medical treatment of migraine comprises preventive (prophylactic) medicine and attack medication.

Preventive medicine is used to reduce the frequency and intensity of migraine days. Many preventive medicines were originally developed with other purposes in mind, e.g., antihypertensives and antiepileptic medication against high blood pressure and epilepsy, respectively. Botulinum toxin, also known as Botox, is approved for the treatment of chronic migraine patients.²⁸ Since 2018, CGRP inhibitors, which were specifically developed to prevent migraine, have been approved by the European Medicines Agency (EMA) as preventive treatment of migraine in adults with at least four MMD.²⁹ In Denmark, CGRP inhibitors are recommended for patients with chronic migraine who

²⁸ Danish Headache Society (2020), Aurora et al. (2010)

²⁹ European Medicines Agency (2018, 2019a-b).

have experienced treatment failure on at least one antihypertensive and one antiepileptic medication.³⁰

Attack medication includes triptans³¹, Treo, ibuprofen, and paracetamol, which can be taken on migraine days to reduce the symptoms. Taking attack medication against migraine too often can trigger serious medication-overuse headaches.³² Medication-overuse headaches may occur if a patient takes, e.g., paracetamol or ibuprofen for 15 or more days per month or attack medication such as triptans for ten or more days per month.³³ When patients take too much attack medication to relieve their symptoms, they run the risk that attacks will increase in frequency as a rebound effect.³⁴ Patients then use more medication to relieve their pain, which induces a vicious cycle. Breaking the cycle involves weaning the patient from the overused medications, setting up a preventive regimen, and setting strict limits on the use of attack medications to relieve acute symptoms.³⁵

³⁰ Danish Medicines Council (2021a).

³¹ See, e.g., Johnston and Rapoport (2010).

³² Olesen (2012).

³³ Westergaard et al. (2020).

³⁴ Tepper and Tepper (2010).

³⁵ Tepper and Tepper (2010).

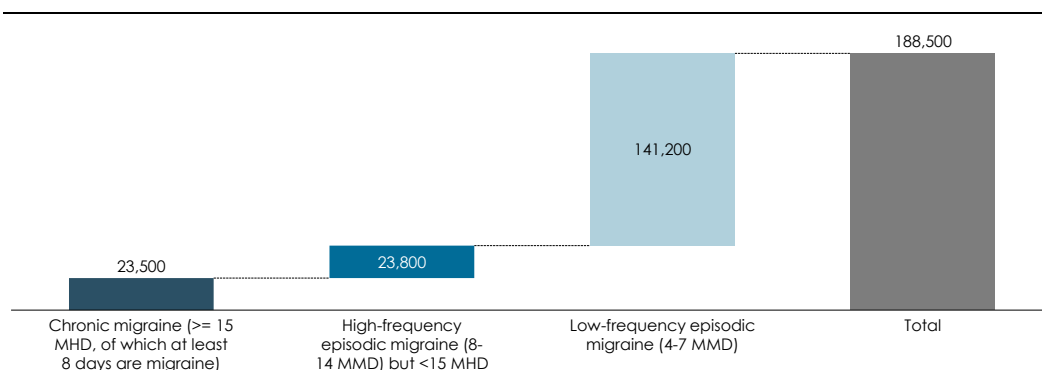
CHAPTER 2

WE ESTIMATE THAT 188,500 ADULTS IN DENMARK LIVE WITH CHRONIC OR EPISODIC MIGRAINE

We estimate that 188,500 adults are living with chronic or episodic migraine in Denmark; see Figure 4 below. Of these, we find that 23,500 adults live with chronic migraine, 23,800 with high-frequency episodic migraine, and 141,200 with low-frequency episodic migraine.

Figure 4

The population of people with migraine and at least four monthly migraine days
Number of adults with migraine and at least four monthly migraine days



Note: Based on expert interviews (see Appendix C for an overview of background interviews), we estimate that 50% of people with chronic migraine with medication overuse will continue to have chronic migraine after medicine overuse has been phased out. Of this 50%, we assume an unchanged share of people experiencing treatment failures, as in the other groups. Chronic migraine is defined according to the ICHD-3 classification.

Source: Copenhagen Economics based on Danish Health Authority (2018), Westergaard et al. (2020), sundhed.dk (2020), Katsarava et al. (2011), Naegel and Obermann (2010), Couch for the Amitriptyline Versus Placebo Study Group (2011), Chalmer et al. (2020), Pozo-Rosic et al. (2021) hereinafter called *Copenhagen Economics population mapping*, and Headache Classification Subcommittee of the International Headache Society (2018).

The estimation of the total population and subcategories of chronic and episodic conditions is based on a comprehensive literature review and interviews with experts³⁶ in the field of migraine. We focus on adults since in the EU CGRP inhibitors are approved for use in adults only.³⁷

³⁶ See Appendix C for an overview of background interviews.

³⁷ European Medicines Agency (2018, 2019a-b).

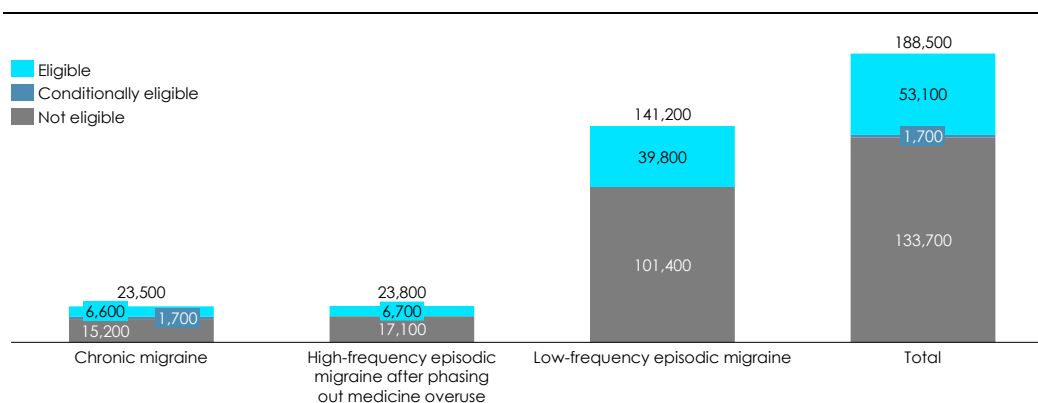
WE ESTIMATE THAT 8,300 ADULT CHRONIC MIGRAINE PATIENTS ARE ELIGIBLE OR CONDITIONALLY ELIGIBLE FOR TREATMENT WITH CGRP INHIBITORS IN DENMARK

The Danish Medicines Council has made a recommendation regarding the use of CGRP inhibitors³⁸ that includes only a subset of the group they are approved for in the EU.³⁹ We estimate that the group counts 8,300 adult patients with chronic migraine that are recommended (6,600) or recommended conditionally upon terminating their overuse of attack medication (1,700); see Figure 5. Our estimate is higher than the Danish Medicine Council's initial estimate of 350 adults with chronic migraine in Denmark and their updated estimate of 3,500 adults⁴⁰ but lower than estimates from leading experts in the field of up to 20,000 patients.⁴¹ In Appendix C, we perform a sensitivity analysis of the results of our economic model using patient populations based on these estimates. We are not aware of what methodology the Danish Medicines Council has employed to reach their estimate.

Figure 5

Migraine patients' eligibility for treatment with CGRP inhibitors

Number of adults with migraine and at least four monthly migraine days



Note: Note that we only include patients with chronic migraine and episodic migraine if they have experienced treatment failure on at least one antihypertensive and one antiepileptic medicine. We assume that the share of patients with medication overuse in a group is the same as the share of patients with at least 15 MHD who have medication overuse as reported in Westergaard et al. (2020). We assume that the share of people with treatment failure is identical for chronic migraine, high-frequency episodic migraine, and low-frequency episodic migraine as reported for patients with migraine in Pozo-Rosich (2021).

Source: Copenhagen Economics' population mapping.

To arrive at the population of 8,300 adult migraine patients who can receive treatment in Denmark, we first employ the following two criteria to filter the 188,500 Danish adult migraine patients that CGRP inhibitors are approved for in Europe:

- patients must have chronic migraine as defined by ICHD-3, and

³⁸ Danish Medicines Council (2021a).

³⁹ The European Medicines Agency has approved CGRP inhibitors for patients with four or more monthly migraine days (EMA 2018, 2019a-b).

⁴⁰ Danish Medicines Council (2021c).

⁴¹ Sundhedspolitisk Tidsskrift (20 February 2022), Propatienter.dk (23 January 2020), and expert interviews; see Appendix C for an overview of background interviews.

- patients must have experienced treatment failure on previous preventive treatment with at least one antihypertensive and one antiepileptic medication.⁴²

This amounts to 6,600 adult patients who are recommended for treatment in Denmark.

In addition, we include patients who are recommended conditional on phasing out their medication overuse by applying the following criteria:

- patients must still require preventive treatment after detoxification⁴³, and
- patients must have experienced treatment failure on previous preventive treatments with at least one antihypertensive and one antiepileptic medication.⁴⁴

This amounts to 1,700 adult patients who are conditionally eligible in Denmark.

WE ESTIMATE THAT 54,800 MIGRAINE PATIENTS WITHIN THE INDICATION APPROVED BY EMA HAVE EXPERIENCED TWO TREATMENT FAILURES

If we consider all adult migraine patients contained in the indication approved by the EMA who we estimate have experienced treatment failure on at least one antihypertensive and one antiepileptic medication, we arrive at a group of 54,800 adult migraine patients. We base Chapter 5 below, in which we consider the societal implications that CGRP inhibitors can give rise to, on this group of 54,800 adult migraine patients.

As shown in Figure 5, the group of 54,800 adult migraine patients is composed of 8,300 adult chronic migraine patients, 6,700 adult high-frequency episodic migraine patients, and 39,800 adult low-frequency episodic migraine patients. The groups, who are all adult patients with at least four MMD, correspond to 29% of adult migraine patients that CGRP inhibitors are approved for by the EMA.

⁴² Danish Medicines Council (2021a).

⁴³ Olesen (2012).

⁴⁴ Danish Medicines Council (2021a).

CHAPTER 3

**WE HAVE COLLECTED REAL-WORLD DATA
ON DANISH PATIENTS WITH CHRONIC OR
EPISODIC MIGRAINE**

To estimate the economic implications of CGRP inhibitors as preventive treatment of migraine in Denmark, we have collected real-world data (RWD) on Danish patients with at least four MMD. Our methodological approach is explained in more detail in Appendix A and briefly summarised here.

First, we developed an economic model tailored to the important implications of migraine based on elements identified in the literature.⁴⁵ Second, we identified other non-economic implications of migraine and CGRP inhibitors for a wider qualitative analysis. Third, we developed a tailored survey to collect RWD on Danish patients for use in the economic model and the wider qualitative analysis. The survey was administered between 11 January and 7 March 2022 via social media by two Danish patient organisations (the Danish Headache and Migraine Association and Migraine Denmark) and two informal Facebook groups. A total of 440 patients qualified for the study (at least four MMD now or in the absence of preventive treatment and at least 18 years old). Of these 440, 362 respondents completed and are used in the health economic model, 303 respondents are used in the socio-economic model, and 307 respondents are used in the qualitative analysis. A total of 16.3% of the 362 respondents receive treatment with CGRP inhibitors. Among the remaining 303 respondents not receiving treatment with CGRP inhibitors, 33.3% receive another preventive treatment; see Table A.2 in Appendix A for descriptive characteristics.

All patients were asked a wide range of questions covering medicine use, healthcare resource utilisation, labour market participation, educational and career choice, QoL, and other implications. Patients who were receiving treatment with CGRP inhibitors at the time of the survey were, in addition, asked to reply to the same questions by recalling a period before they initiated treatment with CGRP inhibitors. This forms a basis for estimating the ‘treatment effect’ of CGRP inhibitors on a wider range of health economic and socioeconomic outcomes than is available in the literature. A similar approach has been used in previous studies.⁴⁶

The data were subsequently analysed to obtain real-world evidence on the economic implications of CGRP inhibitors as preventive treatment of migraine in Denmark. In Chapter 4, we show the implications of CGRP inhibitors on patients’ QoL. We show the economic implications of CGRP inhibitors in Chapter 5 and outline the societal implications of the bottleneck in access to treatment in Chapter 6. In Chapter 7, we cover qualitative implications of CGRP inhibitors and migraine more broadly, including the interictal burden of migraine, i.e., that patients are not only affected by their migraine during but also between migraine attacks.⁴⁷

⁴⁵ Lipton et al. (2003), Stewart et al. (2008), Schultz et al. (2009), Rees and Sabia (2015), Danish Health Authority (2015), Buse et al. (2018), Sussman et al. (2018), Vo et al. (2018), Danish Medicines Council (2021a), and Autio et al. (2022).

⁴⁶ Castaldo et al. (2021).

⁴⁷ See, e.g., Brandes (2008), Buse et al. (2009), Lampl et al. (2016) and Leonardi and Raggi (2019).

CHAPTER 4

CGRP INHIBITORS IMPROVE MIGRAINE PATIENTS' QUALITY OF LIFE

In this chapter, we first focus on the effects of CGRP on migraine patients' QoL as measured on three different and validated QoL instruments; our second focus is on how migraine has traditionally been an under-prioritised condition.

PATIENTS WHO RECEIVE CGRP INHIBITORS EXPERIENCE AN INCREASE IN QUALITY OF LIFE

We consistently find that CGRP inhibitors have a substantial and positive effect on migraine patients' QoL across three different validated QoL instruments.

Using the EQ-5D-5L instrument⁴⁸, we find an improvement from a utility of 0.355 before initiating treatment with CGRP inhibitors to 0.712 after initiation, which constitutes an increase of 101%; see Figure 6. The increase indicates a significant improvement in patients' QoL (0.355 before initiation vs. 0.712 after), and patients treated with CGRP inhibitors have an average EQ-5D-5L score (0.712) closer to the average EQ-5D scores in the general Danish public (0.90) after initiation of treatment. However, the utility level of patients with chronic migraine is still lower than that of the general population. The EQ-5D is a short questionnaire designed to measure patient-reported health in a broad, 'generic' manner. Its strength lies both in its brevity and its ability to measure patient health in a manner that can be compared across patients, diseases, and treatments. Since its development nearly three decades ago, it has become the most widely used Patient-Reported Outcomes questionnaire internationally, used in population health surveys, clinical studies and routine outcomes measurement in healthcare systems.⁴⁹ The EQ-5D is the preferred instrument for the Danish Medicines Council's assessment of new treatments.⁵⁰ We rely on the new preference weights in our estimations.⁵¹

We find an improvement in the EQ-5D Visual Analog Scale (VAS)⁵² from 45.2 before initiating treatment with CGRP inhibitors to 64.6 after initiation, which constitutes an increase of 43%; see Figure 6. As for the EQ-5D-5L instrument, the EQ-5D VAS shows a significant improvement in patients with chronic migraine who are treated with CGRP inhibitors (64.6 compared to 45.2 before initiation) with a score after initiation closer to the general Danish public (82.4). However, the patients still score lower than the general Danish population. Because of its simplicity and practical applicability, the EQ-5D VAS has been widely used to elicit individuals' health value functions, either through measuring preferences for specific health states or through evaluating their own health-related QoL.⁵³

⁴⁸ Herdman et al. (2011); see further explanation and description of the instrument in Appendix A.

⁴⁹ Devlin et al. (2020).

⁵⁰ Danish Medicines Council (2021d).

⁵¹ Jensen et al. (2021a).

⁵² See further description and explanation of the EQ-5D Visual Analog Scale in Appendix A.

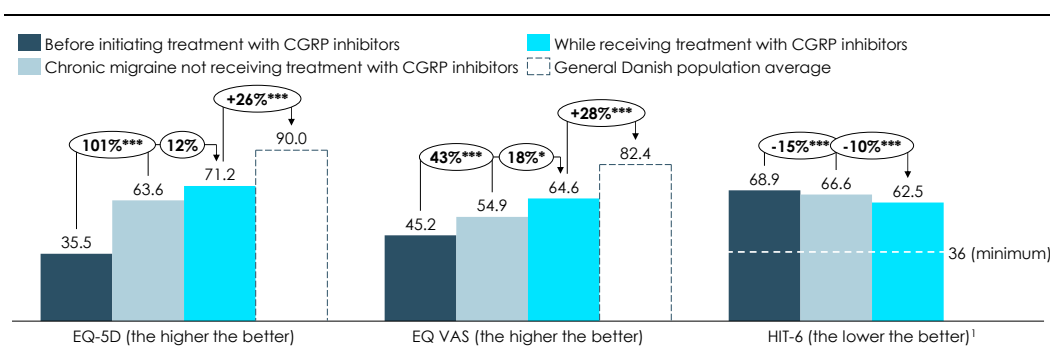
⁵³ Schueli (2005).

Using the Headache Impact Test-6 (HIT-6)⁵⁴, we find an improvement from 68.9 before initiating treatment with CGRP inhibitors to 62.5 after initiation, which constitutes a decrease of 15%; see Figure 6. All scores above 60 are categorised as ‘severe impact’ of migraine.⁵⁵ Note that HIT-6 differs from the other two instruments above in that a lower score indicates a better state of health. HIT-6 is a disease-specific instrument; it was developed to measure a wide spectrum of the factors contributing to the burden of headaches and has demonstrated an ability to generate quantitative and pertinent information on the impact of headaches. HIT-6 consists of six items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. The patient answers each of the six related questions using one of the following five responses: *never*, *rarely*, *sometimes*, *very often*, or *always*. These responses are summed to produce a total HIT-6 score that ranges from 36 to 78, where a higher score indicates a greater impact of headaches on the daily life of the respondent. Extensive testing has shown that HIT-6 is highly reliable and internally consistent.⁵⁶ The relatively low change compared to changes in EQ-5D is likely driven by the range of the HIT-6 scores (36 to 78) and a low correlation between EQ-5D and HIT-6 due to a lack of conceptual overlap.⁵⁷

Figure 6

CGRP inhibitors’ effect on quality of life

Change amongst people currently receiving treatment with CGRP inhibitors



Note: The analysis in the non-economic model is based on 307 respondents. EQ-5D is scaled up with a factor of 100 for illustrative purposes. *** significant at 0.1% significance level; ** significant at 1% significance level; * significant at 5% significance level. /1) HIT-6 ranges from 36 to 78. A change from 68.9 to 62.5 (6.5, difference due to rounding) is thus a change of $6.5 / ((78-36)/100) = 15\%$.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022), and the Danish value set for the EQ-5D (Jensen et al., 2021a). Results for the general Danish population from Jensen et al. (2021b).

We find that respondents may underestimate their QoL as it was before they initiated treatment with CGRP inhibitors. For instance, other research suggests that chronic migraine patients’ QoL assessed by the EQ-5D when not treated with CGRP inhibitors is 68.9, which is in line with our estimate from the group of patients with chronic migraine who do not receive treatment with CGRP inhibitors.⁵⁸ This is, however, considerably higher than the 35.5 we find in our survey for the research

⁵⁴ Kosinski et al. (2003); see further explanation and description of the instrument in Appendix A.

⁵⁵ Impact severity categories are little or no impact (49 or less), some impact (50–55), substantial impact (56–59), and severe impact (60–78); see Yang et al. (2011).

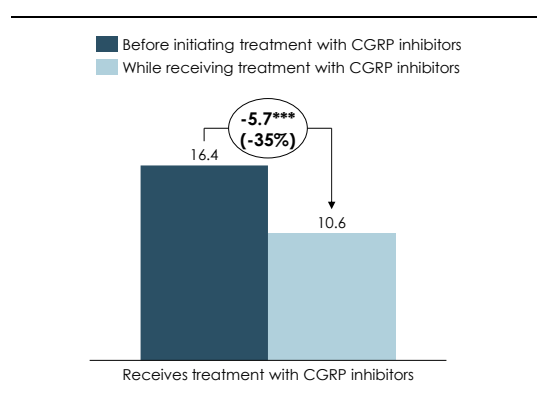
⁵⁶ Shin et al. (2008).

⁵⁷ Oliveira Gonçalves et al. (2022).

⁵⁸ Oliveira Gonçalves et al. (2022).

project on real-world evidence of the economic implications of CGRP inhibitors. The difference may be explained by one of two reasons: recall bias or the prioritisation of most severely affected patients in access to CGRP inhibitors. Recall bias is the extent to which respondents recall their QoL before they initiated treatment with CGRP inhibitors as worse than it was.⁵⁹ Prioritisation would occur if those chronic migraine patients who receive treatment with CGRP inhibitors today were among those most severe patients with chronic migraine, e.g., in terms of lower QoL and/or more MMDs. According to expert interviews, such a prioritisation is not conducted in Denmark, so it does not explain the difference between EQ-5D before and after initiating treatment. We thus believe that patients' self-reported QoL before initiating treatment with CGRP inhibitors may involve a recall bias.

Figure 7
Reduction in monthly migraine days
Number of monthly migraine days (MMD)



Note: The change in MMD for patients receiving treatment with CGRP inhibitors is significant at a 0.1% significance level. Differences are due to roundings.

Source: Copenhagen Economics based on the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022).

The improved QoL following the initiation of treatment with CGRP inhibitors may largely be a consequence of a reduced number of MMD and fewer missed social activities.

Specifically, we find that patients who are currently treated with CGRP inhibitors experience a 35% reduction on average in the number of MMD from 16.4 to 10.6, as compared to before the initiation of their treatment with CGRP inhibitors; see Figure 7.⁶⁰ In Denmark, only patients experiencing at least a 30% response will be allowed to continue with their treatment.⁶¹ Clinical trials of CGRP inhibitors show smaller improvements than estimated here⁶², but a recent RWE study on efficacy and safety in adults with chronic migraine in Denmark finds MMD reductions between 6.5 and 9.5 depending on dosing and time since initiation⁶³, which is a larger estimated reduction in MMD than our estimated difference of 5.7.

One migraine patient who has experienced a dramatic decrease in the number of MMD and an increase in her QoL because of CGRP inhibitors is Marie, as explained in Case 2 below.

⁵⁹ Schmier and Halpern (2004).

⁶⁰ Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022). Note that the results are based on patients currently treated with CGRP inhibitors. A requirement to stay on CGRP inhibitors is a 30% decrease in the number of monthly migraine days, which is aligned with the results. However, patients who have recently initiated treatment with CGRP inhibitors and are still to have the treatment and its effect evaluated may experience less than a 30% decrease. This means that the treatment effect may be higher than 35% if those patients who do not respond to treatment with CGRP inhibitors are excluded from the calculations.

⁶¹ Danish Medicines Council (2021a).

⁶² For example, Tepper et al. (2017).

⁶³ Cullum et al. (2022).

Case 2: “CGRP inhibitors gave me my life back”, Marie**Marie suffers from chronic migraine and is treated with CGRP inhibitors**

Marie, aged 27, has lived with migraine since she was ten years old. In 2018, Marie's migraine worsened, and Marie was now experiencing 28 monthly migraine days. According to the Danish Medicines Council's recommendation, Marie is eligible for treatment with CGRP inhibitors because her monthly migraine days place her in the category of chronic migraine. After about one year on the waiting list, Marie started treatment with CGRP inhibitors in January 2020. Marie responded extraordinarily positively to the treatment and now has just two monthly migraine days, corresponding to a reduction of 26 days per month or 93%.

Marie experienced treatment failure on conventional preventive migraine medicines

Before starting treatment with CGRP inhibitors, Marie was treated with several types of conventional preventive migraine medicines, but they all either led to treatment failure or significant side effects. To relieve her migraine symptoms, Marie was left with attack medication, which she could take on up to nine of her 28 monthly migraine days. This implies that during most days with migraine, Marie's migraine was untreated. Today, having just two monthly migraine days, Marie can reduce the intensity and length of her migraine by taking attack medication every time.

CGRP inhibitors have greatly improved Marie's quality of life

Before treatment with CGRP inhibitors, Marie's quality of life was greatly reduced due to the 28 monthly migraine days. Not only was she unable to work, but she also had to delay her studies by six months, and often cancelled appointments with friends. During the few monthly days without attacks, Marie was always affected by either a recent migraine day or the fear of another upcoming migraine attack. With 28 monthly migraine days, Marie was looking into a future on social benefits or early retirement despite her dreams of becoming a medical doctor. Now, having only two monthly migraine days, Marie is currently finalising her studies and can make appointments with friends. Migraine is no longer dictating Marie's life, and she is looking forward to graduating as a medical doctor. In short, CGRP inhibitors gave Marie her life back.

Note: The interviewee has approved the case and provided informed consent for its use in this report. See Appendix D for an outline of our methodology regarding patient interviews.

Source: Copenhagen Economics' interview with Marie, who has opted to participate anonymously, on 26 October 2021.

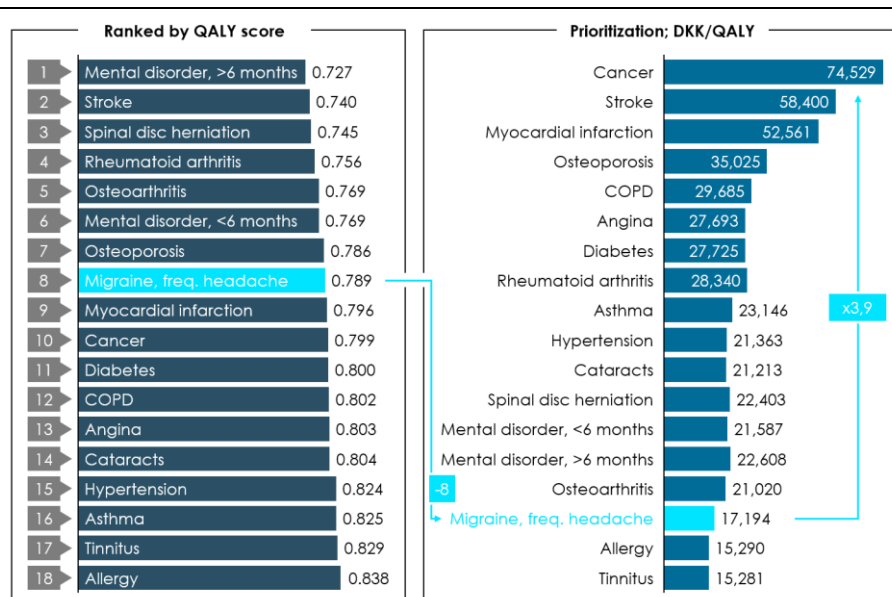
MIGRAINE HAS HISTORICALLY BEEN UNDER-PRIORITISED

Migraine has historically been under-prioritised in Danish healthcare in terms of spending if measured by the average QALY score and the cost of gaining one additional QALY across different chronic conditions, which is used in the Danish Medicines Council's assessment of new treatments.⁶⁴ A QALY is a unit of measurement to assess a person's health-related quality of life on a scale from 0-1, where 1 is a year in perfect health and 0 is death.

In a Danish QALY catalogue⁶⁵, several chronic⁶⁶ conditions have been listed according to patients' self-assessed QALY scores. According to the QALY catalogue, persons suffering from mental disorders for more than six months are most adversely affected and report having a QALY score of just 0.727. This can be seen from the left-hand side of Figure 8, which ranks 18 chronic conditions by their QALY scores from lowest to highest based on data from 2013. Migraine and frequent headaches are eighth from the top, associated with a QALY score of 0.789. We note that the QALY score associated with migraine and frequent headaches shows that it is a serious condition, as it has a lower QALY score than, e.g., cancer and diabetes, conditions that are broadly acknowledged as debilitating. The average QALY score of the general population is 0.846, which is higher than in any of the 18 groups contained in the figure.

Figure 8

Ranking of 18 chronic conditions according to their QALY scores and prioritisation
QALY score, DKK/QALY



Source: Ehlers et al. (2014).

⁶⁴ Danish Medicines Council (2021d).

⁶⁵ Ehlers et al. (2014).

⁶⁶ Please note that the term 'chronic' in this respect refers to conditions that are of a chronic nature and is unrelated to the distinction between chronic and episodic migraine employed in this report.

Moving to the right-hand side of Figure 8, the QALY scores are combined with data on average expenses per person suffering from the individual chronic conditions. The average expenses vary from 59,519 DKK per person diagnosed with cancer to 12,665 DKK per person diagnosed with tinnitus. The average expense per person diagnosed with migraine or frequent headaches is 13,559 DKK.

The study finds that migraine and headaches are among the most under-prioritised conditions in terms of spending. Whereas the condition 'migraine and frequent headaches' is ranked eighth by QALY score, it is ranked just sixteenth in terms of spending. The highest prioritised chronic condition is cancer at 74,529 DKK/QALY, which is 3.9 times as much as the 17,194 DKK/QALY for migraine and frequent headaches. The results can roughly be interpreted as the healthcare sector's 2013 cost of gaining one additional QALY across chronic conditions.⁶⁷ Whether the results would be different if they were based on more recent data is not clear. Note that migraine is grouped with frequent headaches, implying that the QALY score for migraine patients is likely to be overestimated, and hence that migraine patients may be prioritised even lower than is reflected on the right-hand side of Figure 8.

⁶⁷ Ehlers et al. (2014).

CHAPTER 5

THE POTENTIAL ECONOMIC GAIN OF CGRP INHIBITORS AMOUNTS TO 4.4BN DKK PER YEAR

In this chapter, we estimate the economic implications of using CGRP inhibitors to initiate treatment⁶⁸ of the group of 54,800 adult migraine patients experiencing at least four monthly migraine days and treatment failure on at least one antihypertensive and one antiepileptic medication. This is the group of patients that are included in the EMA's approvals⁶⁹, who in addition are required to have experienced treatment failure under the Danish Medicines Council's recommendation.⁷⁰ If one only considers the patients that are recommended for treatment with CGRP inhibitors in Denmark according to the Danish Medicines Council, the relevant patient population is the subgroup of 8,300 patients with chronic migraine. In Appendix C, we perform a sensitivity analysis of the results of our economic model using patient populations based on estimates from the Danish Medicines Council and leading experts in the field.⁷¹

We find a total potential societal gain of 4,432m DKK per year from initiating treatment with CGRP inhibitors in 54,800 adult migraine patients in Denmark; see Figure 9 on the next page.⁷² The cost of CGRP inhibitors and the costs associated with administering CGRP inhibitors are not included in the estimate above. The vast majority of the potential societal implications remain unrealised today as about 1,950 chronic migraine patients are currently treated with CGRP inhibitors in Denmark.⁷³ The total economic gains of 4,432m DKK can be broken down into treatment of 8,300 adult chronic migraine patients, which contributes an economic gain of 895m DKK, treatment of 6,700 adult high-frequency episodic migraine patients, which contributes an economic gain of 535m DKK, and treatment of 39,800 adult low-frequency episodic migraine patients, which contributes an economic gain of 3,002m DKK.

The Danish Medicines Council employs a so-called 'limited societal perspective' in their evaluations of new treatments⁷⁴, which puts migraine treatment at a disadvantage. The limited societal perspective comprises this report's health economic savings as presented above. As health economic costs associated with migraine are relatively small, so are potential savings. For instance, one frequently used response to migraine is sleep, which does not affect health economic spending at all. On the other hand, the Danish Medicines Council's methodology guide states that companies should never include productivity costs in their applications.⁷⁵ In other words, the Danish Medicines Council

⁶⁸ Only patients who experience a response defined as a reduction in monthly migraine days of at least 30% will continue the treatment. We use the words 'treat' and 'initiate treatment' interchangeably throughout the report.

⁶⁹ European Medicines Agency (2018a-b, 2019).

⁷⁰ Danish Medicines Council (2021d).

⁷¹ Danish Medicines Council (2021c), Sundhedspolitisk Tidsskrift (20 February 2022), Propatienter.dk (23 January 2020), and expert interviews; see Appendix C for an overview of background interviews.

⁷² The full savings are calculated as the difference between treating all 54,800 adult migraine patients with **either** CGRP inhibitors **or** other preventive medicines such as topiramate, amitriptyline, and Botox, where the latter is limited to chronic migraine patients. In addition, not all patients respond to CGRP inhibitors, so the population who will continue to receive treatment (those 71.4% experiencing response) is fewer than 54,800 patients.

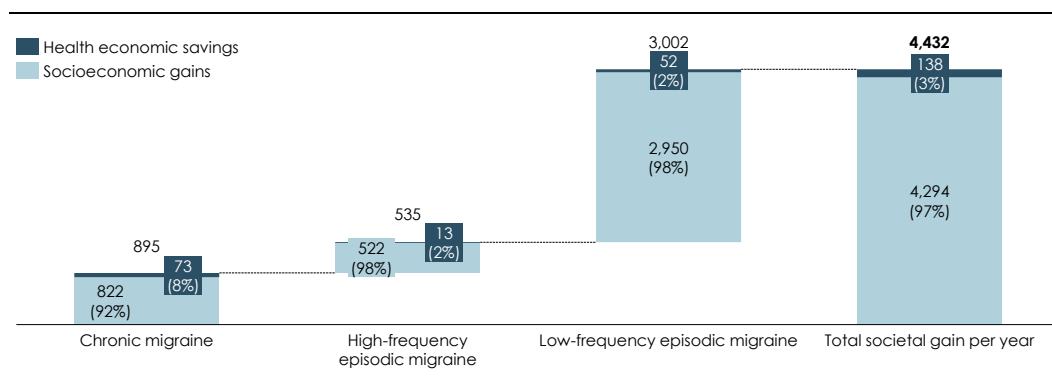
⁷³ Novartis based on patients treated in the secondary sector.

⁷⁴ Danish Medicines Council (2021d).

⁷⁵ Danish Medicines Council (2021d).

disregards socioeconomic implications, which make up the vast majority of total savings in the case of migraine through reduced labour market participation as shown in the figure above.

Figure 9
Societal economic gain of treatment with CGRP inhibitors in Denmark
 Million DKK per year (% within the group)



Note: The health economic model is based on 362 respondents, and the analysis in the socioeconomic model is based on 303 respondents; see Appendix A for methodology. We assume that 71.4% of the eligible and conditionally eligible population from the Copenhagen Economics population mapping will respond to treatment with CGRP inhibitors based on Cullum et al. (2022); see Appendix B for a sensitivity analysis.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), Cullum et al. (2022), and Statistics Denmark (2022a,b).

Health economic savings and socioeconomic gains are theoretically different concepts that in principle should not be directly added together. The reason is that the former has a direct implication for healthcare budgets while the latter is a GDP contribution through increased labour supply. Throughout this report, we nonetheless allow ourselves to make this aggregation to make a relative comparison of the two sources of societal gains. It should be noted that a large part of the socioeconomic GDP contribution will directly affect the Danish budget through increased tax payments.

We use an estimate from the literature based on Danish real-world observational evidence, which shows that 71.4% of migraine patients receiving treatment with CGRP inhibitors will experience a treatment response, i.e., a reduction in their number of monthly migraine days of at least 30%.⁷⁶ The patients who will continue to receive CGRP inhibitors will thus be 71.4% of those initiating treatment.⁷⁷ In Appendix B, we perform a sensitivity analysis on how different response rates will affect the main result.

HEALTH ECONOMIC SAVINGS AMOUNT TO 138M DKK

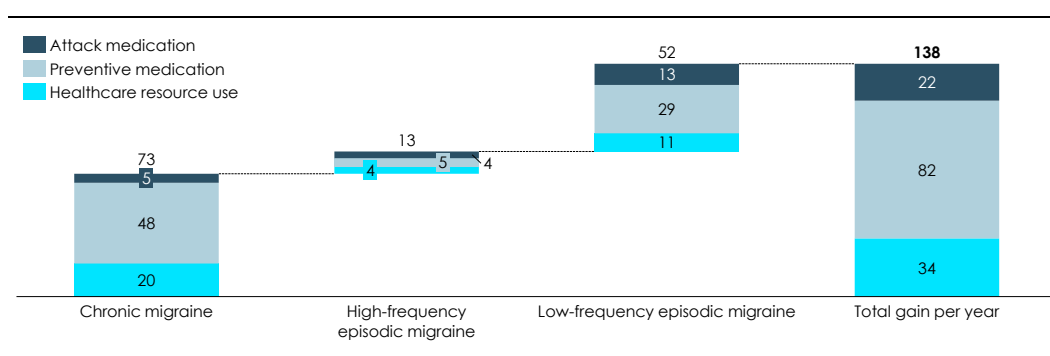
The health economic savings make up 138m DKK, of which 73m DKK stems from patients with chronic migraine; see Figure 10 below. This corresponds to 3% of the total societal gain. Most of the savings stem from reduced spending on preventive treatment of chronic migraine (48m DKK), especially with Botox. Savings on healthcare resource use stems mainly from a reduction in

⁷⁶ Cullum et al. (2022).

⁷⁷ Danish Medicines Council (2021a).

hospitalisations; see Figure A.4 in Appendix A. The health economic savings per patient are the largest for patients with chronic migraine compared to the other patients; see the results per patient in Appendix A. For example, a patient with chronic migraine experiences more monthly migraine days than a patient with low-frequency episodic migraine and is therefore more likely to utilise healthcare resources. The estimated savings per patient in Appendix A are lower than estimates of the total direct cost per patient with chronic migraine thus supporting the validity of our estimates since the entire cost of patients will not be avoided.⁷⁸

Figure 10
Health economic savings of treatment with CGRP inhibitors in Denmark
 Million DKK per year



Note: The health economic model is based on 362 respondents. We assume that 71.4% of the eligible and conditionally eligible population from the Copenhagen Economics population mapping will respond to treatment with CGRP inhibitors based on Cullum et al. (2022); see Appendix B for a sensitivity analysis.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgro (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), Cullum et al. (2022), and Statistics Denmark (2022a,b).

The health economic savings consist of three different and mutually exclusive components: attack medication, preventive medication, and healthcare resource use; see Table 1 below.

Table 1
Components of the health economic savings

SAVINGS	EXPLANATION OF SAVINGS
Attack medication	Reduced healthcare spending due to reduced use of simple analgesics (painkillers), antiemetics (tablet or injection), Treo, and triptans (tablet, melt tablets, nose spray, or injection)
Preventive medication	Reduced healthcare spending due to reduced use of antidepressants, antiepileptics, antihypertensives, beta-blockers, and botulinum toxin (Botox) (latter for chronic migraine only)
Healthcare resource use	Reduced healthcare spending due to reduced healthcare resource use of hospitalisations, emergency room (ER) visits, general practitioner (GP) visits, specialist visits, and outpatient visits

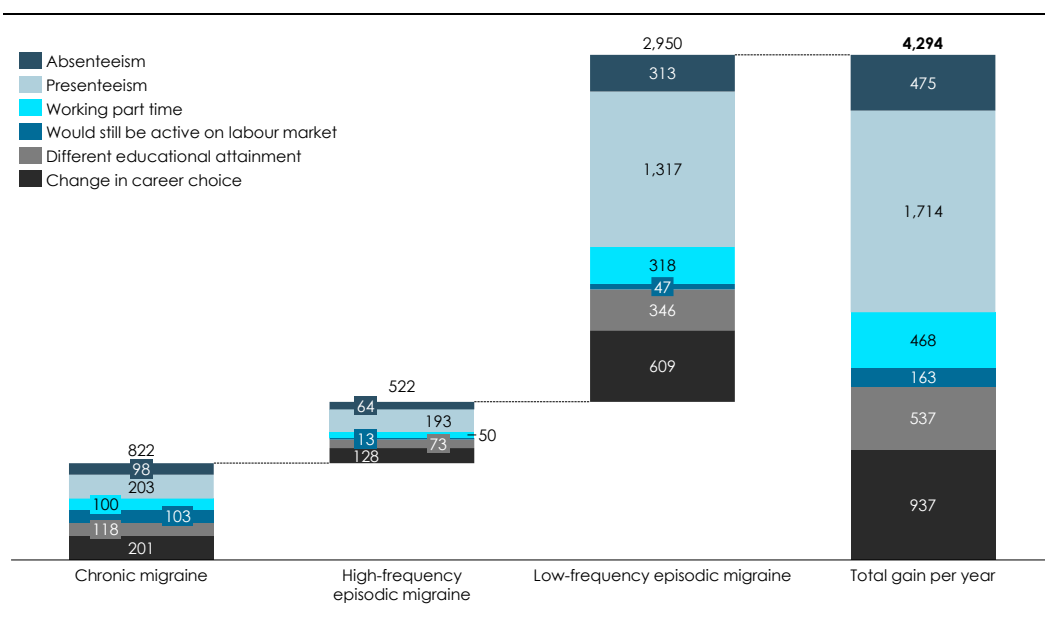
Source: Copenhagen Economics.

⁷⁸ Silberstein et al. (2018).

SOCIOECONOMIC GAINS AMOUNT TO 4,294M DKK

The socioeconomic gains make up 4,294m DKK, corresponding to the remaining 97% of total economic gain; see Figure 11 below. The socioeconomic gain per patient is largest for patients with chronic migraine compared to the other patients; see the results per patient in Appendix A. For example, a patient with chronic migraine experiences more monthly migraine days than a patient with, e.g., low-frequency episodic migraine and therefore often has more sick days due to migraine.

Figure 11
Socioeconomic gain of CGRP inhibitor treatment in Denmark
 Million DKK GDP contribution



Note: The socioeconomic model is based on 303 respondents; see Appendix A for methodology. We assume that 71.4% of the eligible and conditionally eligible population from the Copenhagen Economics population mapping will respond to treatment with CGRP inhibitors based on Cullum et al. (2022); see Appendix B for a sensitivity analysis.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors (2022)* and earnings levels based on education and industry from Statistics Denmark (2022a-b).

The socioeconomic gain of the treatment with CGRP inhibitors in Denmark consists of six different and mutually exclusive components; see Table 2 below.

Table 2
Components of the socioeconomic gain

GAIN	EXPLANATION OF GAIN
Absenteeism	Absenteeism is absence from work and is measured as the number of sick days due to migraine. We measure absenteeism using Item 2 of the Work Productivity and Activity Impairment (WPAI) instrument ¹ and quantify the monetary impact using respondents' self-reported earnings.
Presenteeism	Presenteeism is reduced productivity while working due to migraine. We measure presenteeism using the six-item Stanford Presenteeism Scale (SPS-6) ² and quantify the monetary impact using respondents' self-reported earnings. As a sensitivity analysis, we estimate presenteeism using Item 5 of the WPAI Questionnaire; see Appendix B.
Working part-time	Some patients work part-time due to their migraine, and of these, we include an estimated share who would not work part-time if they had received treatment with CGRP inhibitors and quantify the monetary impact using respondents' self-reported earnings.
Labour market participation	Some patients are out of the labour force, and of these, we include an estimated share who would not have left the labour force if they had received treatment with CGRP inhibitors and quantify the monetary impact using respondents' self-reported earnings.
Educational choice	This gain includes the implications of some patients pursuing different education than they would have liked due to their migraine, which is associated with lower earnings and thus lower GDP contribution and quantify the monetary impact using the average earnings from such a higher educational attainment.
Career choice	This gain includes the implications of some patients not pursuing certain career goals due to their migraine, which is associated with lower earnings and thus lower GDP contribution and quantify the monetary impact using self-reported expected increases in earnings.

Note: 1) Reilly et al. (1993) / 2) Koopman et al. (2002).

Source: Copenhagen Economics.

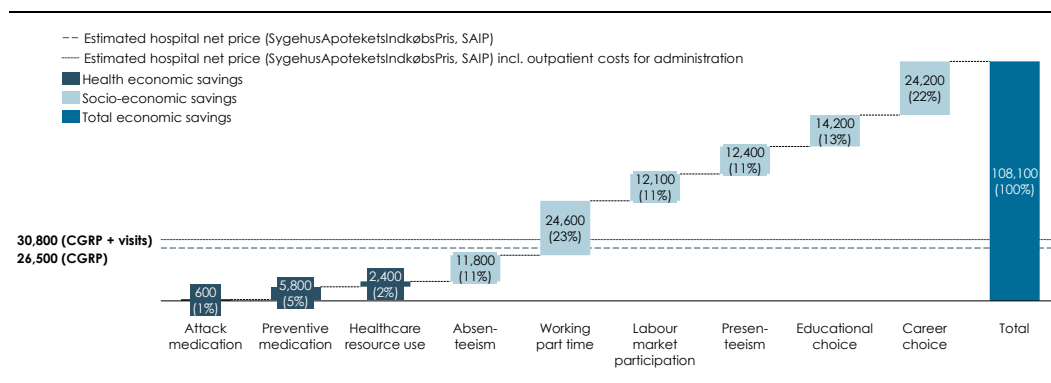
THE SOCIETAL GAINS OUTWEIGH THE AVERAGE HOSPITAL NET PRICE OF CGRP INHIBITORS

The societal gains generated by treating chronic migraine patients with CGRP inhibitors far outweigh the cost of CGRP inhibitors. We estimate that the total societal gain by treating one chronic migraine patient amounts to 108,100 DKK per year. This is significantly higher than the estimated average hospital net price of CGRP inhibitors available on the market in Denmark of 26,500 DKK per year⁷⁹ or 30,800 DKK per year including the additional cost of three outpatient visits to the hospital to receive training in administration⁸⁰; see Figure 12 below.

⁷⁹ Based on the average pharmacy purchase 2022 price (*Apotekets IndkøbsPris, AIP*) of the three CGRP inhibitors marketed in Denmark from the Danish Medicines Agency (2022a) per defined daily dose (DDD; see WHO (2022)) minus an average discount of 35.39% within products purchased for hospital pharmacies (*SygehusApotekets IndkøbsPris, SAIP*) characterised by limited competition (i.e., no generic products) and administered solely in hospitals (See Amgros, 2022).

⁸⁰ Danish Medicines Council (2021a). Patients must receive treatment with CGRP inhibitors every month; however, they are trained to self-administer the treatment and only have to visit the hospital after three, six, and 12 months for a check-up visit and to get additional doses of medicine. The additional cost of three outpatient visits per month is an upper limit, as many patients will decrease the frequency to six months after 18 months of treatment.

Figure 12
Societal gains for patients with chronic migraine and the price of CGRP inhibitors
 DKK per year per patient



Note: See Appendix A for methodology. The estimated price of CGRP inhibitors is based on the average pharmacy purchase price in 2022 (*Apotekets IndkøbsPris, AIP*) of the three CGRP inhibitors marketed in Denmark by the Danish Medicines Agency (2022a) per defined daily dose (DDD; see WHO (2022)) subtracted an average discount of 35.39% within products purchased for hospital pharmacies (*SygehusApotekets IndkøbsPris, SAIP*) characterised by limited competition (i.e., no generic products) and administered solely in hospitals (see Amgros, 2022). The estimated hospital new price, including outpatient costs for administration, includes the cost of three additional outpatient visits per year (Danish Medicines Council, 2021a). Patients must receive treatment with CGRP inhibitors every month; however, they are trained to self-administer the treatment and only have to visit the hospital after three, six, and 12 months for a check-up visit and to get additional doses of medicine. The additional cost of three outpatient visits per month is an upper limit, as many patients will decrease the frequency to six months after 18 months of treatment. Health economic savings and socioeconomic gains are theoretically different concepts that in principle should not be directly added together. The reason is that the former has a direct implication for healthcare budgets while the latter is a GDP contribution through increased labour supply. Throughout this report, we nonetheless allow ourselves to make this aggregation to make a relative comparison of the two sources of societal gains. It should be noted that a large part of the socioeconomic GDP contribution will directly affect the Danish budget through increased tax payments.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022), *pro.medicin.dk* (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), Statistics Denmark (2022a,b), and Danish Medicines Council (2021a).

We estimate that there is a net societal gain in treating chronic migraine patients with CGRP inhibitors even in a scenario where we disregard many of the socioeconomic savings. As mentioned, health economic savings and socioeconomic gains are theoretically different concepts that in principle should not be directly added together. The reason is that the former has a direct implication for healthcare budgets while the latter is a GDP contribution through increased labour supply. Throughout this report, we nonetheless allow ourselves to make this aggregation to make a relative comparison of the two sources of societal gains. In light of this, if we subtract the cost including outpatient visits from all health economic and socioeconomic gains results in a “net gain” of 77,300 DKK per year. It should be noted that a large part of the socioeconomic GDP contribution will directly affect the Danish budget through increased tax payments.

By considering the health economic savings to attack medication, preventive medication, and healthcare resource use in combination with the two socioeconomic gains of absenteeism and working part-time, we arrive at a total gain of 45,200 DKK per year, which already exceeds the 26,500 DKK per year cost of CGRP inhibitors.

The Danish Medicines Council focuses on health economic savings in their evaluations and does not directly incorporate socioeconomic gains. As shown here, only 3% of the total societal gain for patients with chronic migraine from CGRP inhibitor treatment stems from health economic savings. This implies a risk that treatments associated with a societal gain will not be recommended in Denmark.

By combining our estimate of the quality of life gained from Chapter 4 with the information in Figure 12, we can obtain an estimate of the cost per QALY. We find a cost per QALY of 7,200 DKK.⁸¹ The difference in ED-5D scores between patients with chronic migraine who receive treatment with CGRP inhibitors (0.712) and patients with chronic migraine who do not (0.636) from Chapter 4 used in this estimation is not statistically significant.

THE SOCIETAL GAINS ACCRUE TO PEOPLE LIVING WITH MIGRAINE, EMPLOYERS, AND PUBLIC SECTOR BUDGETS

The total societal gain will appear in different budgets as indicated in the National Danish Health Authority's study on the burden of illnesses.⁸²

On the one hand, health economic savings will appear in public sector budgets because resources used in the healthcare system and attack medication are fully publicly financed if patients with at least low-frequency episodic migraine meet the out-of-pocket medicine co-payment threshold of 4,320 DKK in 2022.⁸³

On the other hand, socioeconomic gains will be divided between the migraine patients, their employers, and public sector budgets. Migraine patients will benefit to the extent that they can pursue a career with a higher income level, employers will benefit to the extent that their employees living with migraine can generate more value while having fewer sick days, i.e., less absenteeism, and being more productive while at work, i.e., less presenteeism, and public sector budgets will improve since increased labour supply translates into increased value creation among employees suffering from migraine, leading to higher tax payments.

A note on the educational and career choice gains is warranted. These effects may not occur directly for all patients due to a timing effect. For example, a person aged 45 years old who pursued a different education than the person would otherwise have done when they were deciding on their education, e.g., in their twenties, may not redo their educational choice after initiating treatment with CGRP inhibitors today.

⁸¹ The cost per QALY consists of two elements: 1) the incremental cost of treatment and 2) the incremental outcome measured in QALYs. We calculate the incremental cost of treatment as the estimated average hospital net price including outpatient costs for administration (30,800 DKK) minus the health economic savings of 8,800 DKK, resulting in a total incremental cost of 21,900 DKK per year. The incremental outcome measure in QALY is calculated as the difference in QALY between CM patients not receiving treatment with CGRP inhibitors and patients currently receiving treatment. The mean age is 44 years, and 97% of the respondents in the survey are women. Treatment with CGRP inhibitors does not affect mortality, and the expected life years for the two groups of patients are identical. From Statistics Denmark (Table HISB8) we find that the mean remaining life years for 44-year-old women is 40.22 years. This allows us to calculate a QALY before treatment of $0.64 * 40.22 = 25.6$ and after treatment of $0.71 * 40.22 = 28.6$. This implies a QALY increase of 3.0. Thus, the cost per QALY is $21,900 / 3.0 = 7,200$ DKK per QALY. Differences are due to rounding.

⁸² Danish Health Authority (2015).

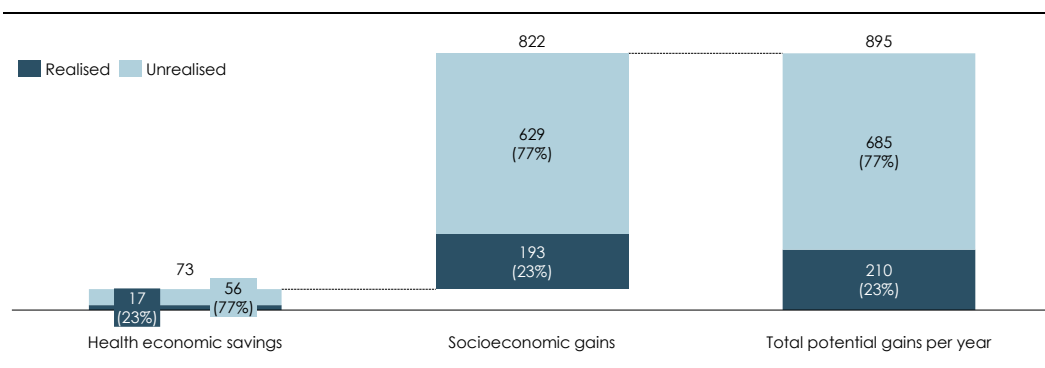
⁸³ Danish Medicines Agency (2021). In cases where migraine patients do not meet the threshold, their out-of-pocket co-payment can still be as low as 15% of the margin, meaning that the attack medicine is still predominantly publicly financed.

CHAPTER 6

THE DANISH ECONOMY IS MISSING OUT ON 685M DKK PER YEAR DUE TO LONG WAITING TIMES

We estimate that the Danish economy is missing out on 685m DKK per year due to a bottleneck in access to CGRP inhibitors representing waiting times of up two years within the group of chronic migraine patients who are recommended for the treatment in Denmark (8,300 patients); see Figure 13 below. This implies that 77% of the total societal gain associated with initiating treatment in all eligible patients with chronic migraine in Denmark is unrealised. The total health economic savings for patients with chronic migraine (73m DKK) are outlined in Figure 10, and the total socio-economic gains for patients with chronic migraine (822m DKK) are outlined in Figure 11.

Figure 13
Realised societal economic gains of CGRP inhibitors and unrealised economic gains due to lack of access
 Million DKK per year



Note: The analysis in the health economic model is based on 362 respondents, and the analysis in the socio-economic model is based on 303 respondents; see Appendix A for methodology. We assume that 71.4% of the eligible and conditionally eligible population from the Copenhagen Economics population mapping will respond to treatment with CGRP inhibitors based on Cullum et al. (2022); see Appendix B for a sensitivity analysis. In the split between realised and unrealised, we include all patients with chronic migraine who are recommended for treatment according to the criteria by the Danish Medicines Council (2021a) and conditionally recommended chronic migraine patients who are eligible after phasing out their medicine overuse.

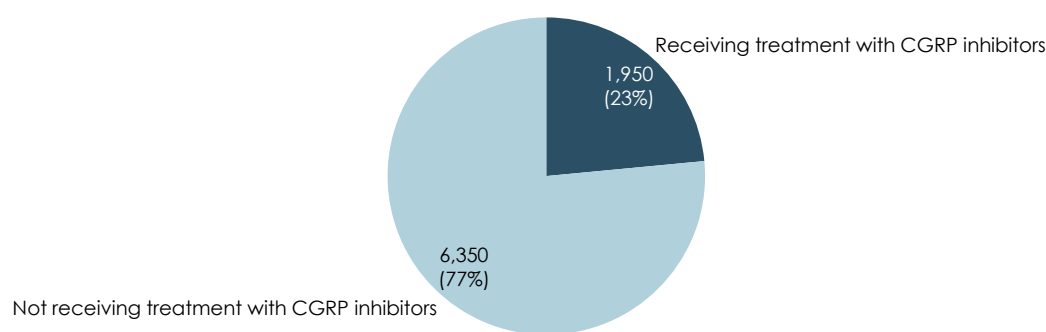
Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgro (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), Cullum et al. (2022), and Statistics Denmark (2022a,b).

LESS THAN 1 IN 4 OF THE 8,300 ELIGIBLE PATIENTS ARE CURRENTLY RECEIVING TREATMENT WITH CGRP INHIBITORS

Approximately 1,950 migraine patients are currently being treated with CGRP inhibitors at the Danish headache centres.⁸⁴ This is just 23% of the 8,300 recommended or conditionally recommended patients with chronic migraine as defined by the Danish Medicines Council's recommendation; see Figure 14 below.

Figure 14
Patients with chronic migraine eligible for treatment with CGRP inhibitors by treatment status

Number of chronic migraine patients (%)



Note: In the split between realised and unrealised, we include all patients with chronic migraine who are eligible for treatment according to the criteria set by the Danish Medicines Council and conditionally recommended chronic migraine patients who are eligible after phasing out their medicine overuse.

Source: Based on Copenhagen Economics population mapping and information shared by Novartis.

However, the missed potential gains may be considerably larger if we consider that 54,800 migraine patients who have experienced treatment failure on at least one antihypertensive and one antiepileptic medication are approved by the European Medicine Agency. This is more than six times the number of migraine patients included in the Danish Medicines Council's recommendation. Notwithstanding the much larger patient population within the indication approved by EMA, in this chapter, we focus solely on the 8,300 patients the Danish Medicines Council has recommended for treatment with CGRP inhibitors.

As an example of the frustration patients experience by not receiving access to treatments, which they are recommended for according to the criteria by the Danish Medicines Council see the case of Dorte in Case 3 below.

⁸⁴ Information shared by Novartis.

Case 3: “It is a waste of resources to send me back and forth between neurologists to try more conventional preventive medicines when I know that I respond positively to CGRP inhibitors”, Dorte**Dorte suffers from chronic migraine with 15 monthly migraine days**

Dorte, aged 58, has suffered from migraine for almost 30 years. Dorte currently has 15 monthly migraine days, which is categorised as chronic migraine. She has experienced treatment failure on conventional preventive medicines, including at least one antihypertensive medicine and one antiepileptic medicine. According to the current recommendation by the Danish Medicines Council, Dorte is eligible for treatment with CGRP inhibitors. However, Dorte has been on the waiting list since January 2021 and is currently looking forward to an appointment scheduled with a headache centre in May 2022.

Dorte went from 15 to one monthly migraine day during a clinical trial with CGRP inhibitors

The preventive treatments Dorte has tried have led to treatment failure, and she has often experienced side effects such as dizziness and feeling groggy. In 2013, Dorte's search for an effective treatment led her to participate in a clinical trial with CGRP inhibitors. Dorte responded well to the treatment, and her monthly migraine days were reduced from 15 to one. However, when the clinical trial ended in 2014, Dorte's treatment with CGRP inhibitors was discontinued.

Since the termination of the clinical study, Dorte has been interested in resuming treatment with CGRP inhibitors. For several years, Dorte was told that this was not possible because the treatment had not yet received marketing approval from the authorities. Today, Dorte treats her migraine solely with attack medication, which makes the waiting time stressful. The stress is to a large extent caused by the limit on attack medication, which prevents her from treating herself on more than nine monthly migraine days. With 15 monthly migraine days in total, this leaves Dorte with approximately six days per month where she cannot relieve her pain. On those days, Dorte can only wait for the migraine attack to cease.

Migraine negatively affects Dorte's life and her ability to work

Dorte is active in the labour market, but she is not working to the extent she would like to. Dorte has a flexible employer and supportive colleagues, which makes it possible for her to put in some hours on days with migraine. However, Dorte stresses that she is not performing at her usual level of productivity during the hours she works on days with migraine.

Note: The interviewee has approved the case and provided informed consent for its use in this report. See Appendix D for an outline of our methodology regarding patient interviews.

Source: Copenhagen Economics' interview with Dorte, who has opted to participate anonymously, on 27 October 2021.

CAPACITY CONSTRAINTS LEAD TO LONG WAITING TIMES

The main reason for the long waiting times to receive treatment with CGRP inhibitors is that up until the autumn 2022 only six headache centres in Denmark could prescribe them and monitor patients. Today, 11 headache centres can prescribe and/or monitor the treatment.⁸⁵ Despite this change, only around 1,950 chronic migraine patients are treated with CGRP inhibitors⁸⁶ at the headache centres. Hence, the headache centres are unable to initiate treatment of additional migraine patients because they spend resources monitoring those already receiving CGRP treatment, which results in long waiting lists.

Today, private neurologist can also prescribe treatment with CGRP inhibitors⁸⁷ which has the potential to reduce the waiting lists going forward. However, it requires a large uptake of private neurologists initiating treatment with CGRP inhibitors if the remaining 6,350 chronic migraine patients are to receive treatment without waiting several years on a waiting list.

⁸⁵ Migræne & Hovedpineforeningen (2023).

⁸⁶ Novartis based on patients treated in the secondary sector.

⁸⁷ Pro.medicin.dk (2023).

CHAPTER 7

OTHER QUALITATIVE EFFECTS OF MIGRAINE AND TREATMENT WITH CGRP INHIBITORS

In this chapter, we present other qualitative effects of migraine and treatment with CGRP inhibitors collected as part of the survey for this research project. More specifically, we present results regarding the implications of CGRP inhibitors on sleep, relationships with family and friends, missing out on social activities, the implications of migraine on planning, ER and hospital visits, and the inter-ictal burden of migraine⁸⁸ by assessing quality of life between attacks.

TREATMENT WITH CGRP INHIBITORS IS ASSOCIATED WITH IMPORTANT IMPROVEMENTS IN PATIENTS' EVERYDAY LIVES

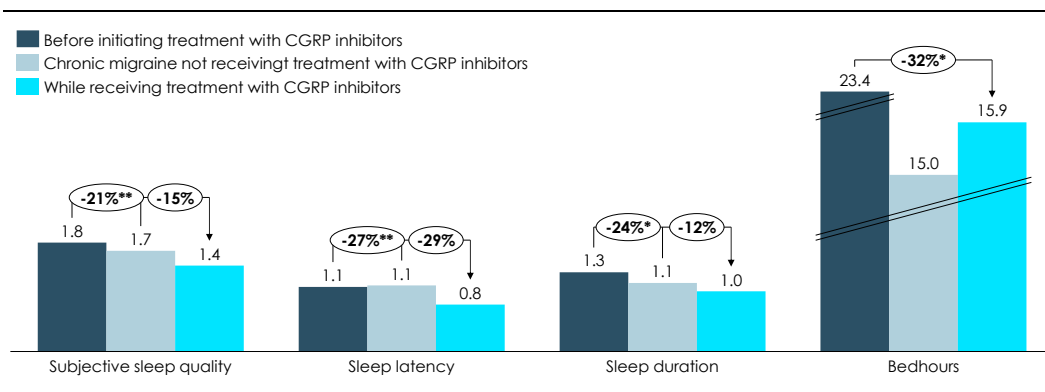
Patients receiving CGRP inhibitors experience better sleep

We find that treatment with CGRP inhibitors unambiguously results in better sleep among migraine patients, assessed using four different instruments; see Figure 15.

Figure 15

Implications on sleep for CGRP inhibitors in Denmark

Change amongst people currently receiving treatment with CGRP inhibitors (lower is better)



Note: The analysis in the non-economic model is based on 307 respondents. *** significant at 0.1% significance level; ** significant at 1% significance level; * significant at 5% significance level.

Source: Copenhagen Economics based on the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022).

First, subjective sleep quality decreases from 1.8 before initiating treatment with CGRP inhibitors to 1.4 following initiation, which constitutes a decrease of 21%. Note that in all quality of sleep-related instruments used in this report, a lower score indicates better sleep. Second, sleep latency decreases from 1.1 before initiating treatment with CGRP inhibitors to 0.8 following initiation, which

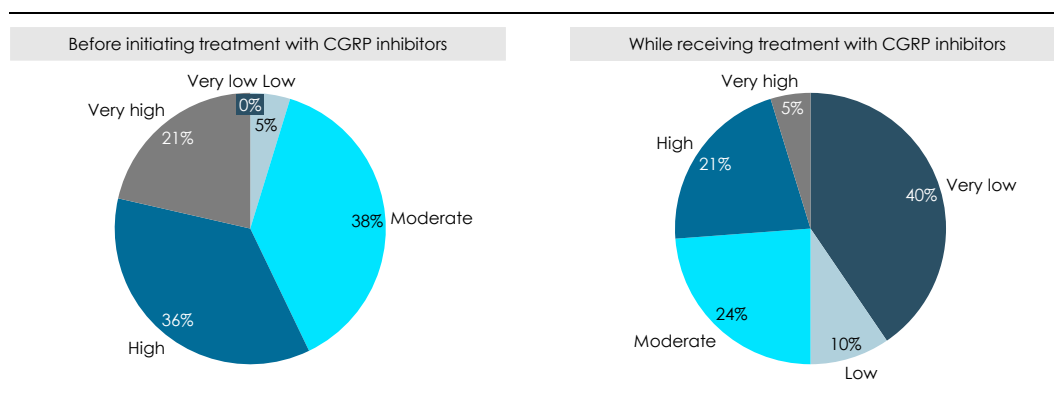
⁸⁸ See, e.g., Brandes (2008), Buse et al. (2009), Lampl et al. (2016) and Leonardi and Raggi (2019).

constitutes a decrease of 27%. Third, sleep duration decreases from 1.3 before initiating treatment with CGRP inhibitors to 1.0 following initiation, which constitutes a decrease of 24%. Fourth, bed hours decrease from 23.4 before initiating treatment with CGRP inhibitors to 15.9 following initiation, which constitutes a decrease of 32%. Overall, patients receiving treatment with CGRP inhibitors experience better sleep, fall asleep more quickly, and spend less time in bed but sleep for more hours.

Fewer patients report negative effects on relationships with family and friends after initiating treatment with CGRP inhibitors

A total of 69% of respondents with chronic migraine state that their migraine had a very high or high negative effect on their relationships with family and friends before initiating treatment with CGRP inhibitors; see Figure 16. In contrast, only 38% of the same patients state that this was the case after they initiated treatment with CGRP inhibitors.

Figure 16
Effect of migraine on relationships with family and friends
 Share of respondents



Note: The analysis in the non-economic model is based on 307 respondents. Self-reported effect on a scale from 0-10: Very low negative effect = 0-2, low negative effect = 3-4, moderate negative effect = 5-6, high negative effect = 7-8, and very high negative effect = 9-10.

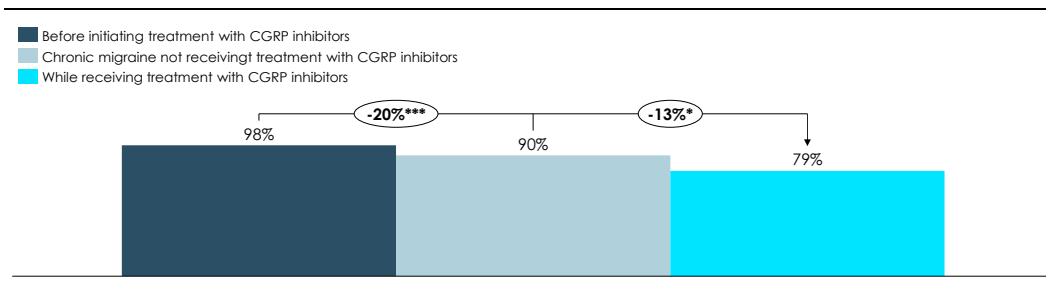
Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022).

Patients receiving CGRP inhibitors are less likely to miss social activities due to their migraine

A total of 79% of patients who receive treatment with CGRP inhibitors report missing social activities in the last three months due to their migraine; see Figure 17. This is a significantly lower share than both patients with chronic migraine who do not receive CGRP inhibitors and patients receiving CGRP inhibitors who recall a period before initiating treatment with CGRP inhibitors. Despite the large improvement, around four in five patients still miss social activities due to their migraine even after initiating treatment with CGRP inhibitors. This is likely driven by the fact that most patients still experience migraine attacks even after initiating treatment with CGRP inhibitors.

Figure 17
CGRP inhibitor treatment and missing social activities

Share of respondents that have missed social activities in the last three months due to their migraine



Note: The analysis in the non-economic model is based on 307 respondents. *** significant at 0.1% significance level; ** significant at 1% significance level; * significant at 5% significance level.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022).

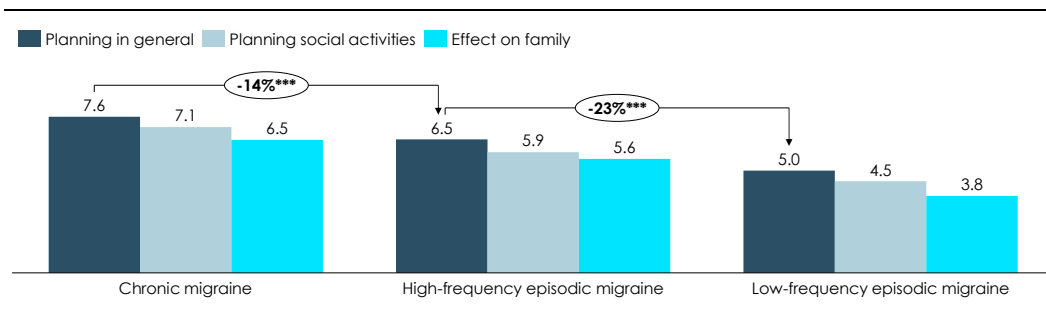
MIGRAINE HAS LARGE IMPLICATIONS FOR PATIENTS BOTH DURING AND BETWEEN ATTACKS

Uncertainty about the next migraine attack hampers planning

We find that migraine patients' ability to perform general planning is hampered by their condition; see Figure 18 below. We find that chronic migraine patients are hampered to a greater extent than high-frequency episodic migraine patients, who are hampered to a greater extent than low-frequency episodic migraine patients. The same pattern is present when we focus on the planning of social activities and the effect on the family.

Figure 18
Effect of uncertainty about next migraine attack on planning

Average score between 0 and 10 (the lower the score, the less the effect)



Note: The analysis in the health economic model is based on 362 respondents. *** significant at 0.1% significance level; ** significant at 1% significance level; * significant at 5% significance level. The changes in planning social activities from CM to HFEM and from HFEM to LFEM are significant at 0.1% and 1% significance levels, respectively. The changes in effect on the family from CM to HFEM and from HFEM to LFEM are significant at 5% and 0.1% significance levels, respectively.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022).

Approximately one in three chronic migraine patients have been to the ER or hospitalised due to their condition

We find that around one-third of chronic migraine patients have been to the ER or hospitalised at least once in their life due to their migraine or symptoms associated with migraine, e.g., speech impairment. More specifically, we find that 37% of chronic migraine patients have been to the ER at least once in their life due to their condition and that 31% of chronic migraine patients have been hospitalised at least once in their life due to their condition. When we focus on high-frequency migraine patients, we find that 21% and 19% have been to the ER and hospitalised, respectively, and when we focus on low-frequency migraine patients, we find the shares to be 17% and 14%, respectively; see Figure 19.

Figure 19

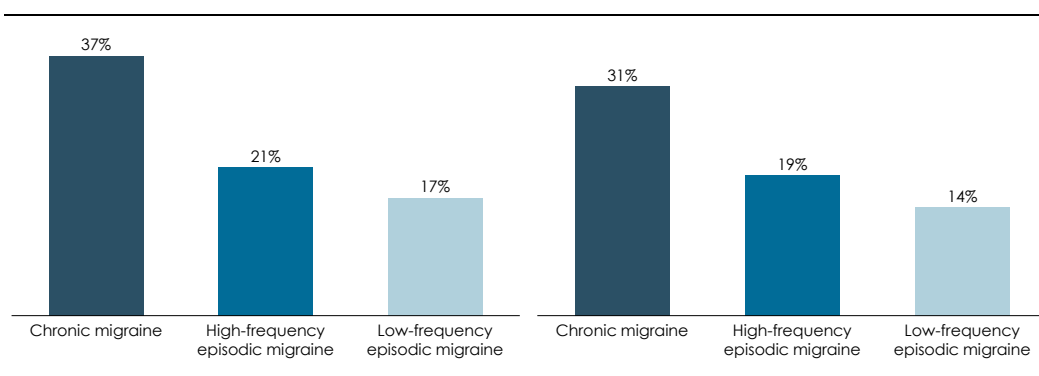
Approximately one in three chronic migraine patients has been to the ER or hospitalised at least once in their life due to migraine

Patients that have been to the ER due to migraine at some point in their life

Share of respondents

Patients that have been hospitalised due to migraine at some point in their life

Share of respondents



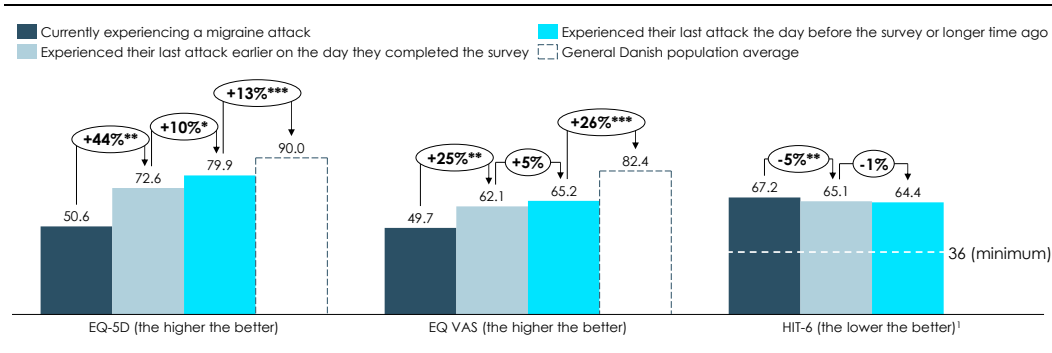
Note: The analysis in the non-economic model is based on 362 respondents.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022).

Quality of life is also negatively impacted between migraine attacks. Migraine patients' quality of life (QoL) is potentially always negatively affected by their conditions due to the interictal burden of migraine.⁸⁹ The negative impact of migraine peaks during migraine attacks, but results from three different QoL instruments suggest that QoL is lower than the average public even when patients are not experiencing an attack. More specifically, we find that a migraine patient currently experiencing a migraine attack has a self-assessed QoL of 50.6 when using the EQ-5d-5L QoL instrument; see Figure 20. During the rest of the day following a migraine attack, we find that the self-assessed QoL increases to 72.6, and further to 79.9 during the following days. This is significantly lower than the average EQ-5D score in the general public. The same results are seen when migraine patients assess their QoL using the EQ-VAS and HIT-6 QoL instruments during and following migraine attacks; see Figure 20 for explanations of the three different QoL instruments.

⁸⁹ See, e.g., Brandes (2008), Buse et al. (2009), Lampl et al. (2016) and Leonardi and Raggi (2019).

Figure 20
Quality of life depends on the time of the last migraine attack
 Differences in QoL scores between patients



Note: The analysis in the non-economic model is based on 307 respondents. EQ-5D is scaled up with a factor of 100 for illustrative purposes. *** significant at 0.1% significance level; ** significant at 1% significance level; * significant at 5% significance level.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on *Real-world evidence on the economic implications of CGRP inhibitors* (2022) and Jensen (2021a,b).

Based on the results in Figure 20, it is evident that migraine is a condition that does not just affect patients intermittently during attacks, as shown by the significantly lower EQ-5D score compared to the general public, even in patients who experienced their last attack the day before the survey or a longer time ago. Secondly, QoL is worse for patients who are currently experiencing an attack *and* patients who very recently (earlier on the day they completed the survey) experienced an attack compared to patients who experienced their last attack the day before the survey or a longer time ago. Attempts to assess migraine patients' QoL should therefore include the interictal burden of migraine between attacks. In other words, it would be incorrect to assume that migraine patients' QoL is unaffected by their conditions between attacks as this would lead to an overestimation of migraine patients' QoL.

REFERENCES

- Amgros (2022). Markedet og årsslides 2021. Shared by Amgros, will be available online later.
- Aurora, S. K., Dodick, D. W., Turkel, C. C., DeGryse, R. E., Silberstein, S. D., Lipton, R. B., Diener, H. C. & Brin, M. F. (2010). OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT I trial. *Cephalalgia*, 30(7), 793-803.
- Autio, H., Purmonen, T., Kurki, S., Mocevic, E., Korolainen, M. A., Tuominen, S.,... & Nissilä, M. (2022). Erenumab Decreases Headache-Related Sick Leave Days and Health Care Visits: A Retrospective Real-World Study in Working Patients with Migraine. *Neurology and Therapy*, 11(1), 223-235.
- Belam, J., Harris, G., Kernick, D., Kline, F., Lindley, K., McWatt, J.,... & Reinhold, D. (2005). A qualitative study of migraine involving patient researchers. *British Journal of General Practice*, 55(511), 87-93.
- Brandes, J. L. (2008). The migraine cycle: patient burden of migraine during and between migraine attacks. *Headache: The Journal of Head and Face Pain*, 48(3), 430-441.
- Buse, D. C., Rupnow, M. F., & Lipton, R. B. (2009). Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life. *Mayo Clinic Proceedings*, 84(5), 422-435.
- Buse, D. C., Manack, A., Serrano, D., Turkel, C., & Lipton, R. B. (2010). Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *Journal of Neurology, Neurosurgery & Psychiatry*, 81(4), 428-432.
- Buse, D. C., Lipton, R. B., Hallström, Y., Reuter, U., Tepper, S. J., Zhang, F.,... & Lenz, R. A. (2018). Migraine-related disability, impact, and health-

related quality of life among patients with episodic migraine receiving preventive treatment with erenumab. *Cephalalgia*, 38(10), 1622-1631.

Buysse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*, 28(2), 193-213.

Castaldo, A. J., Jervelund, C., Corcoran, D., Boysen, H. B., Christiansen, S. C., & Zuraw, B. L. (2021, March). Assessing the cost and quality-of-life impact of on-demand-only medications for adults with hereditary angioedema. *Allergy and Asthma Proceedings*, 42(2), 108-117.

Chalmer, M. A., Hansen, T. F., Lebedeva, E. R., Dodick, D. W., Lipton, R. B., & Olesen, J. (2020). Proposed new diagnostic criteria for chronic migraine. *Cephalalgia*, 40(4), 399-406.

Couch, J. R., & Amitriptyline Versus Placebo Study Group. (2011). Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache: The Journal of Head and Face Pain*, 51(1), 33-51.

Cullum, C. K., Do, T. P., Ashina, M., Bendtsen, L., Hugger, S. S., Iljazi, A., ... & Amin, F. M. (2022). Real-world long-term efficacy and safety of erenumab in adults with chronic migraine: a 52-week, single-center, prospective, observational study. *The Journal of Headache and Pain*, 23(1), 1-8. Danish Headache Society (2020). *Dansk Hovedpine Selskab*. Referenceprogram. Diagnostik og behandling af hovedpinesygdomme og ansigtssmerter, se https://dhos.dk/wp-content/uploads/2020/06/2932-Referenceprogram_2020_final_web-24.06.20.pdf (in Danish). Accessed 2 November 2021.

Danish Health Authority (2015). *Sundhedsstyrelsen*. Sygdomsbyrden i Danmark, see https://www.sst.dk/da/nyheder/2015/~/_media/00c6825b11bd46f9b064536c6e7dfba0.ashx (in Danish). Accessed 8 November 2021.

Danish Health Authority (2018). *Sundhedsstyrelsen*. Danskernes Sundhed – Den Nationale Sundhedsprofil 2017, see <https://www.sst.dk/>

/media/Udgivelser/2018/Den-Nationale-Sundhedsprofil-2017.ashx?la=da&hash=421C482AEDC718D3B4846FC5E2B0EED2725AF517 (in Danish). Accessed 8 November 2021.

Danish Health Data Authority (2017). *Sundhedsdatastyrelsen*. DAGS rates 2017, see <https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2017> (in Danish). Accessed 6 April 2022.

Danish Health Data Authority (2022). *Sundhedsdatastyrelsen*. DRG rates 2022, see <https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022> (in Danish). Accessed 6 April 2022.

Danish Medicines Agency (2021). *Lægemiddelstyrelsen*. Medicintilskudsgrænser, see <https://laegemiddelstyrelsen.dk/da/tilskud/beregn-dit-tilskud/tilskudsgraenser/> (in Danish). Accessed 9 November 2021.

Danish Medicines Agency (2022a). *Lægemiddelstyrelsen*. <https://medicinpriser.dk> (in Danish). Accessed 5 April 2022.

Danish Medicines Agency (2022b). *Lægemiddelstyrelsen*. Omregning fra apotekernes indkøbspris (AIP) til forbrugerpris (ESP), see <https://laegemiddelstyrelsen.dk/da/tilskud/priser/omregning-til-forbrugerpris/> (in Danish). Accessed 6 April 2022.

Danish Medicines Council (2019). *Medicinrådet*. Baggrund for Medicinrådets anbefaling vedrørende erenumab som mulig standardbehandling til forebyggelse af migræne, see https://medicinraadet.dk/media/u2qdr04f/baggrund-for-medicinraadets-anbefaling-vedr-erenumab-til-migraene-vers-10_adlegacy.pdf (in Danish). Accessed 8 November 2021.

Danish Medicines Council (2021a). *Medicinrådet*. Medicinrådets samling af vurderinger af anti-CGRP-antistoffer til behandling af kronisk migræne, herunder kriterier for opstart, monitorering og seponering, see <https://medicinraadet.dk/media/ddzhzc5c/medi>

[cinr%C3%A5dets samling af vurderinger af anti-cgrp-antistoffer til kronisk migr%C3%A6ne-vers-1-0 - m- bilag_adlegacy.pdf](#) (in Danish). Accessed 8 November 2021.

Danish Medicines Council (2021b). *Medicinrådet*.
Medicinrådets lægemiddelrekommandation vedrørende lægemidler til kronisk migræne – inkl. kriterier for opstart, opfølgning og seponering, see https://medicinraadet.dk/media/qjrkw42c/mediciner%C3%A5dets_l%C3%A6gemiddelrekommandation_vedr-l%C3%A6gemidler_til_kronisk_migr%C3%A6ne-vers-1-1_adlegacy.pdf (in Danish). Accessed 8 November 2021.

Danish Medicines Council (2021c). *Medicinrådet*.
Medicinrådet fastholder anbefalinger af migræne-lægemidler, see <https://medicinraadet.dk/nyheder/2021/medicinraadet-fastholder-anbefalinger-af-migraene-laegemidler> (in Danish). Accessed 8 November 2021.

Danish Medicines Council (2021d). *Medicinrådet*.
Medicinrådets metodevejledning for vurdering af nye lægemidler, see https://medicinraadet.dk/media/hciai0yz/mediciner%C3%A5dets_metodevejledning_for_vurdering_af_nye_l%C3%A6gemidler-vers-1-2_adlegacy.pdf (in Danish). Accessed 8 November 2021.

Danish Ministry of Finance (2021). Finansministeriet.
Danmarks Konvergensprogram 2021, see <https://fm.dk/udgivelser/2021/april/danmarks-konvergensprogram-2021/> (in Danish).. Accessed 6 April 2022.

Devlin, N., Parkin, D., & Janssen, B. (2020). Methods for analysing and reporting EQ-5D data (p. 102). Springer Nature.

Dodick, D. W., Ashina, M., Brandes, J. L., Kudrow, D., Lanteri-Minet, M., Osipova, V., Palmer, K., Picard, H., Mikol, D. D. & Lenz, R. A. (2018). ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*, 38(6), 1026-1037.

Ehlers, L. H., Christiansen, P., Larsen, P., & Olesen, A. V. (2014). QALY-katalog som prioriteringsinstrument. *Danish Health Care Journal*, 90(4), 4-9.

European Medicines Agency (2018). Emgality (galcanezumab), see https://www.ema.europa.eu/en/documents/overview/emgality-epar-medicine-overview_en.pdf. Accessed 9 November 2021.

European Medicines Agency (2019a). Aimovig (erenumab), see https://www.ema.europa.eu/en/documents/overview/aimovig-epar-summary-public_en.pdf. Accessed 9 November 2021.

European Medicines Agency (2019b). Ajovy (fremanezumab), see https://www.ema.europa.eu/en/documents/overview/ajovy-epar-medicine-overview_en.pdf. Accessed 9 November 2021.

EuroQol Research Foundation. (2019). EQ-5D-5L User Guide, see <https://euroqol.org/publications/user-guides>. Accessed 6 April 2022.

Foreningen af Speciallæger (FAS) (2018). Overenskomst om speciallægehjælp mellem foreningen af speciallæger (FAS) og regionernes lønnings- og takstnævn (RLTN), see https://www.laeger.dk/sites/default/files/endelig_faps_ok18.pdf (in Danish). Accessed 6 April 2022.

Frattale, I., Caponnetto, V., Casalena, A., Assetta, M., Maddestra, M., Marzoli, F.,... & Ornello, R. (2021). Association between response to triptans and response to erenumab: real-life data. *The Journal of Headache and Pain*, 22(1), 1-6.

Goadsby, P. J., Reuter, U., Hallström, Y., Broessner, G., Bonner, J. H., Zhang, F.,... & Lenz, R. A. (2017). A controlled trial of erenumab for episodic migraine. *New England Journal of Medicine*, 377(22), 2123-2132.

Goadsby, P. J., Dodick, D. W., Martinez, J. M., Ferguson, M. B., Oakes, T. M., Zhang, Q.,... & Aurora, S. K. (2019). Onset of efficacy and duration of response of galcanezumab for the prevention of episodic migraine: a post-hoc analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, 90(8), 939-944.

Headache Classification Subcommittee of the International Headache Society (2004). The

- International Classification of headache disorders, 2nd edition. *Cephalalgia*, 24(1), 9-160.
- Headache Classification Committee of the International Headache Society (2018). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*, 38(1), 1-211.
- Herdman, M., Gudex, C., Lloyd, A., Janssen, M. F., Kind, P., Parkin, D.,... & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research*, 20(10), 1727-1736.
- James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N.,... & Briggs, A. M. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, 392(10159), 1789-1858.
- Jedynak, J., Eross, E., Gendolla, A., Rettiganti, M., & Stauffer, V. L. (2021). Shift from high-frequency to low-frequency episodic migraine in patients treated with Galcanezumab: results from two global randomized clinical trials. *The Journal of Headache and Pain*, 22(1), 1-10.
- Jensen, C. E., Sørensen, S. S., Gudex, C., Jensen, M. B., Pedersen, K. M., & Ehlers, L. H. (2021a). The Danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data. *Applied Health Economics and Health Policy*, 19(4), 579-591.
- Jensen, M. B., Jensen, C. E., Gudex, C., Pedersen, K. M., Sørensen, S. S., & Ehlers, L. H. (2021b). Danish population health measured by the EQ-5D-5L. *Scandinavian Journal of Public Health*, 14034948211058060.
- Johnston, M. M., & Rapoport, A. M. (2010). Triptans for the management of migraine. *Drugs*, 70(12), 1505-1518.
- Katsarava, Z., Manack, A., Yoon, M. S., Obermann, M., Becker, H., Dommès, P.,... & Diener, H. C. (2011). Chronic migraine: classification and comparisons. *Cephalalgia*, 31(5), 520-529.

- Katsarava, Z., Buse, D. C., Manack, A. N., & Lipton, R. B. (2012). Defining the differences between episodic migraine and chronic migraine. *Current pain and headache reports*, 16(1), 86-92.
- Koller, L. S., Diesner, S. C., & Voitl, P. (2019). Quality of life in children and adolescents with migraine: an Austrian monocentric, cross-sectional questionnaire study. *BMC pediatrics*, 19(1), 1-9.
- Koopman, C., Pelletier, K. R., Murray, J. F., Sharda, C. E., Berger, M. L., Turpin, R. S.,... & Bendel, T. (2002). Stanford presenteeism scale: health status and employee productivity. *Journal of occupational and environmental medicine*, 14-20.
- Kosinski, M., Bayliss, M. S., Bjorner, J. B., Ware, J. E., Garber, W. H., Batenhorst, A.,... & Tepper, S. (2003). A six-item short-form survey for measuring headache impact: The HIT-6™. *Quality of life research*, 12(8), 963-974.
- Lampl, C., Thomas, H., Stovner, L. J., Tassorelli, C., Katsarava, Z., Láinez, J. M.,... & Steiner, T. J. (2016). Interictal burden attributable to episodic headache: findings from the Eurolight project. *The Journal of Headache and Pain*, 17(1), 1-10.
- Lebedeva, E. R., Kobzeva, N. R., Gilev, D., & Olesen, J. (2016). Prevalence of primary headache disorders diagnosed according to ICHD-3 beta in three different social groups. *Cephalalgia*, 36(6), 579-588.
- Leonardi, M., & Raggi, A. (2019). A narrative review on the burden of migraine: when the burden is the impact on people's life. *The journal of headache and pain*, 20(1), 1-11.
- Lipton, R. B., Bigal, M. E., Kolodner, K., Stewart, W. F., Liberman, J. N., & Steiner, T. J. (2003). The family impact of migraine: Population-based studies in the USA and UK. *Cephalalgia*, 23(6), 429-440.
- Lipton, R. B., Bigal, M. E., Diamond, M., Freitag, F., Reed, M. L., & Stewart, W. F. (2007). Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*, 68(5), 343-349.
- Lipton, R. B., & Silberstein, S. D. (2015). Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention.

Headache: The Journal of Head and Face Pain, 55, 103-122.

Migræne & Hovedpineforeningen (2023). Hovedpineklivnikker of Smertecentre i Danmark, see <https://www.hovedpineforeningen.dk/behandlingsssteder.html>. Accessed 17 July 2023.

Naegel, S., & Obermann, M. (2010). Topiramate in the prevention and treatment of migraine: efficacy, safety and patient preference. *Neuropsychiatric disease and treatment*, 6, 17-28.

Nationalt Videnscenter for Hovedpine (2022). National Hovedpinesurvey 2021, see <https://videnscenterforhovedpine.dk/national-hovedpinesurvey-2021/>. Accessed 6 April 2022.

Olesen, J., & Steiner, T. J. (2004). The international classification of headache disorders, 2nd edn (ICDH-II). *Journal of Neurology, Neurosurgery & Psychiatry*, 75(6), 808-811.

Olesen, J. (2012). Detoxification for medication overuse headache is the primary task. *Cephalalgia*, 32(5), 420-422.

Oliveira Gonçalves, A. S., Panteli, D., Neeb, L., Kurth, T., & Aigner, A. (2022). HIT-6 and EQ-5D-5L in patients with migraine: assessment of common latent constructs and development of a mapping algorithm. *The European Journal of Health Economics*, 23(1), 47-57.

Pozo-Rosich, P., Lucas, C., Watson, D. P., Gaul, C., Ramsden, E., Ritter, S.,... & Snellman, J. (2021). Burden of Migraine in Patients With Preventive Treatment Failure Attending European Headache Specialist Centers: Real-World Evidence From the BE-COME Study. *Pain and therapy*, 10(2), 1691-1708.

Praktiserende Lægers Organisation (PLO). (2021). Honorartabel dagtid. Overenskomst om almen praksis, 1. oktober 2021 til 31. marts 2022, see https://www.laeger.dk/sites/default/files/honorartabel_2021_oktober.pdf. Accessed 22 October 2021.

Pro.medicin.dk (2022). Look-up for medicine prices, see <https://pro.medicin.dk/>. Accessed 6 April 2022.

- Pro.medicin.dk (2023). CGRP-antistoffer og antagonistter mod migræne, see <https://pro.medicin.dk/Laegemiddelgrupper/Grupper/318765>. Accessed 17 July 2023.
- Propatienter.dk (23 January 2020). Patienter med kronisk migræne fredes foreløbig: Kan stadig få dyr, forebyggende medicin, <https://propatienter.dk/helbred/smerter/2605-patienter-med-kronisk-migraene-fredes-forelobig-kan-stadig-fa-dyr-forebyggende-medicin.html> (in Danish). Accessed 5 November 2021.
- Pryse-Phillips, W., Aubé, M., Bailey, P., Becker, W. J., Bellavance, A., Gawel, M.,... & Wilson, K. (2006). A clinical study of migraine evolution. *Headache: The Journal of Head and Face Pain*, 46(10), 1480-1486.
- Rees, D. I., & Sabia, J. J. (2015). Migraine headache and labor market outcomes. *Health economics*, 24(6), 659-671.
- Reilly, M. C., Zbrozek, A. S., & Dukes, E. M. (1993). The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*, 4(5), 353-365.
- Russell, M. B., & Olesen, J. (1995). Increased familial risk and evidence of genetic factor in migraine. *Bmj*, 311(7004), 541-544.
- Russo, A., Silvestro, M., di Clemente, F. S., Trojsi, F., Bisecco, A., Bonavita, S.,... & Tedeschi, G. (2020). Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. *The Journal of Headache and Pain*, 21(1), 1-14.
- Rutberg, S., & Öhrling, K. (2012). Migraine—more than a headache: Women's experiences of living with migraine. *Disability and rehabilitation*, 34(4), 329-336.
- Schmier, J. K., & Halpern, M. T. (2004). Patient recall and recall bias of health state and health status. *Expert review of pharmacoeconomics & outcomes research*, 4(2), 159-163.
- Schultz, A. B., Chen, C. Y., & Edington, D. W. (2009). The cost and impact of health conditions on

- presenteeism to employers. *Pharmacoeconomics*, 27(5), 365-378.
- Shin, H. E., Park, J. W., Kim, Y. I., & Lee, K. S. (2008). Headache Impact Test-6 (HIT-6) scores for migraine patients: Their relation to disability as measured from a headache diary. *Journal of clinical neurology*, 4(4), 158-163.
- Shmueli, A. (2005). The visual analog rating scale of health-related quality of life: an examination of end-digit preferences. *Health and quality of life outcomes*, 3(1), 1-5.
- Siersbæk, N., Kilsdal, L., Jervelund, C., Antic, S., & Bendtsen, L. (2023). Real-world evidence on the economic implications of CGRP-mAbs as preventive treatment of migraine. *BMC Neurology*, 23(1), 1-11.
- Silberstein, S. D., Lee, L., Gandhi, K., Fitzgerald, T., Bell, J., & Cohen, J. M. (2018). Health care resource utilization and migraine disability along the migraine continuum among patients treated for migraine. *Headache: The Journal of Head and Face Pain*, 58(10), 1579-1592.
- Silberstein, S. D., Stauffer, V. L., Day, K. A., Lipsius, S., & Wilson, M. C. (2019). Galcanezumab in episodic migraine: subgroup analyses of efficacy by high versus low frequency of migraine headaches in phase 3 studies (EVOLVE-1 & EVOLVE-2). *The journal of headache and pain*, 20(1), 1-11.
- Statistics Denmark (2021a). Befolkningstal, see <https://www.dst.dk/da/Statistik/emner/borgere/befolkning/befolkningstal> (in Danish). Accessed 21 October 2021
- Statistics Denmark (2021b). Arbejdsproduktivitets efter branche og prisenhed, see table NP23 (in Danish). Accessed 6 April 2022.
- Statistics Denmark (2022a). Løn efter uddannelse, sektor, aflønningsform, lønmodtagergruppe, lønkomponenter og køn, table LONS11 (in Danish). Accessed 6 April 2022.
- Statistics Denmark (2022b). Løn efter branche (DB07), sektor, aflønningsform, lønmodtagergruppe, lønkomponenter og køn, table LONS40. Accessed 6 April 2022.

- Steiner, T. J., Stovner, L. J., Jensen, R., Uluduz, D., & Katsarava, Z. (2020). Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019.
- Stewart, W. F., Wood, G. C., Razzaghi, H., Reed, M. L., & Lipton, R. B. (2008). Work impact of migraine headaches. *Journal of occupational and environmental medicine*, 50(7), 736-745.
- Stovner, L. J., Nichols, E., Steiner, T. J., Abd-Allah, F., Abdelalim, A., Al-Raddadi, R. M.,... & Murray, C. J. (2018). Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, 17(11), 954-976.
- Sundhed.dk (2020). Kronisk migræne, see <https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/neurologi/tilstande-og-sygdomme/hovedpine/kronisk-migraene/> (in Danish). Accessed 20 October 2021.
- Sundhedspolitisk Tidsskrift (20 February 2020). Medicinrådet godkender nationale kriterier for forebyggende migrænebehandling. <https://sundhedspolitisktidsskrift.dk/nyheder/3047-medicinraadet-godkender-protokol-for-forebyggende-migraenebehandling.html> (in Danish). Accessed 5 November 2021.
- Sundhedspolitisk Tidsskrift (7 April 2022). Danske patienter køber dyr medicin i Sverige: Helle Tønder bruger 50.000 kr. årligt. <https://sundhedspolitisktidsskrift.dk/nyheder/6112-danske-migraenepatienter-kober-dyr-medicin-i-sverige-vi-er-et-rent-land-nar-det-kommer-til-moderne-migraene-medicin.html>. Accessed 13 April 2022.
- Sussman, M., Benner, J., Neumann, P., & Menzin, J. (2018). Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: results from the US societal and payer perspectives. *Cephalalgia*, 38(10), 1644-1657.
- Tepper, S. J., & Tepper, D. E. (2010). Breaking the cycle of medication overuse headache. *Cleveland Clinical Journal of Medicine*, 77(4), 236-42.

- Tepper, S., Ashina, M., Reuter, U., Brandes, J. L., Dolezil, D., Silberstein, S., Winner, P., Leonardi, D., Mikol, D., & Lenz, R. (2017). Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomized, double-blind, placebo-controlled phase 2 trial. *Lancet Neurology*, 16, 425-434.
- Vo, P., Fang, J., Bilitou, A., Laflamme, A. K., & Gupta, S. (2018). Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *The journal of headache and pain*, 19(1), 1-11.
- Westergaard, M. L., Lau, C. J., Allesøe, K., Gjendal, S. T., & Jensen, R. H. (2020). Monitoring chronic headache and medication-overuse headache prevalence in Denmark. *Cephalalgia*, 40(1), 6-18.
- WHO (2022). DDD – Definition and general considerations. https://www.whooc.no/ddd/definition_and_general_considera/. Last accessed 5 April 2022.
- Yang, M., Rendas-Baum, R., Varon, S. F., & Kosinski, M. (2011). Validation of the Headache Impact Test (HIT-6™) across episodic and chronic migraine. *Cephalalgia*, 31(3), 357-367.
- Xu, R., Insinga, R. P., Golden, W., & Hu, X. H. (2011). EuroQol (EQ-5D) health utility scores for patients with migraine. *Quality of life research*, 20(4), 601-60.

APPENDIX A

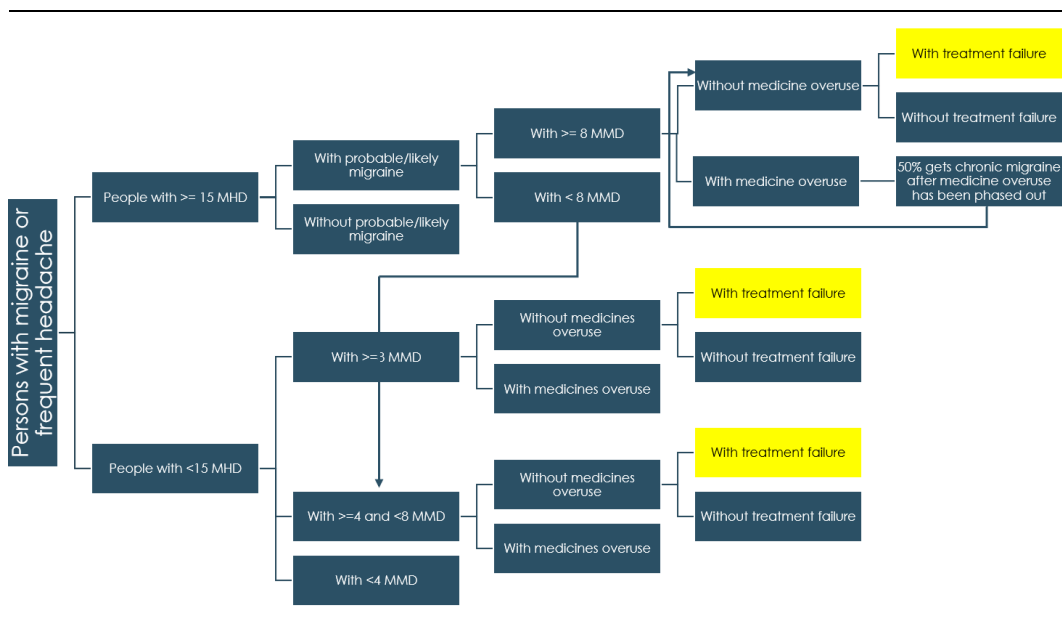
METHODOLOGY

In this appendix, we describe our methodology to estimate the health economic savings and socio-economic gains from using CGRP inhibitors as preventive treatment for migraine in Denmark.

POPULATION MAPPING

Our population mapping is based on estimates from the relevant literature (described in the following sections), Statistics Denmark, and expert interviews. As the first step in our population mapping, we identify the three groups of patients who are within the marketing authorisation of the EMA⁹⁰: chronic migraine (15 or more monthly headache days (MHD) of which at least eight are migraine days (MMD) under the ICHD-3 definition⁹¹), high-frequency episodic migraine (eight to 14 MMD but fewer than 15 MHD) and low-frequency episodic migraine (four to seven MMD). These three groups differ in their numbers of MHD and MMD; see Figure A.1.

Figure A.1
Population mapping



Note: MHD: monthly headache days. MMD: monthly migraine days.
Source: Illustration by Copenhagen Economics.

⁹⁰ European Medicines Agency (2018, 2019a-b).

⁹¹ Headache Classification Committee of the International Headache Society (2018).

We start by estimating the number of people with migraine and frequent headaches. The Danish Health Authority (2018) finds that 16.3% of the adult population in Denmark have migraine or frequent headaches. This corresponds to 747,600 adults in 2021. This group of people is then divided into adults with 15 or more MHD and those with fewer than 15 MHD. This division is based on a recent Danish study (Westergaard et al., 2020), which finds that 3.0% of a representative Danish sample has 15 or more headache days. We then divide the population into those who have at least 15 MHD and probable/likely migraine according to ICHD-2 and those who have at least 15 MHD but *not* probable/likely migraine. This division is based on Katsarava et al. (2011), who find that 2.0% of the German population have 15 or more MHD and probable migraine. This corresponds to 94,000 adults in Denmark. To identify patients with chronic migraine among the 94,000 adults, we further divide the group into patients with eight or more migraine days and fewer than eight migraine days. Katsarava et al. (2011) estimate that 0.5% of the German population has chronic migraine. Katsarava et al. (2011) use the ICH-2 definition of chronic migraine; however, in their actual analysis chronic migraine includes those with and without medication overuse. This corresponds with the ICHD-3 definition of chronic migraine, and it is thus an estimate we can use in our population mapping. We assume that the share of people with chronic migraine is identical in Germany and Denmark and based on population data from Statistics Denmark (2021a), we estimate that 23,500 adults have 15 or more MHD of which eight or more are migraine days; the result is our group of people with chronic migraine. However, only people *without* medication overuse and *with* treatment failure are recommended for treatment according to the Danish Medicine Council's recommendation on CGRP inhibitors. Katsarava et al. (2011) report that 33.3% of people with chronic migraine overuse acute headache medication, and we assume that the share is identical for Danes with chronic migraine. Further, Pozo-Rosich et al. (2021) find that 42.3% of patients with migraine experience treatment failure on two or more medications. This leaves us with $23,500 * (100\% - 33.3\%) * 42.3\% = 6,600$ patients with chronic migraine who are eligible for treatment according to the recommendation by the Danish Medicine Council.⁹² All patient population estimates are rounded to the nearest hundred in the report but used without rounding in calculations.

Some patients who currently suffer from medication overuse-induced chronic migraine will continue to have chronic migraine after their medication overuse has been phased out. Based on expert interviews and Olesen (2012), we estimate that 50% of patients with current medication overuse will continue to be categorised as patients with chronic migraine after their medication overuse has been phased out. This corresponds to 3,900 patients who feed into the 'without medication overuse' group afterwards; see Figure A.1. Again, we subtract patients without treatment failure, i.e., 42.3%, and we label the remaining group of patients 'conditionally eligible' because they fall within the Danish Medicines Council's criteria once their medication overuse has been phased out. In total, 8,300 patients with chronic migraine (CM) can thus receive treatment with CGRP inhibitors in Denmark.

⁹² Danish Medicines Council (2021a).

We apply the same logic as described above to identify patients with high and low-frequency episodic migraine. High-frequency episodic migraine (HFEM) is categorised as people with *fewer* than 15 MMD and between eight and 14 MMD. Chalmer et al. (2020) find that the group of patients with HFEM in Denmark is 101% of the number of patients with CM. This implies that 23,800 patients have HFEM in Denmark. As with CM, we further divide this group into people with or without medication overuse and with or without treatment failure, using the same sources and hence the same shares as for CM. The final group, consisting of $23,800 * (100\% - 33.3\%) * 42.3\% = 6,700$ patients without medication overuse and with treatment failure, makes up the HFEM population.

The group of low-frequency episodic migraine (LFEM) (four to seven MMD) consists of 141,200 people. This is based on Katsarava et al. (2011), who find that 25.5% of the German population has low-frequency episodic *headaches*, corresponding to 660,000 people in Denmark. This estimate is too high because a headache day need not be a migraine day. We therefore scale it down using the relationship between Katsarava et al.'s (2011) result for high-frequency episodic headaches and Chalmer et al.'s (2020) result for HFEM to identify the relationship between headache days and migraine days. We find that migraine days are 21.1% of the headache days, so the group with LFEM is scaled down to $660,000 * 21.1\% = 138,600$ patients. In addition to this group, we know from our mapping of CM that some patients have more than 15 MHD but fewer than eight MMD. This group of patients ($94,000 - 23,500 = 70,500$) feeds into our group of LFEM. To identify the share with four to seven MMD within this group, we calculate the relationship between HFEM and the remaining people with migraine and frequent headaches with 15 or more MHD: $23,800 / (748,000 - 94,000) = 3.6\%$, i.e., 3.6% of the residual group are patients with EM. This leads to a total of $138,600 + 3.6\% * 70,500 =$ approximately 141,200 patients who have LFEM in Denmark. As for CM and HFEM, we only consider people with LFEM without medication overuse and with treatment failure. Using the same sources as for the two other groups, we find that 39,800 people with LFEM are approved for treatment with CGRP inhibitors in Denmark by the EMA and have experienced treatment failure.

COLLECTION OF REAL-WORLD DATA AND GENERATION OF REAL-WORLD EVIDENCE

To estimate the economic implications of CGRP inhibitors as preventive treatment for migraine in Denmark, we have collected real-world data (RWD) on Danish patients with at least four MMD.

First, we developed an economic model tailored to important implications of migraine, e.g., healthcare resource use and absenteeism. Second, we identified other non-economic implications of migraine and preventive treatment with CGRP inhibitors for a wider qualitative analysis. All the elements included and parameters in the respective models are described in further detail in the paragraphs below. Third, we developed a tailored survey to match our tailored economic model. In the survey, we collect RWD. To our knowledge, no previous studies have examined the health economic, socioeconomic, and non-economic aspects of migraine in Denmark simultaneously using RWD.

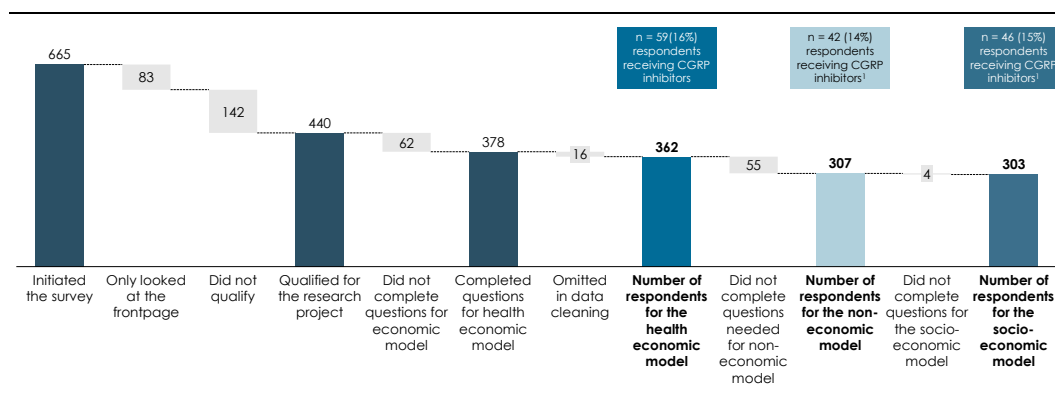
The tailored survey was created by Copenhagen Economics, and the survey was administered via social media by the Danish Migraine and Headache Association (*Migræne og Hovedpineforeningen*) and Migraine Denmark (*Migræne Danmark*), who posted information about the survey on their Facebook pages. The Danish Migraine and Headache Association and

Migraine Denmark have approximately 13,200 and 2,200 followers on Facebook respectively as of 6 April 2022. The survey was open from 11 January through 7 March 2022. The survey and communication regarding the survey were formulated in Danish.

To increase the number of respondents, we made additional posts in the Facebook groups “Migraine – is NOT just headache!” (“*Migræne – er IKKE bare hovedpine*”) and “Migraine and ME!” (“*Migræne og MIG!*”) with approximately 7,500 and 5,300 followers respectively as of 7 April 2022. This has the potential to reach approximately 28,200 patients with migraine. However, we expect a large overlap of patients on the four Facebook pages. Finally, a physician at the headache clinic in Aarhus informed patients about the survey.

When it was closed on 7 March 2022, a total of 665 persons had initiated the survey. However, 83 only looked at the front page and 142 had fewer than four MMD (in the absence of treatment with CGRP inhibitors) and therefore did not qualify for the research project; see Figure A.2. Additionally, 62 respondents did not complete the questions relevant to the health economic analysis and a further 16 respondents were omitted in data cleaning. In total, 362 respondents are included in the health economic model and analysis. Of these, 59 respondents (16%) receive treatment with CGRP inhibitors.

Figure A.2
Overview of respondents



Note: 1) Students are excluded. The number of respondents varies across the different models, as we have applied different requirements for each of the models. Respondents are categorised as having completed the questions needed if they have answered all questions relevant to that model.

Source: Copenhagen Economics based on the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022).

Due to missing replies, not all respondents in the health economic model are included in the non-economic and socioeconomic model. We end up with a sample size of 307 respondents in the non-economic model, and 303 respondents in the socioeconomic model. The 307 and 303 respondents are not 1-to-1 the same as we apply different requirements to the two groups. These different requirements result in 42 of 307 (14%) respondents in the non-economic group receiving treatment with CGRP inhibitors. The corresponding number for the socioeconomic model is 46 out of 303 (15%). The descriptive statistics can be seen in Table A.1 and Table A.2 below. To our knowledge, not much literature exists that we can benchmark our survey results against. However, the National

Knowledge Center for Headache (*Nationalt Videnscenter for Hovedpine*) has published the results of the *National Hovedpinesurvey 2021* (National Headache Survey 2021).⁹³ The respondents are patients with frequent headaches and/or migraine. The mean age in this survey is 43 years, and in our survey, the mean age is 44 years. Thus, the results of the two surveys seem to be in line with each other. It is worth noticing, however, that a larger share of the respondents in the *National Hovedpinesurvey* are men than in our survey. This can be caused by a slightly different epidemiology of migraine compared to frequent headaches.

Table A.1
Descriptive statistics, continuous variables

VARIABLE		MEAN	STD. DEV.	N
Age		44.05	11.46	359
Earnings		347,761	202,267	335 ¹
MMD	Chronic migraine	12.95	7.09	199
	High-frequency episodic migraine	10.45	3.49	80
	Low-frequency episodic migraine	5.20	1.08	83
MHD	Chronic migraine	18.38	7.76	197
	High-frequency episodic migraine	12.76	5.47	80
	Low-frequency episodic migraine	7.96	4.35	83

Note: Std. dev: Standard deviation. / 1) Patients with missing information on earnings are assigned the average earnings based on their gender and educational attainment. This implies that all 362 respondents have average earnings of 349,101 (std. dev. = 199,989).

Source: Copenhagen Economics based on the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022).

⁹³ Nationalt Videnscenter for Hovedpine (2022).

Table A.2
Descriptive statistics, other variables

VARIABLE		SHARE	N
Gender	Female	97.5%	350
	Male	2.5%	9
Education	Elementary school	3.6%	13
	Qualifying education	0.6%	2
	Gymnasium	6.4%	23
	Vocational training	15.2%	55
	Bachelor's degree	16.6%	60
	Short higher education	6.4%	23
	Medium-term higher education	25.1%	91
	Long higher education	25.4%	92
	Other	0.8%	3
Employment	Full-time	34.9%	126
	Self-employed	6.4%	23
	Part-time	26.6%	96
	Student	8.0%	29
	Unemployed	3.0%	11
	Not active in the labour market	14.4%	52
	Other	6.7%	24
Civil status	Married	52.1%	188
	In a relationship	26.9%	97
	Single	20.2%	73
	Does not want to answer/other	0.8%	3
Migraine type	Chronic migraine	55.0%	199
	High-frequency episodic migraine	22.1%	80
	Low-frequency episodic migraine	22.9%	83
Share receiving treatment with CGRP inhibitors		16.3%	362
Share receiving other prophylaxis treatments, disregarding the CGRP group		33.3%	303

Note: Std. dev: Standard deviation. The difference in the sum of shares from 100% is due to rounding. Sample sizes below 362 are due to missing observations.

Source: Copenhagen Economics based on the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022).

TREATMENT EFFECT

Based on the survey results, we estimate the effect of receiving treatment with CGRP inhibitors on a variety of parameters in the health economic, socioeconomic, and non-economic models. These estimates lay the groundwork for our estimated health economic savings, socioeconomic savings, and non-economic changes.

All patients participating in the survey were asked a wide range of questions covering medicine use, healthcare resource utilisation, labour market participation, educational and career choices, QoL, sleep, and other implications. The respondents are grouped into four groups: CM receiving treatment with CGRP inhibitors, CM not receiving treatment with CGRP inhibitors, HFEM, and LFEM. The patients currently receiving treatment with CGRP inhibitors were asked to answer the questions in the survey twice: once based on their current situation, and once by recalling a period when they did not receive treatment with CGRP inhibitors. The difference between their answers before receiving treatment with CGRP inhibitors and while receiving treatment with CGRP inhibitors is our estimate of the ‘treatment effect’. The treatment effect is then extrapolated to all patients eligible for treatment according to EMA in our model to estimate the potential economic gain. A similar approach has been used in other studies of attack-based conditions.⁹⁴

In our model, we do not assume that all patients receiving treatment will respond to the treatment as clinical trials have shown a response rate lower than 100%.⁹⁵ In clinical studies, the responder rate is often set to 50%. A response rate of 50% implies that a patient is categorised as responding to the treatment if they experience a 50% or greater reduction in MMD. However, in Denmark, the required response rate is 30%. If a patient experiences less than a 30% MMD reduction, treatment with CGRP inhibitors is discontinued. A recent real-world observational Danish study estimates that 71.4% experience at least a 30% MMD reduction, and we use this result in our analysis.⁹⁶ We perform a sensitivity analysis testing how alternating the share of responders affects the results in Appendix B.

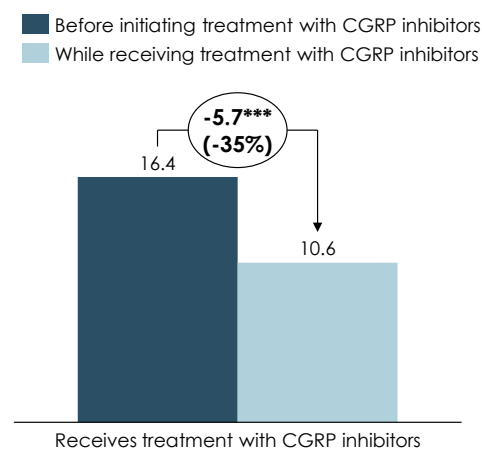
Among the respondents receiving treatment with CGRP inhibitors in the survey, we find a reduction of 5.7 MMD from initiating treatment with CGRP inhibitors; see Figure A.3. The survey results are therefore in line with clinical studies examining the effect of CGRP inhibitors.

⁹⁴ Castaldo et al. (2021).

⁹⁵ Tepper et al. (2017) for CM, Dodick et al. (2018) and Goadsby et al. (2017) for EM, and Frattale et al. (2021) using RWD.

⁹⁶ Cullum et al. (2022).

Figure A.3
Reduction in MMD among survey respondents
Number of MMD



Note: The change in MMD for patients receiving treatment with CGRP inhibitors is significant at a 0.1% significance level (***)

Source: Copenhagen Economics based on the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022).

The analyses in this report have all been carried out in Stata/IC 15 and exported to Microsoft Excel. For all health economic treatment effects and changes in means, we estimate the significance level by using a two-sided t-test. For all socioeconomic treatment effects and changes in means, we estimate the significance level by using a signed-rank Wilcoxon test due to small sample sizes. The results of the tests and significance levels are all reported in the footnotes of the figures in this Appendix.

HEALTH ECONOMIC SAVINGS

The health economic model is split into three main groups described in further detail below: attack medication, preventive medication, and healthcare resource use.

Attack medication

Most patients with migraine use attack medication to treat their migraine when it occurs. In the survey, we ask about the patients' use of painkillers, antiemetic tablets, antiemetic injections, Treo, and triptans as tablets, melt tablets, nose spray, and injections. When a patient initiates treatment with CGRP inhibitors, they may experience fewer attacks and hence decrease the use of attack medication. For example, we find that patients receiving CGRP inhibitors decreased their monthly use of painkillers by 54.7%, from 10.1 to 4.6 tablets per month. We use this relative reduction to calculate the savings if all patients in the patient population received treatment with CGRP inhibitors by using the methodology below.

Patients with chronic migraine, i.e., patients currently receiving treatment with CGRP inhibitors and patients not receiving treatment with CGRP inhibitors on average use 8.4 painkillers per month. This average is calculated as the weighted average of the use among treated patients before

they initiated treatment with CGRP inhibitors and of the current use among CM patients not receiving treatment with CGRP inhibitors. From the Danish Medicines Agency (2022a) we estimate that the average price of one painkiller pill is 1.5 DKK. This implies monthly savings of $8.4 * 54.7\% * 1.5$ DKK = 6.9 DKK per patient with chronic migraine responding to treatment with CGRP inhibitors. As 71.4% of 8,200 eligible patients respond to treatment, this implies annual savings of $71.4\% * 8,200 * (6.9 \text{ DKK} * 12 \text{ months}) = 475,000$ DKK (difference due to rounding). By calculating the mean use of painkillers for patients with HFEM and LFEM, we correspondingly estimate savings of 410,000 DKK and 1,595,000 DKK, respectively. We thereby estimate total savings from painkillers of 2.5m DKK per year.

Using the same methodology, we estimate the savings from a decrease in the use of antiemetic tablets, antiemetic injections, Treo, and triptans. In total, we estimate savings from attack medication of 22m DKK.

Preventive medication

The methodology for calculation of the savings from preventive medication is identical to that of attack medication. However, the price of Botox is not taken directly from the Danish Medicines Agency (2022a) as for the other types of medication, and we therefore explain this estimation in further detail in this section. For the other preventive medications⁹⁷ using the same methodology as for attack medication, we estimate total savings of 56m DKK.

The prices used for medicines in this report are based on ESP prices (consumer price, *Ekspeditionens Samlede Pris*). ESP prices are the prices of medicines at the pharmacy where Danish patients buy their medicine. However, Botox is most often given by a doctor at a hospital, and hospitals do not pay the same price as private persons. Hospitals pay the so-called 'SAIP price' (*Sygehusapotekets IndkøbsPris*), which is the AIP price (*Apotekernes IndkøbsPris*)⁹⁸ minus a negotiated discount. In Denmark, Amgro negotiates the discounts for medicines used at hospitals. From the Danish Medicines Agency (2022a) we find the AIP price of Botox, and based on Amgro (2022), we find that the average discount for the medicines in generic competition that are not reserved for hospitals is 35.39%, allowing us to calculate the SAIP price.⁹⁹ We use the price for all respondents that have had at least one outpatient visit in the previous year, as the patient might have received the Botox injections at the hospital during these visits. For patients receiving Botox and with zero outpatient visits, we use the ESP price. This estimate of the price and potential savings represents a lower limit, as the outpatient visits may have been for something else migraine related. This implies that more patients will have paid the ESP price.

Using this methodology, we find that patients currently receiving treatment with CGRP inhibitors on average had a monthly Botox cost of 500 DKK in 2022 before initiating treatment with CGRP inhibitors. While receiving treatment with CGRP inhibitors this average monthly cost has decreased to 260 DKK, implying a 51% reduction. The survey results show that some patients still receive preventive treatment with Botox despite being treated with CGRP inhibitors. We find that the current Botox expenditure among patients with chronic migraine not receiving treatment with CGRP

⁹⁷ The remaining preventive medications are beta-blockers, antihypertensive medicine, anti-depressive medicine, and antiepileptic medicine.

⁹⁸ The following formula allows for calculation from AIP to ESP: $ESP = 10,00 + 1.25 * (AIP * 0.077 + AIP + 5.46)$; see the Danish Medicines Agency (2022b).

⁹⁹ Amgro (2022).

inhibitors and among CGRP patients before they initiated treatment is 730 DKK per patient per month. This implies annual savings of $71.4\% * 8,200 * (730 \text{ DKK} * (1 - 51\%) * 12 \text{ months}) = 25.3\text{m DKK}$ per year. Botox is not recommended as a preventive treatment for patients with episodic migraine¹⁰⁰, and this recommendation is clear from our survey, where none of the patients with HFEM or LFEM received treatment with Botox.

Adding the savings of 25.3m DKK from Botox to the savings of 56m DKK for other preventive treatments, we find annual savings from preventive medication of 82m DKK.

Healthcare resource use

The included parameters for healthcare resource use in this study are GP visits, specialist visits, outpatient visits, ER visits, and hospitalisations.

The methodology for GP, specialist, outpatient, and ER visits is identical to that of attack and preventive medication. The respondents currently receiving treatment with CGRP inhibitors were asked about the number of visits a year before treatment and while receiving treatment. Based on their answers, we estimate a relative reduction. To estimate the savings, we again find the baseline numbers of visits for the weighted average chronic migraine group, the HFEM group, and the LFEM group. The costs per visit come from different sources; see Table A.3 below.

Table A.3
Cost of healthcare resources

PARAMETER	COST	SOURCE	NOTE
GP visit	147.85 DKK	PLO collective agreement	Consultation fee, regular GP visit
Specialist visit	790 DKK	FAS collective agreement	Average cost for first and second consultation
Outpatient visit	1,413 DKK	DAGS DG30T	The cost from 2017 is projected to the 2022 price level using the change in the diagnosis-related group (DRG) code 01MA10
ER visit	1,423 DKK	DAGS BG50C	Corrected using the growth in consumer prices as reported in the Danish Ministry of Finance (2021)
Hospitalisation, <=1 day	3,618 DKK	DRG 01MA98	
Hospitalisation, >1 day	21,821 DKK	DRG 01MA10	

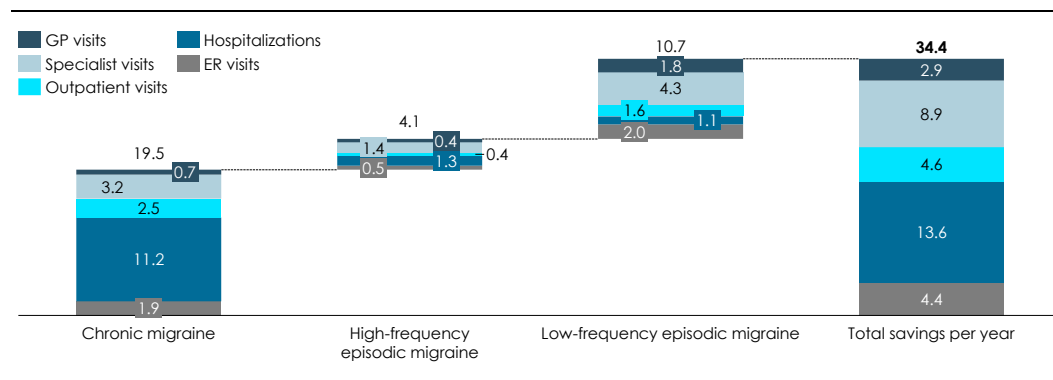
Source: PLO (2021), (FAS) (2018), Danish Health Data Authority (2022), Danish Health Data Authority (2017), and Danish Ministry of Finance (2021) from top to bottom.

¹⁰⁰ Danish Headache Society (2020).

For example, we estimate a reduction of 32.7% in the annual number of GP visits among patients receiving treatment with CGRP inhibitors. At baseline, the weighted average of the annual number of GP visits for patients with chronic migraine is 2.6 visits. This implies total annual savings for all patients with chronic migraine responding to treatment of $71.4\% * 8,200 * (2.6 * 32.7\% * 147.85 \text{ DKK}) = 0.7\text{m DKK}$. We calculate the savings for the remaining parameters except for hospitalisations for all patient groups in the same way. The results can be seen in Figure A.4 below.

Savings from fewer hospitalisations are estimated differently as the costs differ according to the length of stay. Based on the answers in the survey, we can estimate the average length of stay per hospitalisation for each respondent. Based on the average length of stay per hospitalisation for the individual respondent, we assign the one-day DRG rate if the length of stay is less than or equal to one day; if the length of stay is longer than one day, we assign the multiple-day DRG rate. Based on these individually assigned costs, we estimate the relative change in hospitalisation costs for the CGRP group. We find that patients receiving treatment with CGRP inhibitors have decreased their annual hospitalisations costs by 86%. This is primarily driven by a shorter length of stay. We find that baseline annual hospitalisations costs for the CM group, the HFEM group and the LFEM group are 2,200, 320, and 45 DKK per patient per year, respectively. Given the relative reduction, the number of patients, and the responder rate of 71.4%, this implies annual savings of 13.6m DKK.

Figure A.4
Health economic savings from lower use of healthcare resources
Million DKK per year



Note: The analysis in the health economic model is based on 362 respondents. We assume that 71.4% of the eligible and conditionally eligible population from the Copenhagen Economics population mapping will respond to treatment with CGRP inhibitors based on Cullum et al. (2022). The change in mean visits at the GP, specialist and ER are significant at a 5% significance level using a two-sided paired t-test on the null of equal means. The change in mean use of outpatient visits and hospitalisations is not significant.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgro (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), Cullum et al. (2022), and Statistics Denmark (2022a,b).

SOCIOECONOMIC GAINS

The socioeconomic gains stem from six elements described in further detail in this section. For each of the six elements, we look into a specific subgroup of the 303 respondents, and the sample size is

therefore relatively small for some of the socioeconomic analyses. In Table A.4 below, we outline the number of respondents used in each of the analyses in the socioeconomic model.

Table A.4
Overview of respondents in each of the socioeconomic analyses

	CGRP	OTHER CM	HFEM	LFEM	TOTAL	NOTE
All in socio-economic model	46	117	68	72	303	
Absenteeism	29	72	54	67	222	All employed respondents (full-time, part-time, and self-employed)
Presenteeism	29	72	54	67	222	All employed respondents (full-time, part-time, and self-employed)
Working part-time	17	25	9	15	66	All respondents working part-time
Would still be active in the labour market	6	14	1	1	22	Respondents not active in the labour market that would like to work more
Different educational attainment	13	31	12	10	66	Employed respondents that would have liked to obtain a different education
Change in career choice	19	37	21	19	96	Employed respondents that would have liked to obtain a different career

Note: CM: Chronic migraine; HFEM: High-frequency episodic migraine; LFEM: Low-frequency episodic migraine.

Source: Copenhagen Economics based on the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022).

Absenteeism

In the survey, respondents were asked about the hours lost at work in the previous seven days due to migraine and the number of hours they work per week. By dividing the two, we estimate the share of a normal workweek lost due to migraine. The framing and the time horizon of the question stem from the Work Productivity and Activity Impairment (WPAI) Questionnaire: General Health V2.0.¹⁰¹ We assume that the previous week is representative of a usual workweek and set this equal to the share of hours lost during a work year. For patients receiving treatment with CGRP inhibitors, we know the share of hours lost both before and after receiving treatment with CGRP inhibitors. To assign a monetary value to the share of a work year lost, we multiply the shares by the current annual gross earnings. This is the potential GDP contribution of absenteeism.

¹⁰¹ Reilly et al. (1993).

For patients receiving treatment with CGRP inhibitors, we find that people working (full-time, part-time, and self-employed) on average lost 5 hours of working time due to their migraine in the last seven days. While being treated with CGRP inhibitors, this is reduced to 3.6 hours corresponding to a reduction of 28.2%. To estimate the effect in term of potential GDP contribution, we need to measure the hours worked relative to the individuals' normal working time, e.g. 37 hours per week. Doing so, we find that people working on average lost 19% of hours worked before initiating the treatment, and while being treated with CGRP inhibitors, this share dropped to 12%, corresponding to a reduction of 35% (differences due to rounding). The weighted share of hours lost in the group of patients with chronic migraine is 18%. The average annual earnings among the same respondents are 421,000 DKK. Given that 62% of all respondents with chronic migraine are working and only 71.4% are responding to treatment, this implies an annual potential GDP contribution of $62\% * 71.4\% * 8,200 * (421,000 * 18\% * 35\%) = 98\text{m DKK}$ (difference due to rounding).

We calculate the savings for HFEM and LFEM in the same way, using the group-specific hours lost, earnings, and share working.

Presenteeism

Presenteeism is calculated based on the same respondents as in the absenteeism analysis. For the estimate of presenteeism, we use the questions and scoring developed in the Standard Presenteeism Scale (hereinafter called SPS-6).¹⁰² The result of the SPS-6 is a number between 6 and 30. We invert the scoring and standardise the score to a number between 0 and 100 so that a score of 6 implies the least possible presenteeism and is assigned the value 0. For example, if a person is assigned the value 10, we interpret this as 10% of the working time being 'lost' due to presenteeism. We assign this a monetary value of 10% of the person's annual earnings.

The treatment effect for presenteeism is a reduction of 19 percentage points, from 73% to 59%. This presenteeism measure is a bit lower than the results from the *National Hovedpinesurvey 2021*,¹⁰³ which finds that 82% of respondents with frequent headaches and/or migraine report going to work or school despite having a headache.

We assign the relative reduction found in our survey of 19 percentage points to the baseline share of work lost due to presenteeism among patients with CM, HFEM, and LFEM. The weighted average for patients with CM is 70%. This implies an annual potential GDP contribution of $62\% * 71.4\% * 8,200 * (421,000 * 70\% * 19\%) = 203\text{m DKK}$ (differences caused by rounding) among patients with CM.

In the same way, we calculate the savings HFEM and LFEM, using group-specific hours lost, earnings, and share working.

Working part-time

The respondents working part-time were asked if they would like to work more in the absence of their migraine, and if yes, how many hours. The treatment effect for patients receiving treatment with CGRP inhibitors is an 18% increase in hours they wanted to work. We estimate the annual potential GDP contribution by multiplying the relative increase in hours worked and the respondents'

¹⁰² See Koopman et al. (2002).

¹⁰³ Nationalt Videncenter for Hovedpine (2022).

average annual earnings. The weighted average annual earnings for patients with CM working part-time are 373,000 DKK, implying a potential GDP increase of $18\% * 373,000 \text{ DKK} = 66,000 \text{ DKK}$. However, this GDP contribution is only relevant for the share of employed that would like to work more and *not* all working part-time. From the survey, we find that 42% of the 62% employed would like to work more. This implies an annual potential GDP contribution among people with CM of $42\% * 62\% * 71.4\% * 8,200 * 66,000 \text{ DKK} = 100\text{m DKK}$ (differences caused by rounding).

We calculate the savings for HFEM and LFEM in the same way, using the group-specific share of hours wanted to work, earnings, and share working.

Labour market participation

Some patients with migraine have had to withdraw from the labour market because of their migraine. For these patients, the withdrawal from the labour market implies a missed GDP contribution as they could have had earnings from labour market participation and paid taxes. In the survey, only six people in the CGRP group had withdrawn from the labour market but would have liked to work in the absence of their migraine. The corresponding numbers are 14 respondents in the CM group and one respondent each in both the HFEM group and the LFEM group. The results for labour market participation therefore must be interpreted with caution, as the sample size is small.

In the survey, the respondents in the CGRP group who had withdrawn from the labour market but would have liked to work more were asked how likely it was that they would have continued to work if they had been treated with CGRP inhibitors at the time. All this information combined allows us to calculate a potential GDP contribution. As a first step, we assign a potential earnings level to the respondents. This potential earnings level is the average earnings from Statistics Denmark¹⁰⁴ given their gender and educational attainment. As a second step, we calculate the share that would like to work among the ones not active in the labour market. For all with CM, this share is 51%. Among those receiving CGRP inhibitors, 50% answered that they would have worked if they had received CGRP inhibitors. This is the treatment effect in this analysis; in other words, the likelihood is 50% that the respondents who would like to work would actually be working and receive the potential earnings when being treated with CGRP inhibitors. For patients with CM, this implies potential *extra* earnings (adjusted with the 50% likelihood of actually working) of 72,500 DKK on top of their current earnings. However, this is only a potential effect among the share of respondents not active in the labour market. From the survey, we find that 24% of patients with CM are not active in the labour market. This implies an annual potential GDP contribution of $24\% * 71.4\% * 8,200 * 72,500 \text{ DKK} = 103\text{m DKK}$ (differences caused by rounding).

We calculate the savings for HFEM and LFEM in the same way, using the group-specific labour market participation and potential earnings.

Different educational attainment

For some patients with migraine, their migraine has had such a large impact on their life that they have decided, due to their migraine, to obtain a different education than the one they dreamed of. For these patients, having 'settled' for a different educational level might lead to foregone earnings and hence a potential loss of GDP contribution. In the survey, respondents were therefore asked if they would have obtained a different education than their actual one in the absence of their

¹⁰⁴ Statistics Denmark (2022a), table LONS11.

migraine. For these patients, we again calculate their potential earnings given information on average earnings based on potential educational level and gender from Statistics Denmark (2022a). As the next step, we again calculate the likelihood of obtaining this educational level while being treated with CGRP inhibitors. This question was asked of the patients receiving treatment with CGRP inhibitors, and we find a likelihood of 35%. Note that we implicitly assume that patients who did not have migraine when making a choice about their education will reply that they are unlikely (0%) to have chosen a different educational attainment. For patients with CM, their extra potential earnings are 73,900 DKK. However, this is only a potential effect among the share of respondents that would have liked to obtain a different education. From the survey we find that 44% of patients with CM would have liked to obtain a different education, reducing the average potential gain to 32,200 DKK. This is only an effect among the 62% currently active in the labour market, and thereby the annual potential GDP contribution is $62\% * 71.4\% * 8,200 * 32,200 \text{ DKK} = 118\text{m DKK}$ (differences caused by rounding).

We calculate the savings for HFEM and LFEM in the same way, using group-specific educational attainment, potential earnings, and share working.

Change in career choice

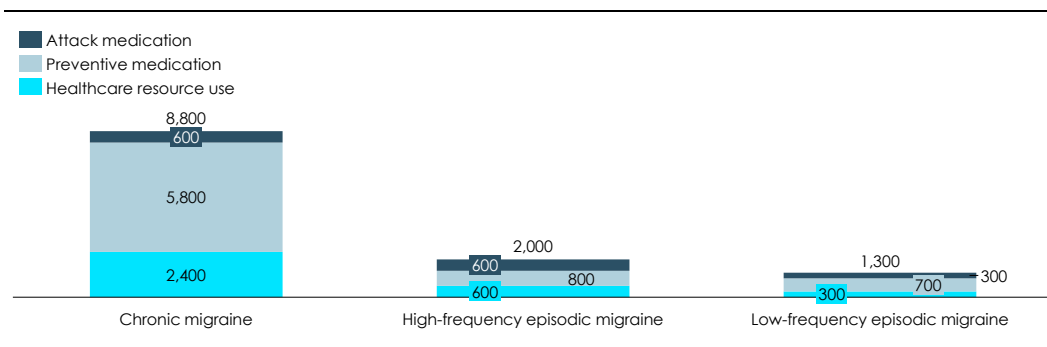
The last socioeconomic element is a change in career choice. For some patients with migraine, their migraine has had such a large impact on their life that they have decided to alter their career due to migraine e.g., say no to a promotion. For these patients, having declined career opportunities might lead to foregone earnings and hence a potential GDP contribution. In the survey, respondents were therefore asked if they had altered their careers because of their migraine. If the patients replied yes, they were asked to estimate by what percentage they think their earnings could be lower or higher. Based on this reported percentage change, we estimate their potential earnings. As the next step, we again calculate the likelihood of pursuing this career if the patients had been treated with CGRP inhibitors. This question was asked to the patients receiving treatment with CGRP inhibitors, and we find a likelihood of 39%. For patients with CM, their extra potential earnings are 98,700 DKK. However, this is only a potential effect among the share of respondents that would have liked to obtain a different education. From the survey we find that 55% of patients with CM would have pursued a different career, reducing the average potential gain to 54,700 DKK. This is only an effect among the 62% currently active in the labour market, and thereby the annual potential GDP contribution is $62\% * 71.4\% * 8,200 * 54,700 \text{ DKK} = 201\text{m DKK}$ (differences caused by rounding).

We calculate the savings for HFEM and LFEM in the same way, using the group-specific changes in career choice, potential earnings, and share working.

SAVINGS PER PATIENT

Another way to present the health economic savings and socioeconomic gains is to show the savings and gains per patient. In the graphs below, we show the savings and gains per patient for patients with CM, HFEM, and LFEM, respectively. The result per patient is calculated as a step in all the savings calculations described above, without multiplying by the actual number of patients. In other words, the result per patient takes into account that 71.4% of patients are responding to treatment. The health economic and socioeconomic gains savings per patient can be seen in Figure A.5 and Figure A.6 below.

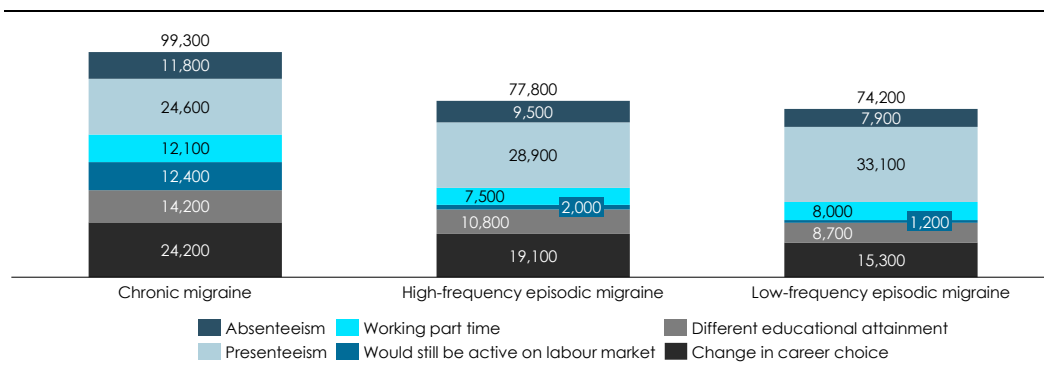
Figure A.5
Health economic savings of treatment with CGRP inhibitors
DKK per person per year



Note: The analysis in the health economic model is based on 362 respondents. We assume that 71.4% of the eligible and conditionally eligible population from the Copenhagen Economics population mapping will respond to treatment with CGRP inhibitors based on Cullum et al. (2022). The change in the use of medication following attacks is significant at a 0.1% significance level: antiemetic tablets and triptans tablets. The change in the mean use of Treo is significant at a 1% significance level. The following changes in preventive medications are significant at a 0.1% significance level: antiepileptic. The mean change in the use of beta-blockers and antihypertensive is significant at a 1% significance level. The change in mean use of Botox is significant at a 5% significance level. The changes in mean GP, specialist and ER visits are significant at a 5% significance level. The changes in mean use of painkillers, antiemetic injections, triptan melt tablets, triptan spray, triptan injection, antidepressant tablets, outpatient visits and hospitalisations are not significant. Significance levels are estimated using a two-sided paired Student's t-test of the null hypothesis of equal means.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), Cullum et al. (2022), and Statistics Denmark (2022a,b).

Figure A.6
Socioeconomic gains from treatment with CGRP inhibitors in Denmark
DKK per person per year



Note: The analysis in the socioeconomic model is based on 303 respondents. We assume that 71.4% of the eligible and conditionally eligible population from the Copenhagen Economics population mapping will respond to treatment with CGRP inhibitors based on Cullum et al. (2022). The mean change in career choice is significant at a 0.1% significance level. The mean change in the presenteeism score and educational attainment is significant at a 1% significance level, and the mean change in labour market participation is significant at a 5% significance level. The changes in absenteeism and working part-time are not significant. Significance levels are estimated using a Wilcoxon signed-rank test on the null hypothesis of no difference in population mean ranks.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022) and earning levels based on education and industry from Statistics Denmark (2022a,b).

NON-ECONOMIC EFFECTS

Common for all the non-economic effects is that we do not assign a monetary value to them. For many of the variables, the treatment effect is therefore comparing the mean before and after initiating treatment with CGRP inhibitors. This is the case for the following variables: share missing social activities, bed hours, planning in general, planning social activities, effect on family, ability to do regular activities, e.g., household work, relationships with family and friends, stress due to migraine, and ability to carry out everyday activities. To highlight one example, 90% of respondents with CM not receiving treatment with CGRP inhibitors report having missed social activities within the last three months. Nationalt Videnscenter for Hovedpine (2022) reports that 67% of patients with frequent headaches experience that their headaches limit their involvement in social activities.¹⁰⁵ For many of these variables, we report the current mean for patients with CM not receiving treatment with CGRP inhibitors. We do this to see if patients receiving treatment with CGRP inhibitors have ‘recall bias.’¹⁰⁶ Recall bias describes the fact that the human mind might remember something as being better or worse than it was. For example, a patient currently receiving treatment with CGRP inhibitors looks back and recalls missing out on social activities every week, but in fact, it was ‘only’ every second week. It appears to be the case that patients receiving treatment with CGRP inhibitors have some degree of recall bias; however, the effects of treatment are still positive when compared to the remaining group of patients with CM.

¹⁰⁵ Nationalt Videnscenter for Hovedpine (2022).

¹⁰⁶ See for example Schimer and Halpern (2014).

The remaining parameters on QoL and sleep have been scored and estimated, and in the following paragraphs, we will describe the methodology used for this.

EQ-5D-5L and EQ-VAS

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol Group to provide a simple generic measure of health for clinical and economic appraisal. The EQ-5D-5L is a set of questions along five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with five response levels; no problems, slight problems, moderate problems, severe problems, unable to/extreme problems.¹⁰⁷ The responses to the survey are coded based on the respondents' answers. This results in a five-digit code e.g., 11234, based on which each respondent's answer is assigned a utility weight drawn from recent Danish utility weights by Jensen et al. (2021a). The final score of the EQ-5D-5L is a number lower than 1, where 1 is perfect health. For illustrative purposes, the numbers reported in the report are scaled up with a factor of 100. The respondents in the CGRP group were asked these questions based on their current health state and their health state before receiving treatment with CGRP inhibitors. The numbers reported in the main text are simple averages of their responses.

EQ-VAS is the final part of the EQ-5D-5L. Respondents are asked to assess their overall current health on a scale from 0 to 100, where 0 is 'the worst health you can imagine' and 100 is 'the best health you can imagine'.¹⁰⁸ The respondents in the CGRP group were asked this question based on their current health state and their health state before receiving treatment with CGRP inhibitors. The numbers reported in the main text are simple averages of their responses.

Headache Impact Test (HIT-6)

The respondents were asked about the severity of their headaches through the six items in the Headache Impact Test (HIT-6). The HIT-6 has been validated as a tool to estimate the impact of headaches among both episodic and chronic migraine.¹⁰⁹ The HIT-6 consists of six questions with five possible answers: never, rarely, sometimes, very often, and always. Each answer is given a score between 6 and 13, and the total score is therefore between 36 and 78. Yang et al. (2010) find an average score of 62.5 for American patients with CM. Patients in our survey report an average of 68.9 and 66.6 for the CGRP group before initiating treatment and the remaining CM group, respectively. After initiating treatment, the score drops to 62.5. The result in our survey is therefore in line with results from the academic literature.

The HIT-6 score decreases by less than the increase in the EQ-5D-5L score, indicating a low correlation between the EQ-5D-5L and HIT-6. This finding is supported in the literature; see, for example, Gonçalves et al. (2022).

QoL between migraine attacks

In the report, we show how the QoL depends on when the respondents had their last migraine attack. The EQ-5D-5L and HIT-6 are calculated in the same manner as described above; however, the simple average is calculated based on when the respondent had their last migraine attack. These results show that QoL increases with the length of time since the last migraine attack. This is in line

¹⁰⁷ EuroQol Research Foundation (2021), EQ-5D-5L User Guide, version 3.0.

¹⁰⁸ EuroQol Research Foundation (2021), EQ-5D-5L User Guide, version 3.0.

¹⁰⁹ Yang et al. (2010).

with Xu et al. (2010), who find that the disutility of a mild, moderate, and severe migraine attack is 0.140, 0.186, and 0.493, respectively. In other words, the disutility of a migraine attack increases with the severity of the attack.

The Pittsburgh Sleep Quality Index (PSQI)

A final non-economic measure of great importance for patients with migraine is sleep. For this reason, we included five questions on sleep from the PSQI.¹¹⁰ The full questionnaire consists of 19 items; however, in this study, they are not all relevant. We therefore only included Questions 1, 2, 3, 4, and 6 in the survey, realising that this means we cannot calculate the correct score of the PSQI. We follow the scoring instructions from Buysse et al. (1988) for the questions included in the survey. The chosen questions shed light on four relevant aspects of sleep: subjective sleep quality, sleep latency (how long it takes to fall asleep), sleep duration, and time spent in bed. The numbers reported in the main text are simple averages of their responses.

¹¹⁰ Buysse et al. (1988).

APPENDIX B

SENSITIVITY ANALYSES

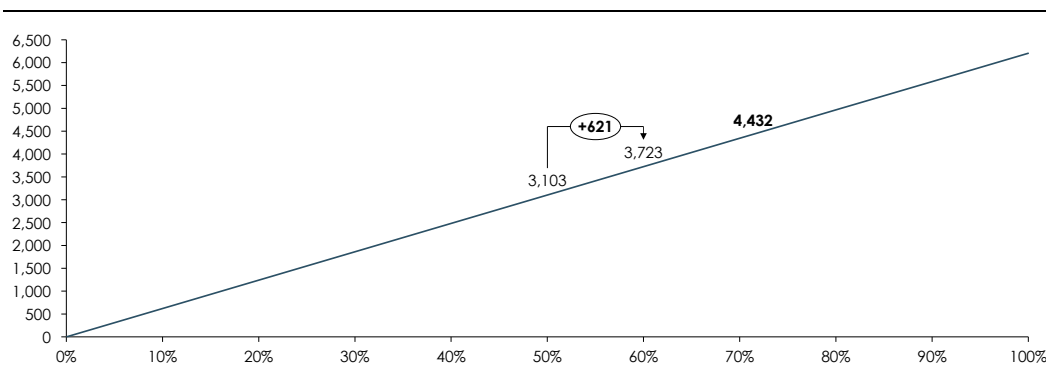
In this appendix, we test the robustness of the results reported in the main text by performing four sensitivity analyses. In the sensitivity analyses, we change some of the key parameters. The results are presented in the following paragraphs.

EFFECT OF CHANGING THE SHARE OF PATIENTS RESPONDING TO TREATMENT

One key parameter in the report is the share of patients responding to treatment, i.e., the share of patients experiencing at least a 30% reduction in MMD. Based on Cullum et al. (2022), we assume that 71.4% of patients respond to treatment. However, the share of responders amongst *all* Danish patients may differ from this Danish study amongst the first patients receiving treatment with CGRP inhibitors. We therefore test the robustness of the results by changing the share of patients responding to treatment.

We find that the total economic gain from treating eligible patients with CGRP inhibitors increases by 621m DKK for each increase of ten percentage points in the share responding to the treatment; see Figure B.1 below. In the figure, the main result from the report is shown in bold, representing 71.4% responding to treatment. Had the share of responders been 50%, the total economic gain would be 3.1bn DKK per year. Had the share of responders been 60%, the total economic gain would be 3.7bn DKK per year. This analysis shows a significant economic gain from treating patients eligible for treatment with CGRP inhibitors despite reducing the share responding to treatment.

Figure B.1
Societal economic gains of treatment with CGRP inhibitors for different shares of patients responding to treatment
Million DKK per year



Note: The analysis in the health economic model is based on 362 respondents, and the analysis in the socioeconomic model is based on 303 respondents. We vary the share of eligible patients responding to treatment from the Copenhagen Economics population mapping who will respond to treatment with CGRP inhibitors in this sensitivity analysis.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), and Statistics Denmark (2022a,b).

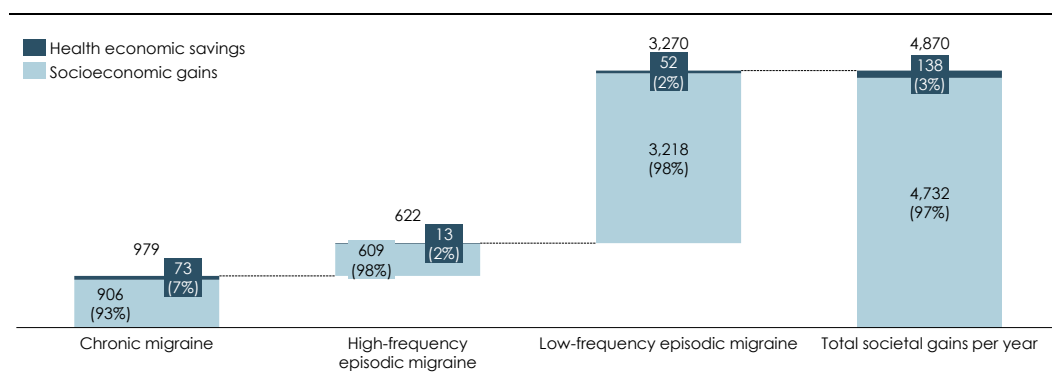
USING A DIFFERENT MEASURE OF PRESENTEEISM

In the main analysis, we use the Stanford Presenteeism Scale (SPS-6) as the foundation for the presenteeism analysis. In the survey, we asked the respondents to answer questions from the Work Productivity Impairment Questionnaire: Migraine V2. In Question 5 of that set of questions, the respondents were asked how much migraine affected their productivity while they were working. The respondents had to rank this question on a scale from 0 to 10, with 0 being 'migraine did not affect my work', and 10 being 'migraine completely prevented me from working'. WPAI Question 5 is therefore an alternative presenteeism measure that we use in this sensitivity analysis.

For our presenteeism measure, we assign the respondents' answers a percentage. We assign 10% to the value 1, 20% to the value 2, etc. This is the share of hours 'lost' while working. As for our SPS-6 presenteeism measure, this share is multiplied by average earnings for the patients working as a measure of the GDP contribution.

Using this presenteeism measure yields a higher potential GDP contribution as the overall share lost is higher. Using the WPAI Question 5 instead of the SPS-6 increases the total economic gain from treatment with CGRP inhibitors to 4.87bn DKK per year; see Figure B.2 below.

Figure B.2
Societal economic gains of treatment with CGRP inhibitors, different presenteeism measure
Million DKK per year



Note: For this analysis, we use the WPAI presenteeism measure instead of the SPS-6. The analysis in the health economic model is based on 362 respondents, and the analysis in the socioeconomic model is based on 303 respondents.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), and Statistics Denmark (2022a,b).

TEST TO SEE IF RECALL BIAS AFFECTS THE RESULTS

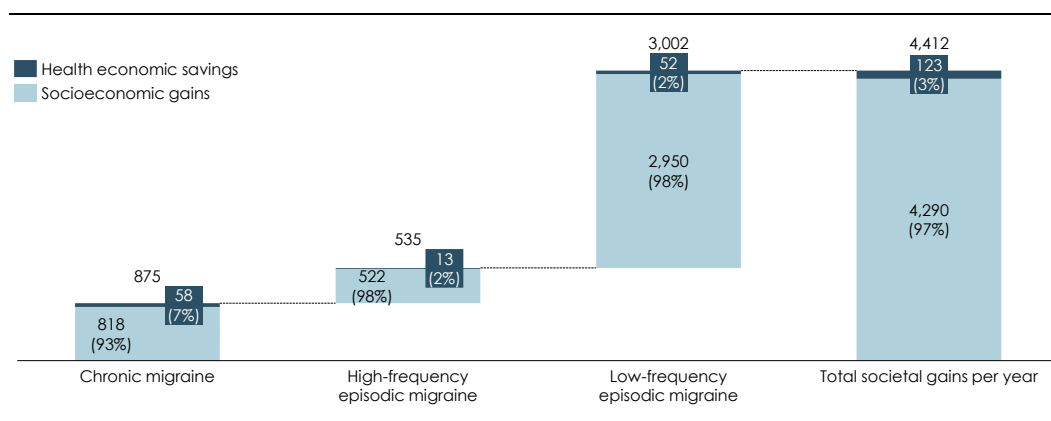
In our estimations, all the savings and gains are calculated based on the change compared to a baseline current level, e.g., the savings from lower consumption of painkillers is calculated based on the baseline current use of painkillers. In our main results, the baseline current level for patients with CM is calculated as a weighted average of patients with CM not receiving treatment with CGRP inhibitors and the recall answers for patients currently receiving treatment with CGRP inhibitors.

When people have to recall a previous use of, e.g., painkillers, they risk remembering wrong. This is the so-called ‘recall bias’.¹¹¹ We test whether recall bias affects our results by using the current levels for patients with CM not receiving treatment with CGRP inhibitors instead of the weighted average. By changing this assumption, the total economic gain in the CM group is decreased by 20m DKK to 875m DKK; see Figure B.3. The relatively small change from our main results shows that recall bias is not an issue in the data and the total savings per year is still approximately 4.4bn DKK.

¹¹¹ Schmier and Halpern (2004).

Figure B.3
Societal economic gains of treatment with CGRP inhibitors, different baseline levels for patients with chronic migraine

Million DKK per year



Note: For this analysis, we change the baseline levels from all patients with chronic migraine to patients with migraine not receiving treatment with CGRP inhibitors. The analysis in the health economic model is based on 362 respondents, and the analysis in the socioeconomic model is based on 303 respondents.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), and Statistics Denmark (2022a,b).

USING DIFFERENT POPULATION ESTIMATES

In the following, we perform a sensitivity analysis on the implications of using alternative estimates of the population of patients with chronic migraine eligible for treatment with CGRP inhibitors in Denmark.

In our population mapping, changing the number of patients eligible for treatment with CGRP inhibitors also affects the number of patients with HFEM and LFEM eligible for treatment. This is because a change in the number of CM patients eligible for treatment affects our overall estimate of the number of patients with chronic migraine as patients eligible for treatment makes up 35% of patients with chronic migraine. In our population mapping, patients with HFEM are 101% of the patients with CM. Changing the number of patients with CM therefore changes the number of patients with HFEM. Finally, changing the number of CM patients also affect our estimation of the number of patients with LFEM, as the number of patients with LFEM is calculated based on the relative relationship between our estimate of HFEM patients and people with non-episodic migraine.

We use three alternative estimates of the population of eligible patients in Denmark; the Danish Medicines Council's initial estimate of 350 patients¹¹², the Danish Medicines Council's updated estimate of 3,500 patients¹¹³, and expert estimates of up to 20,000 eligible patients¹¹⁴.

¹¹² Danish Medicines Council (2021c).

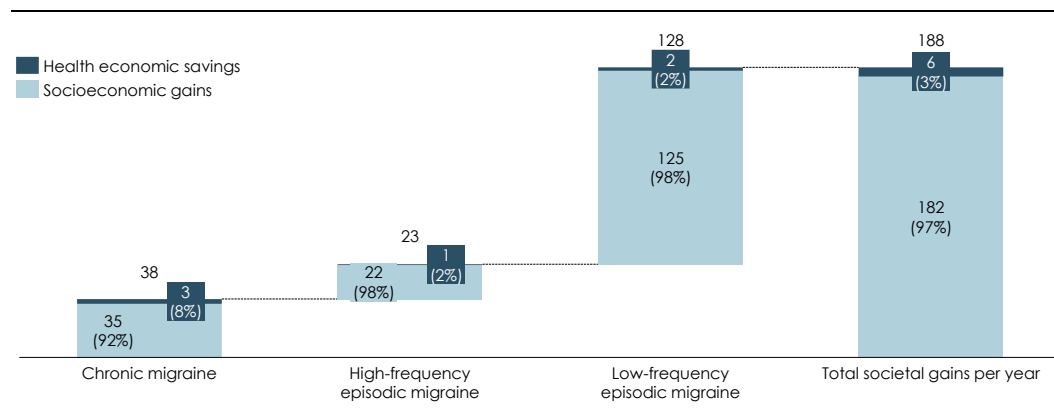
¹¹³ Danish Medicines Council (2021c).

¹¹⁴ Propatienter.dk (23 January 2020).

The Danish Medicines Council's initial estimate of 350 patients

The Danish Medicines Council initially estimated that 350 patients with CM and two prior treatment failures were eligible for treatment.¹⁴⁵ In Figure B.4 below we show the implications of using this patient population in our economic model. The corresponding patient populations for HFEM and LFEM are 283 and 1,692, respectively. Decreasing the number of patients eligible for treatment decreases the total societal gain per year to 188m DKK.

Figure B.4
Societal economic gains of treatment with CGRP inhibitors, 350 patients with chronic migraine eligible for treatment
Million DKK per year



Note: For this analysis, we change the number of patients eligible for treatment to 350, 283, and 1,692 for CM, HFEM, and LFEM, respectively. The analysis in the health economic model is based on 362 respondents, and the analysis in the socioeconomic model is based on 303 respondents.

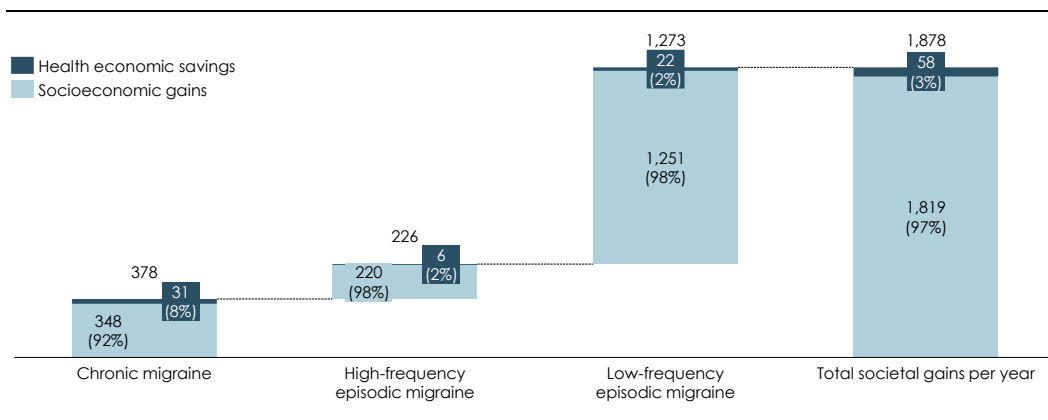
Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), and Statistics Denmark (2022a,b).

¹⁴⁵ Danish Medicines Council (2021c).

The Danish Medicines Council's updated estimate of 3,500 patients

The Danish Medicines Council later increased their patient population estimate of patients with CM and two prior treatment failures ten-fold to 3,500.¹¹⁶ In Figure B.5 below we show the implications of using this patient population in our economic model. The corresponding patient populations for HFEM and LFEM are 2,832 and 16,884, respectively. Decreasing the number of patients eligible for treatment decreases the total societal gain per year to 1.9bn DKK.

Figure B.5
Societal economic gains of treatment with CGRP inhibitors, 3,500 patients with chronic migraine eligible for treatment
Million DKK per year



Note: For this analysis, we change the number of patients eligible for treatment to 3,500, 2,832, and 16,884 for CM, HFEM, and LFEM, respectively. The analysis in the health economic model is based on 362 respondents, and the analysis in the socioeconomic model is based on 303 respondents.

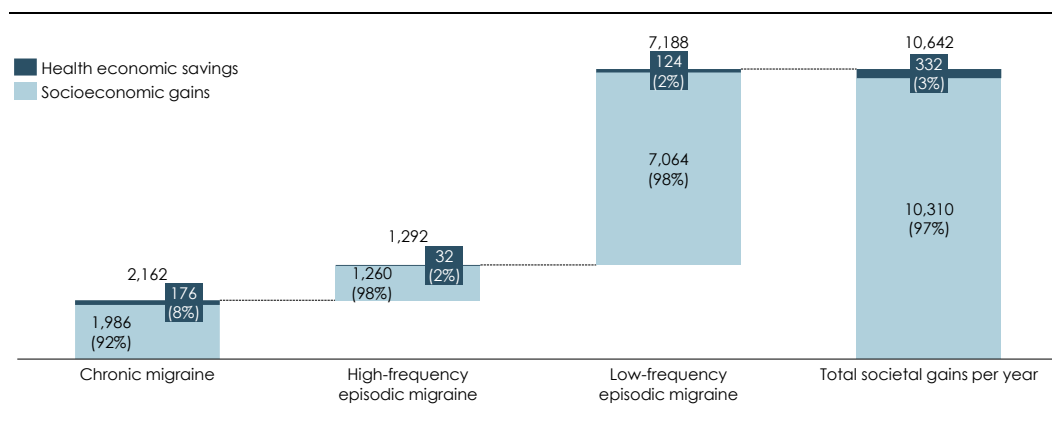
Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), and Statistics Denmark (2022a,b).

¹¹⁶ Danish Medicines Council (2021c).

Expert estimates of up to 20,000 patients

The patient population estimated by the Danish Medicines Council was criticised by many experts, and some estimates that up to 20,000 patients with chronic migraine are eligible for treatment.¹¹⁷ In Figure B.6 below we show the implications of using this patient population in our economic model. The corresponding patient populations for HFEM and LFEM are 16,184 and 95,320, respectively. Increasing the number of patients eligible for treatment increases the total societal gain per year to 10.6bn DKK.

Figure B.6
Societal economic gains of treatment with CGRP inhibitors, 20,000 patients with chronic migraine eligible for treatment
Million DKK per year



Note: For this analysis, we change the number of patients eligible for treatment to 20,000, 16,184, and 95,320 for CM, HFEM, and LFEM, respectively. The analysis in the health economic model is based on 362 respondents, and the analysis in the socioeconomic model is based on 303 respondents.

Source: Copenhagen Economics based on CE population mapping, the survey for the research project on Real-world evidence on the economic implications of CGRP inhibitors (2022), pro.medicin.dk (2022), Danish Medicines Agency (2022a), Amgros (2022), Danish Health Data Authority (2022), Danish Health Data Authority (2017), PLO (2021), FAS (2018), and Statistics Denmark (2022a,b).

¹¹⁷ Propatienter.dk (23 January 2020).

APPENDIX C

OVERVIEW OF BACKGROUND INTERVIEWS

As a basis for this analysis, we conducted background interviews with several experts and researchers in migraine and health economics; see Table C.1 below. In the interviews with experts and health economists, we discussed, e.g., population estimates, effects of CGRP inhibitors, and received feedback on our preliminary results. In interviews with patients, we discussed their experiences with migraine and their treatments. The conclusions of the analysis are exclusively those of Copenhagen Economics and do not necessarily reflect the opinions of the project's interviewees.

Table C.1
Project interviewees

NAME	TITLE	ORGANISATION
Dorte ¹	Migraine patient	Member of the Danish Migraine and Headache Association
Jakob Kjellberg	Professor of health economics, cand.scient., M.Sc. Health Econ	The Danish Center for Social Science Research (VIVE)
Jes Olesen	Professor of neurology, MD, DMSc, dr. hon.c. (Rome, Italy), dr. hon.c. (Yekaterinburg, Russia), fellow of the Royal College of Physicians (FRCP)	Danish Headache Center and Department of Clinical Medicine, University of Copenhagen
Lars Bendtsen	Associate Professor, PhD, MD, DrMedSci	Danish Headache Center and Department of Clinical Medicine, University of Copenhagen
Lene ¹	Migraine patient	Member of the Danish Migraine and Headache Association
Maren Østergaard Eriksen	Vice President, Nurse	Danish Migraine and Headache Association and Danish Headache Center
Marie ¹	Migraine patient	Member of the Danish Migraine and Headache Association
Rigmor Højlund Jensen	Professor of Headache diseases and neurological pain, Director, MD, DrMedSci	Danish Headache Center and Department of Clinical Medicine, University of Copenhagen

Note: 1) Patient interviewees are identified by their first name only.

Source: Copenhagen Economics.

APPENDIX D

METHODOLOGY REGARDING PATIENT INTERVIEWS

We contacted patient interviewees through the Danish Migraine and Headache Association (*Migræne & Hovedpineforeningen*). The association posted a call in Danish on their Facebook page on 12 October 2021; see Box D.1 below. Following the call, we received e-mails from eight migraine patients expressing interest in participating in an interview. We invited the first four migraine patients who responded to an interview, of whom three accepted, and let the remaining four migraine patients know that we had already scheduled sufficient interviews. Consequently, we asked the Danish Migraine and Headache Association to withdraw the post on 13 October 2021.

All interviews were scheduled for 30 minutes and were conducted in Danish using Microsoft Teams. Based on the interviews, we wrote draft cases. We asked the interviewees to review their draft case and to comment on any potential inaccuracies. Subsequently, we asked for and received all interviewees' approval to include their final case in the report at hand.

By coincidence, the three interviewees were well aligned with the three types of patients we mentioned in our call; a person with chronic migraine who is receiving treatment with CGRP inhibitors, a person with chronic migraine who is not (yet) receiving treatment with CGRP inhibitors, and a person with episodic migraine.

Box D.1**Facebook post with a call for interviewees suffering from migraine (in Danish)**

VIL DU HJÆLPE MED AT KASTE LYS OVER EFFEKTERNE VED MIGRÆNE OG CGRP-HÆMMERE I DANMARK?

Copenhagen Economics er ved at udarbejde en rapport om de økonomiske effekter ved CGRP-hæmmere i Danmark. For at tilføje den menneskelige dimension til beregningerne, håber vi at kunne gennemføre et interview med dig, hvis du enten har:

- kronisk migræne og bliver behandlet med CGRP-hæmmere
- kronisk migræne, men (endnu) ikke bliver behandlet med CGRP-hæmmere
- periodisk migræne

Du har mulighed for at deltage anonymt og vi beder ikke om mere end 30-60 minutter af din tid, når det passer dig.

Hvis du ønsker at bidrage, så tag kontakt til <kontaktperson> på <telefonnummer> eller <e-mail>.

Source: Copenhagen Economics.

ABOUT COPENHAGEN ECONOMICS

Copenhagen Economics is one of the leading economics firms in Europe. Founded in 2000, we currently employ more than 100 staff operating from our offices in Copenhagen, Stockholm, Helsinki, and Brussels. The Global Competition Review (GCR) lists Copenhagen Economics among the Top 20 economic consultancies in the world and has done so since 2006.

www.copenhageneconomics.com

Hard facts. Clear stories.