Press Release
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Grünenthal and Averitas Pharma announce initiation of Phase III study with QUTENZA® to prepare label extension in the US for the treatment of post-surgical neuropathic pain

- Post-surgical neuropathic pain (PSNP) is a debilitating complication of surgery that affects approximately 13 percent of all patients who undergo surgery, which represents 3.3 million patients per year in the US.[1]
- This Phase III study is Grünenthal's next step in making QUTENZA available to even more patients in the United States. QUTENZA is the first and only prescription strength capsaicin that is a topical, non-systemic, non-opioid pain treatment; it is currently approved in the US for the treatment of neuropathic pain associated with postherpetic neuralgia, and for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults.

Aachen, Germany, & Morristown, N.J., 30 March 2021 – Grünenthal announced today that its U.S. subsidiary, Averitas Pharma, Inc. will conduct a Phase III trial to study the efficacy, safety and tolerability of QUTENZA (capsaicin) 8% topical system in post-surgical neuropathic pain (PSNP) with the goal to expand the current U.S. product label. The randomised, double-blind trial AV001 will include between 400 and 500 patients who have been suffering from moderate to severe PSNP for at least six months, and aims to demonstrate a significant reduction in the average pain intensity after 12 weeks and 42 weeks compared to the baseline. In addition, the trial will assess other outcomes like progressive response over time with repeated application, reduction of the treatment area over several applications, and Quality of Life outcomes such as sleep interference, physical activity, anxiety and depression. First patients are expected to be enrolled in the third quarter of 2021 with trial completion expected in 2024.

"A significant number of patients suffer from burning, stabbing or shooting neuropathic pain as a complication of surgery. Commonly used oral, systemically acting medicines often provide unsatisfactory results or are accompanied by considerable side effects," says John Douglas Markman, M.D., coordinating investigator and Professor for Neurosurgery at the University of Rochester School of Medicine and Dentistry. "Averitas is conducting the first double-blind study in PSNP that will explore long-term safety and efficacy in patients with a much-needed non-systemic, non-opioid treatment option."

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[1] Classifying surgeries were factored against their respective time-bound frequency of PSNP to yield the prevalence based on:

- Carroll, I. R., Hah, J. M., Barelka, P. L., Wang, C. K. M., Wang, B. M., Gillespie, M. J., … Mackey, S. C. (2015). Pain Duration and Resolution following Surgery: An Inception Cohort Study. Pain Medicine, 16(12), 2386–2396. doi:10.1111/pme.12842.
- Shipton, E. (2008). POST-SURGICAL NEUROPATHIC PAIN. ANZ Journal of Surgery, 78(7), 548–555. doi:10.1111/j.1445-2197.2008.04569.x
- Borsook, D., Kussman, B. D., George, E., Becerra, L. R., & Burke, D. W. (2013). Surgically Induced Neuropathic Pain. Annals of Surgery, 257(3), 403–412. doi:10.1097/sla.0b013e3182701a7b.

Press Release
GRÜNENTHAL

In July 2020, Grünenthal significantly expanded the reach of QUTENZA in the United States by expanding the label to include the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults. This complication of diabetes affected more than 5 million Americans in 2020[2], and the number of affected patients is expected to double by 2030[3].

"The label extension was a major milestone for our U.S. business and made QUTENZA accessible for millions of adult patients who suffer from painful DPN of the feet", says Gabriel Baertschi, CEO Grünenthal. "More than one in ten patients who undergo surgery are affected by PSNP, and we believe that QUTENZA, a topical, non-opioid pain treatment, could provide a meaningful therapy option. With the new Phase III study in PSNP, we are confident to make QUTENZA available to even more patients."

About QUTENZA

QUTENZA offers physicians a different way to treat neuropathic pain associated with PHN or DPN of the feet in adults. QUTENZA, a specially formulated topical system, delivers prescription strength capsaicin directly to the skin during an in-office procedure. In this way, it can reversibly desensitise and defunctionalize the TRPV1 (Transient Receptor Potential Vanilloid 1) receptor, which plays a critical role in pain signalling.

QUTENZA administered as a single localised procedure can provide sustained pain relief that lasts for up to three months. It has no known drug-drug interactions. The most common adverse reactions include application site reactions, such as erythema, pain, and pruritus. The majority of application site reactions were transient and self-limited.[4]

QUTENZA (capsaicin) 8% topical system is approved in the US for the treatment of neuropathic pain associated with postherpetic neuralgia, and for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults. Important U.S. safety information is available below and at www.qutenza.com.

In Europe, QUTENZA is indicated for the treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for the treatment of pain. For further information please visit www.grunenthalhealth.com.

About post-surgical neuropathic pain

Chronic post-surgical pain is defined as chronic pain that develops after a surgical procedure and persists beyond the healing process, i.e. at least three months after the surgery. The pain is either localised to the surgical field or area of injury, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome

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[2] LTP 2020-2030: Addressable populations by condition (PDPN, PSNP, PHN, CINP). Company data on file. April 30, 2020.

[3] Gore, M., Brandenburg, N. A., Dukes, E., Hoffman, D. L., Tai, K.-S., & Stacey, B. (2005). Pain Severity in Diabetic Peripheral Neuropathy is Associated with Patient Functioning, Symptom Levels of Anxiety and Depression, and Sleep. Journal of Pain and Symptom Management, 30(4), 374-385. doi:10.1016/j.jpainsymman.2005.04.009
https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html.

[4] QUTENZA® [prescribing information]. Morristown, NJ: Averitas Pharma.

(after surgery/injury to deep somatic or visceral tissues).[5] Chronic post-surgical pain is the result of nerve damage and can be due to the surgery itself or other causes of pain including infection, malignancy, etc. It is identified by symptoms of neuropathic nerve pain such as burning, stabbing or shooting pain, numbness and changes to physical sensation or sensitivity to temperature or touch. Post-surgical neuropathic pain affects approximately 13 percent of all patients undergoing surgery, which represents 3.3 million patients per year in the US.[1]

About Averitas Pharma, Inc.

Averitas Pharma is a specialty pharmaceutical company dedicated to delivering innovative, effective, non-opioid pain management options to patients in the U.S. The company was formed in 2018, as a subsidiary of GRT U.S. Holding, Inc. and member of the Grünenthal Group. For more information, visit www.averitaspharma.com.

About Grünenthal

Grünenthal is a global leader in pain management and related diseases. As a science-based, privately-owned pharmaceutical company, we have a long track record of bringing innovative treatments and state-of-the-art technologies to patients worldwide. Our purpose is to change lives for the better – and innovation is our passion. We are focusing all of our activities and efforts on working towards our vision of a world free of pain.

Grünenthal is headquartered in Aachen, Germany, and has affiliates in 29 countries across Europe, Latin America and the US. Our products are available in more than 100 countries. In 2020, Grünenthal employed around 4,500 people and achieved sales of € 1.3 bn.

More information: www.grunenthal.com

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[5] ICD 11 - https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/985186256

Press Release
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IMPORTANT US-SAFETY INFORMATION

Do not dispense QUTENZA to patients for self-administration or handling. Only physicians or healthcare professionals under the close supervision of a physician are to administer and handle QUTENZA.

Unintended exposure to capsaicin can cause severe irritation of eyes, mucous membranes, respiratory tract, and skin in healthcare providers and others. When administering QUTENZA, it is important to follow these procedures:

- Administer QUTENZA in a well-ventilated treatment area.
- Wear only nitrile gloves when handling QUTENZA or any item that makes contact with QUTENZA, and when cleaning capsaicin residue from the skin. Do not use latex gloves as they do not provide adequate protection.
- Use of a face mask and protective glasses is advisable for healthcare providers.
- Keep QUTENZA in the sealed pouch until immediately before use.
- Use QUTENZA only on dry, intact (unbroken) skin.
- In patients treated for neuropathic pain associated with diabetic peripheral neuropathy, a careful examination of the feet should be undertaken prior to each application of QUTENZA to detect skin lesions related to underlying neuropathy or vascular insufficiency.
- During administration, avoid unnecessary contact with any items in the room, including items that the patient may later have contact with, such as horizontal surfaces and bedsheets.
- Aerosolization of capsaicin can occur upon rapid removal of QUTENZA. Therefore, remove QUTENZA gently and slowly by rolling the adhesive side inward.
- Immediately after use, clean all areas that had contact with QUTENZA and properly dispose of QUTENZA, associated packaging, Cleansing Gel, gloves, and other treatment materials in accordance with local biomedical waste procedures.
- If QUTENZA is cut, ensure unused pieces are properly disposed of.

Contraindications

None

Warnings and Precautions

- Unintended exposure to capsaicin can cause severe irritation of eyes, mucous membranes, respiratory tract, and skin.
- Do not apply QUTENZA to the face, eyes, mouth, nose, or scalp to avoid risk of exposure to eyes or mucous membranes. Accidental exposure to the eyes and mucous membranes can occur from touching QUTENZA or items exposed to capsaicin and then touching the eyes and mucous membranes. Wear nitrile gloves when administering QUTENZA and avoid unnecessary contact with items in the room, including items that the patient may later have

contact with, such as horizontal surfaces and bedsheets. If irritation of eyes or mucous membranes occurs, remove the affected individual from the vicinity of QUTENZA and flush eyes and mucous membranes with cool water.

- Aerosolization of capsaicin can occur upon rapid removal of QUTENZA. Therefore, remove QUTENZA gently and slowly by rolling the adhesive side inward. Inhalation of airborne capsaicin can result in coughing or sneezing. If irritation of airways occurs, remove the affected individual from the vicinity of QUTENZA. Provide supportive medical care if shortness of breath develops.
- If skin not intended to be treated is exposed to QUTENZA, apply Cleansing Gel for one minute and wipe off with dry gauze. After the Cleansing Gel has been wiped off, wash the area with soap and water.
- Patients may experience substantial procedural pain and burning upon application and following removal of QUTENZA. Prepare to treat acute pain during and following the application procedure with local cooling (such as a cold pack) and/or appropriate analgesic medication.
- Transient increases in blood pressure may occur during and shortly after the QUTENZA treatment. Blood pressure changes were associated with treatment-related increases in pain. Monitor blood pressure and provide adequate support for treatment-related pain. Patients with unstable or poorly controlled hypertension, or a recent history of cardiovascular or cerebrovascular events, may be at an increased risk of adverse cardiovascular effects. Consider these factors prior to initiating QUTENZA treatment.
- Reductions in sensory function have been reported following administration of QUTENZA. Decreases in sensory function are generally minor and temporary. All patients with pre-existing sensory deficits should be clinically assessed for signs of sensory deterioration or loss prior to each application of QUTENZA. If sensory deterioration or loss is detected or pre-existing sensory deficit worsens, continued use of QUTENZA treatment should be reconsidered.

Adverse Reactions

In all controlled clinical trials, adverse reactions occurring in ≥5% of patients in the QUTENZA group and at an incidence at least 1% greater than in the control group were application site erythema, application site pain, and application site pruritus.

Adverse Event Reporting

Physicians, other healthcare providers, and patients are encouraged to voluntarily report adverse events involving drugs or medical devices. To make a report you can:

- In the U.S., visit **www.fda.gov/medwatch** or call 1-800-FDA-1088; or
- For QUTENZA, you may also call 1-877-900-6479 and select option 1, or press zero on your keypad to talk to an operator to direct your call. **Please see full Prescribing Information.**