LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D.C. 20005-5929
(202) 737-5600

FACSIMILE
(202) 737-9329

www.hpm.com

SARA W. KOBLITZ

Direct Dial (202) 737-9623
SKoblitz@hpm.com

July 29, 2024

BY ELECTRONIC SUBMISSION

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

CITIZEN PETITION

Pursuant to 21 C.F.R. §§ 10.30 and 10.31 and section 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), and on behalf of our client, Aquestive Therapeutics, Inc. ("Aquestive"), we submit this Citizen Petition requesting that the Commissioner of the U.S. Food and Drug Administration ("FDA") refuse to approve any application for a nasal spray drug product that omits studies characterizing food effects if the active moiety, when separately approved for oral use, has demonstrated a food effect. In other words, we request that the Agency require applications for intranasally-administered product—particularly for rescue therapies—to include food-effect studies if the active moiety is known to be subject to a food effect. We further request that FDA investigate complaints of lack of efficacy for such FDA-approved nasal sprays and whether such complaints arise due to an unknown food effect.

FDA does not typically require food-effect studies for intranasally-administered products, largely because the Agency believes that the low volume of nasally-administered product results in negligible amounts swallowed. But various studies, including those looking at intranasal diazepam, have shown that intranasally-administered product is associated with significant swallowing of drugs, which is a particular concern for low volume nasal sprays in which the active product is highly concentrated. Such data, when reviewed in light of FDA's Adverse Event Reporting System ("FAERS") data concerning lack of efficacy, raise concerns that these intranasal drug products may act orally and therefore may be susceptible to food effects. These concerns are especially pronounced where the product is intended as a rescue therapy: where dose adjustments at the time of

administration cannot mitigate lack of food. To address and investigate these concerns, Aquestive contends that FDA should examine whether intranasal versions of oral medications that have known food effects should be subject to such investigation prior to approval of a marketing application—or, if already approved and demonstrating efficacy concerns, subject to postmarket investigation. Accordingly, Aquestive requests that FDA investigate food effects on intranasal versions of products that are known to have food effects when administered orally.

I. Actions Requested

Aquestive respectfully requests that FDA:

- Refuse to approve any nasal spray without food-effect studies where the active moiety has demonstrated a food effect when administered orally; and

- Investigate the lack of efficacy for such FDA-approved nasal sprays documented in FDA's Adverse Event Reporting System.

II. Statement of Grounds

A. Legal Background

i. New Drug Applications

Under the FDCA, FDA must approve a drug before it may be sold lawfully or distributed in interstate commerce. *See* FDCA § 505(a). Sponsors seeking to market new drugs submit a New Drug Application ("NDA"), which must include studies demonstrating that the proposed product is safe and effective for its intended use. *Id.* § 505(b). NDAs that include "full reports of investigations" of safety and effectiveness are filed as "standalone NDAs" under section 505(b)(1) of the FDCA while those that rely on studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference" must be submitted under section 505(b)(2). In practice, a 505(b)(2) NDA allows sponsors to receive FDA approval based on studies that are not developed by the applicant; such studies may have been submitted previously to FDA by another 505(b) applicant or published in literature. FDA, Draft Guidance for Industry: Applications Covered by Section 505(b)(2), at 1 (Draft, Oct. 1999). If a new drug cannot be approved as a 505(b)(2) NDA, a sponsor must conduct clinical and non-clinical studies to demonstrate that the proposed drug is safe and effective for its intended use. *Id.*

To be eligible for submission as a 505(b)(2), an NDA must include bridging studies between the proposed product and the listed drug. *Id.* at 8-9. Such a "bridge" in a 505(b)(2) NDA demonstrates sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA. FDA, Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application, at 4-5 (May 2019). This could include studies that measure the relative bioavailability of the two products or other appropriate scientific information. *Id.* The 505(b)(2) NDA must also include data to support any differences from a listed drug relied upon by including appropriate safety and effectiveness information and meet the same statutory standard for safety and effectiveness as a 505(b)(1) NDA. *Id.*

Bridging studies typically rely on bioavailability and bioequivalence studies and must be performed using the "most accurate, sensitive, and reproducible approach available." 21 C.F.R. § 320.24(a). Several in vivo and in vitro methods can be used to measure bioavailability and bioequivalence, but in general, pharmacokinetic ("PK") studies are the gold standard. *Id.*; *see also* FDA, Draft Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, at 6 (Mar. 2014). FDA regulations "provide for use of PK measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the drug substance from the drug product into the systemic circulation;" and they rely on "AUC to assess extent of systemic exposure and C_{max} and T_{max} to assess rate of systemic absorption." *Id.*

> PK-based comparisons to describe relative bioavailability or make bioequivalence determinations are predicated on an understanding that measuring the active moiety or ingredient at the site of action is generally not possible and on an assumption that some relationship exists between the efficacy/safety and concentration of the active moiety and/or its important metabolite(s) in the systemic circulation. A typical study is conducted as a crossover study.

Id.

ii. Food-Effect Study Requirements

While FDA encourages the development of drug formulations that are not affected by food, applications for orally-administered new drug products typically require the inclusion of studies assessing the effect of food on absorption. FDA, Guidance for Industry: Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations, at 2 (June 2022). Indeed, the Agency recognizes that food-

drug interactions "can have a significant impact on the safety and efficacy of orally administered drug products," manifesting themselves in the increase or decrease of systemic exposure of the drug with a corresponding impact on the safety or efficacy of a given product. *Id.* For that reason, FDA requires well-conducted food-effect studies to "inform how, when, and why drugs should or should not be administered with food" that typically take the form of PK studies. *Id.* Such studies should determine the impact of food, and where necessary the type of food, on the PK of a given drug.

Sponsors assess the effect of a high-fat meal on the PK of a new drug product at several times: "early in development to inform the appropriate dose and administration throughout clinical development and product labeling;" in clinical trials before conducting the pivotal safety and efficacy trials to inform decisions regarding dosing with respect to food; and "using the final to-be-marketed oral formulation." *Id.* at 3-4. Sponsors generally use a single "randomized, balanced, single-dose, two-treatment (*i.e.*, fed versus fasted), two-period, crossover design to study the effects of food on the orally administered drug product." *Id.* at 4.

The Agency typically requires food-effect studies for all new orally-administered drug products. *Id.* at 3. This is because food may influence bioavailability when there is "a high first-pass effect, extensive adsorption, complexation, or instability of the drug substance in the [gastrointestinal] tract." FDA, Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, at 2 (Dec. 2002). Excipients or interactions between excipients and food-induced changes in the gut physiology can also contribute to food effects and influence bioavailability. *Id.* It is for these reasons—orally-administered medications undergo first-pass metabolism and are subject to the food-induced changes in the gut—that FDA requires food-effect studies for oral medications.

FDA does not, however, require food-effect studies for non-orally administered products unless there is a reason to believe that a proportion of the drug product will be swallowed, and thus, subject to a food-effect and first-pass metabolism. FDA, Citizen Petition Response, at 10, Docket No. FDA-2019-P-5121 (Jan. 10, 2020) ("food-effect studies may be recommended for non-orally administered products if there is reason to believe that a proportion of the drug product will be swallowed, and thus, subject to a food-effect and first-pass metabolism."). FDA instead "determines whether a food-effect study is necessary for non-orally administered drug products on a case-by-case basis." *Id.* Because nasal formulations deliver low volumes of medicament, FDA does not typically require them for nasal sprays—even if the active moiety has demonstrated a food effect in an orally-administered version. *See id.* (explaining that "any potential swallowing of a portion of the [intranasal diazepam spray] dose is minimized by the low volume administered per dose."). FDA, however, has not cited to any literature—nor are we aware

of any evidence—suggesting a correlation between low volume nasal sprays and decreased incidence of swallowing.

iii. Nasal Spray Product Requirements

Unlike orally-administered drugs that work systemically after being metabolized and made available in the bloodstream, locally acting drugs like nasal spray products are intended to produce their effects upon delivery to nasal sites of action without relying on systemic absorption. FDA, Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, at 4 (April 2003). Notwithstanding the lack of metabolization and systemic availability, FDA requires bioavailability and bioequivalence assessments for locally acting nasal aerosols and sprays. *Id.* at 3. This is because "[s]ystemic exposure following nasal administration can occur either from drug absorbed into the systemic circulation from the nasal mucosa, or after ingestion and absorption from the gastrointestinal tract." *Id.* FDA therefore recommends PK studies to measure systemic exposure bioavailability or to establish systemic exposure bioequivalence. *Id.* "For suspension products that do not produce sufficient plasma concentrations to allow assessment of systemic exposure, clinical studies or [bioequivalence] studies with a pharmacodynamic or clinical endpoint are recommended to measure systemic absorption [bioavailability] and establish systemic absorption [bioequivalence]." *Id.* Notwithstanding the possibility of ingestion or systemic absorption, such studies generally ***do not include*** food-effect studies—even if oral versions of the active moiety have demonstrated a food effect—because, as noted, there is such a low likelihood of the occurrence of swallowing medicament with low volume nasal spray products. FDA, Citizen Petition Response, at 10, Docket No. FDA-2019-P-5121 (Jan. 10, 2020) ("Any potential swallowing . . . is minimized by the low volume administered per dose.").

b. Factual Background

i. Libervant

Aquestive is the sponsor of a 505(b)(2) NDA for a buccal film dosage form of diazepam, intended "for the acute treatment of intermittent, stereotypical episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years of age." Libervant (diazepam) Approval Letter, NDA 218623 (Apr. 26, 2024). Aquestive received approval on April 26, 2024 and has been marketing ever since. As part of its 505(b)(2) NDA, Aquestive was required to submit food-effect studies to FDA regarding diazepam.

ii. Valtoco

Another diazepam product, Valtoco, is approved under a 505(b)(2) NDA as an intra-nasally administered diazepam product for the "acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older." Valtoco (diazepam) Prescribing Information, NDA 211635, at § 1 (Jan. 2020). Though Valtoco is comprised of diazepam, with a known food effect, FDA has not required food-effect studies of Valtoco due to the low volume of product administered and presumably swallowed. FDA, Citizen Petition Response, at 10, Docket No. FDA-2019-P-5121 (Jan. 10, 2020). As affirmatively stated in the Valtoco NDA Action Package, "[t]here is a potential for part of the drug administered to nasal cavity be absorbed though gastro intestinal tract," but "[f]ood effect was not evaluated on the proposed nasal formulation because of the route of administration and the proposed indication, acute treatment of seizures in patients who require control of intermittent episodes of increased seizure activity." NDA 211635, Clinical Pharmacology Review, at 11-12 (Oct. 3, 2019), available at https://tinyurl.com/ValtocoClinPharm.

iii. Previous Citizen Petition

In November 2019, Aquestive submitted a Citizen Petition asking FDA to, among other things, require a food-effect study for Valtoco because it has the potential for swallowing if not fully absorbed in the nasal cavity. Aquestive contended that Neurelis's T_{max} (*i.e.*, the time to the peak concentration of a drug) data suggest that the product is being swallowed and undergoes gastrointestinal absorption.

FDA denied the Citizen Petition, explaining that food-effect studies are for orally-administered drug products only unless there is reason to believe that a proportion of the drug product will be swallowed and thus subject to a food-effect and first-pass metabolism. FDA, Citizen Petition Response, at 10, Docket No. FDA-2019-P-5121 (Jan. 10, 2020). FDA explained that that Agency determines whether a food-effect study is necessary for non-orally administered drug products on a case-by-case basis. *Id.* In this case, FDA determined that one is unnecessary for Valtoco because of the low volume administered per dose, which suggests that the drug is not absorbed in the gastrointestinal tract. *Id.*

B. Argument

While intranasal administration offers advantages to patients, concerns of efficacy arise when a nasally-administered product is swallowed rather than absorbed through the nasal passages. *See* FDA, Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, at 4 (April 2003) ("Systemic exposure following nasal administration can occur either from drug absorbed into the

systemic circulation from the nasal mucosa, or after ingestion and absorption from the gastrointestinal tract."). This is because an intranasal product becomes a metabolized, orally-administered product once swallowed, and its metabolism and interactions in the gut become relevant. Indeed, if such products are swallowed, not only may they introduce unexpected gastrointestinal-related adverse events like nausea and vomiting, but systemic (rather than local) exposure can affect the PK, and thereby bioavailability and efficacy, of a given product.

While the clinical impact of reduction in PK on efficacy and safety is not necessarily presumed for all conditions, where products are approved under a 505(b)(2) pathway, the working premise is that PK is an acceptable surrogate of effectiveness. Relevant here, both intranasal and buccal film diazepam were approved based on a PK bridge to the listed drug, suggesting that PK is indeed a surrogate measure of efficacy. Thus, there is adequate regulatory precedent within the FDA to utilize PK as a surrogate efficacy marker and sufficient evidence to, at a minimum, prompt further investigation into a possible "lack of efficacy" signal of products in development, under review, and/or currently marketed.

Concerns of PK, bioavailability, and efficacy problems resulting from swallowing of a nasal spray raise particular red flags when the active moiety has a known food-effect. Yet, despite evidence of swallowing of intranasally-administered products, FDA has declined to require food-effect studies for such products, asserting that swallowing of such products is negligible. However, published literature involving many such products contradicts that theory: intranasally-administered products are associated with gastrointestinal adverse events, indicating product is swallowed, and FAERS data cites lack of efficacy-related events, *see infra* § II.B.b., which suggest bioavailability problems. Given the acknowledged potential for systemic absorption of intranasal products, and given concerns about their efficacy, FDA must consider the need for food-effect studies where accidentally swallowed product contributes to the effect of a given drug product.

a. Intranasal drugs like diazepam can be absorbed through the gastrointestinal tract.

FDA has declined to require food-effect studies for most intranasal drugs, including diazepam, because they are unlikely to be swallowed, but Aquestive posits that the likelihood of gastrointestinal exposure to intranasally-administered drugs is higher than FDA presumes. This is evidenced by the adverse events associated with nasal products, which demonstrate that gastrointestinal events like nausea and dysgeusia are not uncommon. *See e.g.* Imitrex (sumatriptan) Prescribing Information, NDA 020626, at § 6.1 (2017) (13.5% of patients reported nausea/vomiting and 24.5% bad or unusual taste). Indeed, adverse events for various nasal spray products include both gastrointestinal events

and neurological events relating to taste, which suggest at least some migration of product from the nasal cavity to the throat, mouth, or gastrointestinal system. *See e.g. id.*; Nayzilam (midazolam) Prescribing Information, NDA 211321, at. § 6.1 (2023) (4% reporting abnormal taste); Valtoco (diazepam) Prescribing Information, NDA 211635, at § 6.1 (2023) (3% reporting dysgeusia).

Indeed, despite FDA's assumptions, more than trace amounts of a nasally-administered product may absorbed through the gastrointestinal tract. Based solely on the anatomy of the nasal passage, an intranasal product can be absorbed through the olfactory mucosa or the respiratory mucosa, but also through enteral absorption in the gastrointestinal tract following posterior drainage through the nasopharynx and swallowing.[1] Steve Chung et al., The Nose Has It: Opportunities and Challenges for Intranasal Drug Administration for Neurologic Conditions Including Seizure Clusters. 21 Epilepsy Behavior Rpts. 100581 (2023). To avoid swallowing and leakage, it is critical to minimize off target deposition. *Id.* This is, presumably, why nasal formulations are limited in dose volume to 100-150 µL per nostril. *Id.* While this "low volume" is the basis of FDA's assumption that any swallowing is negligible, Aquestive notes that there is no standardized definition in FDA Development Guidances (specifically, FDA's Guidance for Industry titled, "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation" (July 2022) for what constitutes a "low volume" nasal spray. In the absence of categorical criteria for defining "low volume," it is even more important and urgent to ensure the exposure of active product to the gastrointestinal tract, and the potential for food effect, to be adequately characterized in a pre-approval setting.

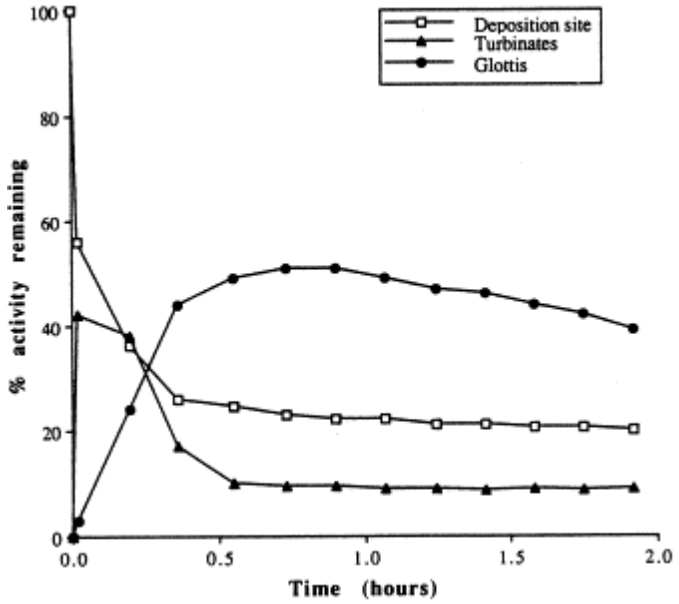
Importantly, a low-volume nasal spray typically requires a higher concentration of a drug. This means that any amount that is swallowed is swallowed in a higher concentration than would have been swallowed if administered orally. These higher concentrations may affect absorption—and the need for food—and too should be considered where it is possible that gastrointestinal absorption may occur.

An additional consideration is that mucociliary clearance via the nasopharynx is a rapid process. In a study of 46 healthy subjects administered radiolabeled nasal spray, approximately 50% of the administered dose is cleared from the ciliated respiratory mucosa within a few minutes (Figure 1) (Batts 1991). This means exposures beyond the

[1] Indeed, FDA acknowledged as much in the review of Valtoco: "[t]here is a potential for part of the drug administered to nasal cavity be absorbed though gastro intestinal [sic] tract." NDA 211635, Clinical Pharmacology Review, at 11-12 (Oct. 3, 2019), available at https://tinyurl.com/ValtocoClinPharm.

administration site can occur quickly post-administration of a nasal spray. This is potentially a large loss, particularly when the volume is highly concentrated.

Figure 1: Deposition and clearance of ^{99}Tc-labelled diethylenetriamine pentaacetic acid solution administered to the nasal cavity of human volunteers. Reprinted from Batts 1991.



Literature also suggests that swallowing is not uncommon. For example, intranasal diazepam has been cited in several studies as swallowed and absorbed through the gastrointestinal tract. In 2009, a study evaluating intranasal diazepam found tolerability problems in a formulation of intranasal diazepam with all subjects swallowing a portion of the intranasal diazepam. Vijay Ivaturi et al., Bioavailability and Tolerability of Intranasal Diazepam in Health Adult Volunteers, 84 Epilepsy Research 120 (2009). The study utilized a randomized, single-blind, three-way crossover design to compare the PK and tolerability of an intravenous diazepam (5 mg) against two intranasal diazepam doses in 8 subjects. While no unanticipated adverse events were reported by subjects following intranasal administration of diazepam, ***all*** subjects reported swallowing a portion of the intranasal dose. *Id.* The gastrointestinal absorption resulted in "lag time" in measured PK such that there were secondary peaks in bioavailability, which contributed to the "highly variable estimates of tmax after nasal administration." *Id.*

In a follow-up study, twelve healthy volunteers were enrolled in an active-control, double-blind, four-period crossover PK and tolerability study with two new intranasal diazepam formulations compared to a dose of rectal gel. Vijay Ivaturi et al., Bioavailability of Intranasal vs. Rectal Diazepam, 103 Epilepsy Research 254 (2013). Again, no unanticipated adverse events were reported, but ***all*** subjects—again—reported swallowing a portion of the nasal dose. *Id.* The study authors identified considerable variability among all the nasal administrations, noting that the "variability was typically associated with a general reduction in relative exposure to a specific formulation within a subject, suggestive of incomplete dosing and/or absorption of the intended dose, or loss of drug through nasal or rectal leakage." *Id.* Further, "[a]ll subjects reported a disagreeable after-taste minutes after nasal administration which was consistent with reports of swallowing of some part of dose after administration." *Id.*

A third study comparing intranasal diazepam to rectally-administered diazepam assessed bioavailability of a single dose of the nasal spray compared to the rectally-administered diazepam, the PK linearity between dose-strengths of the nasal spray formulation, and the tolerability of an intranasal diazepam spray. Herbert Henney III et al., Assessment of Pharmacokinetics and Tolerability of Intranasal Diazepam Relative to Rectal Gel in Healthy Adults, 108 Epilepsy Research 1204 (2014). Twenty-four healthy adults were enrolled in a Phase 1, open-label, 3-period crossover study. *Id.* The study saw nasal leakage in 65% of patients at various time points from 5 to 60 minutes after dosing, but that leakage was not associated with drug loss. *Id.* Nevertheless, dysgeusia, dry throat, and throat irritation were reported in the nasal spray group, implying that some of that leakage indeed was swallowed. *Id.*

In another randomized crossover trial studying bioavailability and safety of intranasal diazepam as compared to oral and rectal, the sample size of 48 healthy subjects recorded 131 mild and 4 moderate treatment-emergent adverse events in all subjects, with nausea as one of the featured events. Elyse Cornett et al., VALTOCO® (Diazepam nasal Spray) for the Acute Treatment of Intermittent Stereotypic Episodes of Frequent Seizure Activity, 13 Neurology Int'l 64 (2021) (citing Robert Hogan et al., Bioavailability and Safety of Diazepam Intranasal Solution Compared to Oral and Rectal Diazepam in Healthy Volunteers, 61 Epilepsia 455 (Mar. 2020). Additionally, the bioavailability of the nasal spray was only 60% of that of the oral diazepam. *Id.* Yet another study on the dosing feasibility and tolerability of intranasal diazepam noted oral and gastrointestinal side effects including dysgeusia (25.8%) and nausea (16.1%). Michael Sperling et al., Dosing Feasibility and Tolerability of Intranasal Diazepam in Adults with Epilepsy, 55 Epilepsia 1544 (2014). Such adverse events indicate that a non-insignificant proportion of the drug is absorbed via the gastrointestinal system. *Id.* Indeed, all of these studies suggest that even for low volume intranasal products such as intranasal diazepam, posterior drainage

may result in a significant amount of the administered drug entering the gastrointestinal tract, rather than just a negligible fraction.

Other intranasal products are subject to the same enteral absorption risk. For example, midazolam nasal spray and sumatriptan nasal spray are associated with substantial enteral absorption. With respect to midazolam, FDA itself has recognized the potential "for part of the drug administered to nasal cavity be absorbed though gastro intestinal tract [sic]." Nayzilam (midazolam), Clinical Pharmacology and Biopharmaceutics Review, NDA 211321, at 10 (Mar. 12, 2019). There, FDA explained that midazolam intranasal spray is 3.7-6.8% higher metabolite to parent AUC_{inf} ratio than intravenous midazolam, which means that "a significant amount of midazolam is more likely absorbed in the gut . . . following intranasal administration of Nayzilam . . . ." *Id.*[2] Notwithstanding this acknowledged concern, FDA still did not require characterization of the food effect potential for the "significant amount of midazolam" that was exposed to the gastrointestinal tract during review of the midazolam intranasal spray NDA.

Similarly, literature estimates that "only about 10 % of the drug delivered by standard nasal spray (Imitrex) is absorbed rapidly across the nasal mucosa within the first 20 min with much of a dose undergoing delayed absorption from the [gastrointestinal] tract with a T_{max} of 90 min." Per Djupesland, Nasal Drug Delivery Devices: Characteristics and Performance in a Clinical Perspective—A Review, 3 Headache 42 (2013). This is consistent with the product being swallowed: "This phenomenon is clearly observed with sumatriptan where a bimodal absorption profile is produced following conventional nasal spray administration: a lower early peak, likely related to intranasal absorption, is produced after 20 minutes and is followed by a higher absorption peak consistent with [gastrointestinal] absorption around 90 minutes." *Id.*

Finally, a study has found low volume intranasal epinephrine spray directly associated with the treatment emergent adverse event of vomiting (16%), linked to swallowing of the epinephrine. David Dworaczyk and Allen Hunt, 13.2mg Intranasal Epinephrine Spray Demonstrates Comparable PK/PD and Safety to 0.3mg Epinephrine Autoinjector, Poster L01 (AAAA I Annual Meeting Poster 2023). There, the authors compared the PK of a single intranasal dose of epinephrine (consisting of 2 consecutive sprays administered to either the same or opposite nostrils) to that of a single intramuscular injection via autoinjector and manual syringe in healthy adult subjects. *Id.* While the PK for the intranasal product provided "an enhanced PK profile" compared to the autoinjector product, the most common event reported in one of the cohorts was vomiting following

[2] The same Review Division denied Aquestive's Citizen Petition requesting a food effect for Valtoco, contradictorily stating that such absorption is unlikely due to the low volume administered. No support was provided for that assumption.

nasal administration, generally occurring 1-4hrs post dose. *Id.* The study authors concluded that vomiting may be related to swallowing the non-absorbed epinephrine. *Id.*

Accordingly, literature suggests that nasal products, including Valtoco, are swallowed more often—and in a greater amount or concentration—than FDA presumes. As a result, the product must be treated as though some amount is administered orally. Where the active moiety is known to have a food effect when administered orally, food-effect studies should be performed for the intranasal product.

b. If intranasal drugs are absorbed through the gastrointestinal tract, and a version of the active moiety has a demonstrated food effect when separately administered orally, a food-effect study is necessary to rule out effects on efficacy.

FDA requires food-effect studies for intranasal drugs only on a case-by-case basis; the presumption is that the low volume of product administered intranasally decreases the likelihood that such drugs enter the gastrointestinal tract. But, as explained *supra*, FDA's presumption that intranasally-administered drug products are not swallowed is belied by a litany of examples, including intranasal diazepam. Unintentional absorption, however, of an intranasal drug through the gastrointestinal tract could raise problems because once swallowed, medication becomes, in effect, an orally administered medication. Stewart Tepper and Merilee Johnstone, Breath-Powered Sumatriptan Dry Nasal Powder: An Intranasal Medication Delivery System for Acute Treatment of Migraine, 11 Med Devices (Auckl) 147 (2018). Thus, certain drug products that, when orally administered, are effective only when taken with food may have bioavailability issues when swallowed. Consequently, patients may be inadvertently taking intranasal products orally but experiencing a lack of efficacy because the product is not being taken with food.

As noted, literature has shown that drug product, including intranasal diazepam, is routinely swallowed during intranasal administration. In addition, FAERS data for intranasal diazepam (Valtoco) suggest that almost 41% of adverse events reported relate to lack of efficacy. *See infra* Table 1. While these data do not explain exactly why the product was not effective in some patients, the fact that the active moiety when administered orally is known to have a food effect—combined with the fact that some product is known to be swallowed—provides a reasonable hypothesis as to the source of the efficacy problems. Given the pronounced effect of food on oral diazepam, the adverse events reported with diazepam nasal spray, and the evidence of enteral absorption with other nasal sprays, there is a high likelihood that food influences the PK of diazepam nasal spray.

In fact, a 2022 study supports the possible effect of food on the PK of diazepam nasal spray.[3] Michael Rogawski and Gary Slatko, A Randomized, Open-Label, Two-Treatment Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of Diazepam Nasal Spray in Healthy Adults, 64 Epilepsia 364 (2023). In a randomized Phase 1, open-label, two-sequence, two-period, two-treatment crossover study comparing intranasal diazepam under fasted and fed conditions in 20 healthy adult male and female participants, PK concentrations were significantly different when dosed 30 minutes after a high-fat high-calorie meal compared with dosed in a fasted state. The data from this study indicate that food can significantly impact PK parameters, which are critical for determining efficacy. According to the study authors, "[t]he results of the current study challenge the conventional view that most diazepam absorption from a nasal spray preparation occurs within the nasal cavity." Indeed, "[t]he significant food effect demonstrated in the current study and the observation that most participants reported tasting the medication following nasal administration suggests that a substantial portion of the diazepam dose is swallowed." *Id.* This suggests that food-effect studies—even for low volume intranasal products like diazepam—are warranted.

PK data, as impacted by food, is a relevant surrogate for assessing the therapeutic threshold and potential efficacy of intranasal diazepam products. While FDA has, in the past, questioned whether there is a clinical impact of reduction in PK exposures on efficacy or safety in the treatment of acute repetitive seizures, the fact that both diazepam nasal spray and diazepam buccal film were approved based on a PK bridge to a listed drug renders PK a clear surrogate measure of efficacy; otherwise, PK data would be insufficient for approval of the 505(b)(2) NDAs for both Valtoco and Libervant. Indeed, reduced PK exposures in the presence of a high-fat meal was the reason that FDA in 2021 issued a Complete Response Letter for the initial version of Libervant (which is tentatively approved due to Valtoco's orphan drug exclusivity), and the approved version of Libervant in children 2-5 years old was approved on the basis of PK comparability. Accordingly, PK is an important surrogate for efficacy in diazepam such that the Agency decides new product approval actions on the basis of PK.

This same concern of reduced efficacy appears in other intranasal products. Indeed, FAERS data for nasal drugs generally suggest that there are efficacy issues (specifically, a decreased (or lack of) efficacy signal from a safety database) for other rescue sprays as well. Data from the FAERS database were extracted for the diazepam-containing product "Diastat" (also "Diastat Acudial") and nasal sprays including diazepam ("Valtoco"),

[3] While the study was funded by Aquestive, an independent Clinical Research Organization conducted the PK crossover study, and the study was published in a reputable journal after an extensive double-blind peer-review process to ensure accurate conclusions based on appropriately executed clinical evaluation.

sumatriptan ("Tosymra"), ketorolac ("Sprix"), midazolam ("Nayzilam"), and dihydroergotamine ("Migranal," "Trudhesa"). Diastat was selected as a representative comparator due to its active moiety (diazepam) with a known food effect and the rectal administration of the product allows for an independent assessment of a signal for both a non-nasal and non-oral administration control.

The methodology of the FAERS database search was reviewed and verified by an independent epidemiologist from a third-party pharmacovigilance service provider. Full FAERS data were extracted on the 14th, 15th and 23rd of July 2024. The reaction term "drug ineffective" and similar terms including "device ineffective," "therapeutic response unexpected," "therapeutic response delayed," "therapeutic response decreased," "therapeutic product effect delayed," "therapeutic product effect incomplete," "therapeutic product effect variable," "therapeutic product effect decrease," "treatment failure," and "therapy non-responder" were included in the analysis. Table 1 summarizes the event reporting for calculation of the reporting ratios and Table 2 summarizes the proportional reporting ratios (PRR) and reporting odds ratios (ROR) for the selected sample of FDA-approved products. These are statistical methods used to detect signals of disproportionate reporting in pharmacovigilance databases (*Doc. Ref. EMEA/106464/2006, Eudravigilance expert working group, guideline on the use of statistical signal detection methods in the eudravigilance data analysis system*). For the purposes of this evaluation, PRR > 1 is considered a signal and ROR >2 is considered the threshold for spontaneous report signals.

Table 1: Summary of post-marketing events in the FAERS database related to 'drug ineffective' in relation to total number of reported events: intranasally delivered products and Diastat

FDA-Approved Products	Event Type	No. of Events
Diazepam rectal gel (Diastat)	Ineffective Events	64
	All AEs	328
	Other AEs	264
Diazepam IN (Valtoco)	Ineffective Events	61
	All AEs	147
	Other AEs	86
Sumatriptan IN (Tosymra)	Ineffective Events	36
	All AE	126
	Other AE	90
Ketorolac IN (Sprix)	Ineffective Events	42
	All AE	368
	Other AE	326
Midazolam IN (Nayzilam)	Ineffective Events	26
	All AE	305

	Other AE	279
Dihydroergotamine IN (Migranal, Trudhesa)	Ineffective Events	147
	All AE	401
	Other AE	254

AE= adverse event; IN= intranasal; PRR= proportional reporting ratio; ROR= reporting odds ratio

Table 2: Calculations of Proportional Reporting Ratios and Reporting Odds Ratios for post-marketing events in the FAERS database related to 'drug ineffective': intranasally delivered products and Diastat

FDA-Approved Product Comparison	PRR	ROR
Diazepam IN (Valtoco) / Diastat	**2.13**	**2.93**
Sumatriptan IN (Tosymra) / Diastat	**1.46**	**1.65**
Ketorolac IN (Sprix) / Diastat	0.58	0.53
Midazolam IN (Nayzilam) / Diastat	0.44	0.38
Dihydroergotamine IN (Migranal, Trudhesa) / Diastat	**1.88**	**2.39**

IN= intranasal; PRR= proportional reporting ratio; ROR= reporting odds ratio

Overall, 3 out of 5 evaluated products are noted to have an elevated PRR and ROR, which confirms a signal that warrants further exploration. If there was, in fact, a signal for decreased (or lack of) efficacy of a rescue treatment, the clinical implications to the patient being sub-optimally treated are worsening or incomplete resolution of the acute clinical presentation for their condition. For these FDA-approved product examples, it would mean continued and/or worsening events of seizure, migraine, or pain that can rapidly escalate when left untreated.

There are, however, known limitations with the FAERs database because it is sourced by unsolicited post-marketing case reports. These concerns include the minimal case details provided in the database: there are no relevant medical history or disease severity data, hospital reports, or details with respect to subject status including whether the subject was fed/fasting at the time of event. There is also a possibility of duplicate or incomplete reports and data is unverified. FDA, however, has broader access to databases that are without these limitations. FDA should explore these data in the interest of the patients that may be treated with subtherapeutic levels of medication. Indeed, the Agency has an obligation to explore this possible safety signal further, as it could seriously affect the effectiveness of a handful of approved intranasal products.

Of course, the signal is based on post-marketing experience and the only definitive way to characterize, label, and account for a potential food effect of intranasal products would be a simple food effect study, pre-approval. The Agency has several guidance

documents that describe expectations for a food effect study in terms of design and pre-defined criteria for meal content. This type of study is commonly performed in a small number of healthy volunteers often in a Phase 1 clinic setting and without extensive serial blood draws relative to other Phase 1 studies. Study conduct is easily completed within a week, depending on the product's PK profile. When designed in accordance with FDA guidance, a single food effect study provides confirmatory evidence of the presence or absence of a food effect and also quantifies the extent of impact on product bioavailability or exposure, which informs the labeling and dosing recommendations. Accordingly, where FDA requires a food-effect study for an oral version of a given intranasally-administered product, it follows that a food-effect study should be required for the intranasal version, as that product is likely to be swallowed to some extent.

C. Conclusion

FDA should require food-effect studies for nasal sprays delivering active moieties with known oral-administration related food effects like diazepam. Literature consistently shows that intranasal products are swallowed and thus are administered, to some degree, orally. As a result, it is important to understand the effect of food on these products—particularly because FAERS data reflect a lack of therapeutic effect for some nasal sprays.

Where, like in the case of diazepam, therapeutic effect is in question ***and*** a food effect is known, FDA has an obligation to the public to investigate whether that lack of therapeutic effect is related to food effect. A food effect study is a simple trial to conduct, and the study does not take long to complete, is not difficult to recruit, and is not an expensive endeavor for Sponsors. A single food effect study provides important data with regards to the presence of and extent of a food effect, which informs the prescribers and patients through labeling and dosing recommendations for a product prior to its entry into the marketplace. These data therefore are essential for the Agency to assess a product's overall benefit/risk profile prior to approval and for guiding patients, caregivers, and prescribers in the appropriate use of the product. Given the clinical implications of subtherapeutic levels of product intended for use as rescue therapy during an acute event (e.g., migraine, seizure) and the limited burden of study conduct, the benefits of the Agency requiring food-effect studies for any application for an intranasal spray where the active moiety is associated with a food effect certainly outweighs any risk. FDA therefore must require such studies.

D. Environmental Impact Statement

The undersigned claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

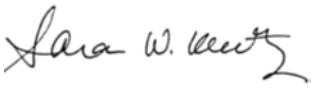
E. Economic Impact Statement

An economic impact statement will be submitted at the request of the Commissioner.

F. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 17, 2019.[4] If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following person or organizations: Aquestive Therapeutics. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully Submitted,



Sara W. Koblitz
Kurt R. Karst
Counsel to Aquestive Therapeutics, Inc.

[4] Aquestive has been aware of this issue since 2019 and previously discussed the issue with the Agency. Aquestive submitted a Citizen Petition to FDA with the same request in November 2019. Now that additional studies have been conducted and additional data made available, Aquestive is reiterating a position it took in a private submission to FDA, as well as the request it made in its 2019 Petition.