Response to Q211873 Additional Information Letter

All text in bold are from the Q211873 AI letter followed by Openwater's response.

The items described below identify areas where deficiencies exist with your Request for Designation as a Breakthrough Device, including an explanation of why the device may not meet the criteria outlined, and what additional information is needed.

1. ***To meet Breakthrough Device designation criterion #1 as defined by section 515B(b)(1) of the Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 360e-3(b)(1)), you need to demonstrate a reasonable expectation that the proposed device could function as intended thereby demonstrating technical success. Although the submission distinguishes between the Openwater LVO Stroke Alert (software device) and the Openwater Headset (hardware device), it is our understanding that the LVO Stroke Alert software is designed to specifically analyze data collected by your proprietary Openwater Headset. Therefore, to support the potential for technical success of the Openwater LVO Stroke Alert software, additional information about the Openwater Headset is needed. We request that you address the following to facilitate understanding of device functionality and support a reasonable expectation of the potential for technical success of both the Openwater LVO Stroke Alert and Openwater Headset to meet Breakthrough Device designation criterion #1:***

    a. ***The proposed indications for use (IFU) related to the Openwater Headset states:***

        "The non-invasive Openwater Headset is intended for monitoring of blood flow in tissue, including the brain. The Openwater headset is intended for monitoring of adults. The prospective clinical value of data from Openwater Headset has not been demonstrated in disease states. Openwater Headset should not be used as the sole basis for diagnosis or therapy."

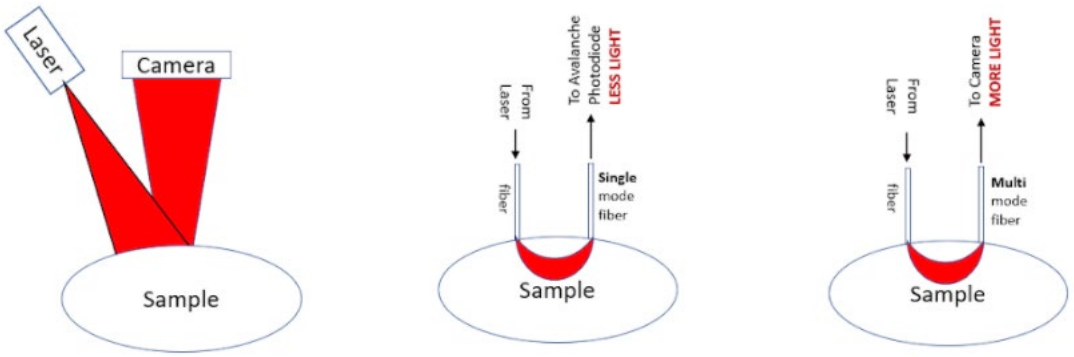
    Additionally, as mentioned in section 2.3 of the submission, various parameters are displayed after the completion of the scan by the Openwater Headset. From this information, it is not clear if the data can be independently interpreted by the clinical user or if it requires software analysis for utilization, and whether there is basic software included for use of the Openwater Headset that is separate from the Openwater LVO Stroke Alert software. To facilitate the understanding of the type of information that will be available to clinical users to inform their assessment of patients suspected of having a large vessel occlusion (LVO), provide complete descriptions of the outputs of both the Openwater Headset and the Openwater LVO Stroke Alert software, accompanied by a discussion of how you intend for these device outputs to be clinically interpreted in the assessment of patients suspected of having a LVO.

    Openwater LVO Stroke Alert is an SaMD that relies on the blood flow and blood volume data recorded by Openwater Headset. As noted in Q211873, Section 2.1, this device includes two components, a head-mounted, wearable headset, and a console that houses all the electronics to drive the headset (described further in Openwater's response to deficiency 1(b)). The Openwater Headset software is independent of the Openwater LVO

Stroke Alert software. The Openwater Headset software has the following functions:

- Provide a user interface to operate the device including initiating a scan,
- Drive the electronics supporting the lasers and sensors in the wearable headset,
- Process the signal collected by the sensors in the headset to measure blood flow and blood volume,
- Present the computed blood flow and blood volume indices to the user.

As discussed in the Q211873 submission, the Openwater Headset (and wand) utilizes proprietary breakthrough technology to measure cerebral blood flow. Compared to traditional laser speckle imaging and diffuse correlation spectroscopy, Openwater's approach achieves significantly improved light collection and scanning depth (Figure S-1). Bench, animal, and human data utilizing this technology was shown in Q211873 submission in Section 3 and summarized in Section 3.4.



(a) Laser Speckle Imaging	*(b) Diffuse correlation spectroscopy*	*(c) Openwater's approach*
Coherence is measured by looking at many speckles on camera. This detects primarily light reflected near the surface	Coherence is measured by looking at a single speckle over time on the detector – an avalanche photodiode. Light is collected with a single-mode fiber with a diameter of a few microns	Coherence is measured by interference on a camera through an aperture of several millimeters and is able to gather 1000 times more light than approach (b). With more light, more depth can be achieved.

Figure S-1: Openwater Headset's technology compared to traditional laser based approaches.

Utilizing this technology, Openwater Headset provides the following two blood flow measurement outputs to the user (as noted in Q211873, Section 2.1):

1. Blood Flow Index (BFI), an Openwater proprietary format, based in laser speckle contrast analysis, that provides a measure of the flow rate of blood in the underlying tissue below the sensor, similar to other transcranial optical devices that provide measurements of relative cerebral blood flow index (rCBFi),
2. Blood Volume Index (BVI), an Openwater proprietary format, based on measurements of the concentration of absorbing chromophores within the underlying tissue below the sensor, and similar to other transcranial optical devices

that provide measurements of relative total tissue hemoglobin concentration (rTHb), which in turn relates to cerebral blood volume (CBV).

Figure S-2 shows an example of the proposed output of Openwater Headset. Note that the BFI and BVI information shown in the example below were measured by placing the Openwater wand prototype at the forehead and the temple location of a healthy control. With the Openwater Headset wearable form factor, such repeated placement would not be necessary.

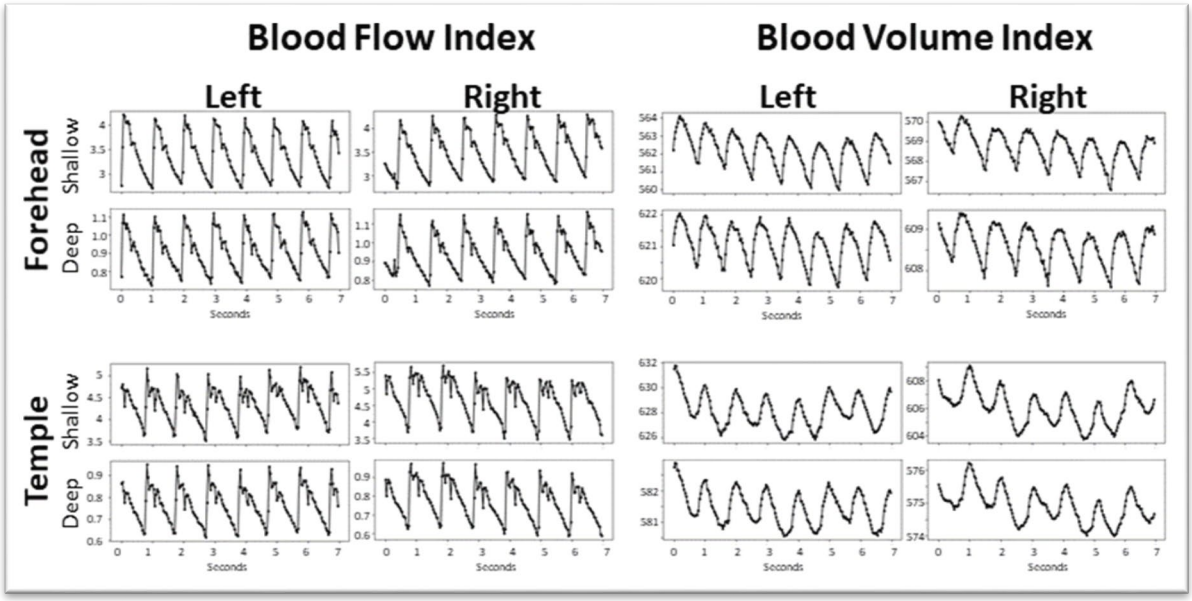


Figure S-2:Example of the proposed Openwater Headset, recorded on a normal control subject

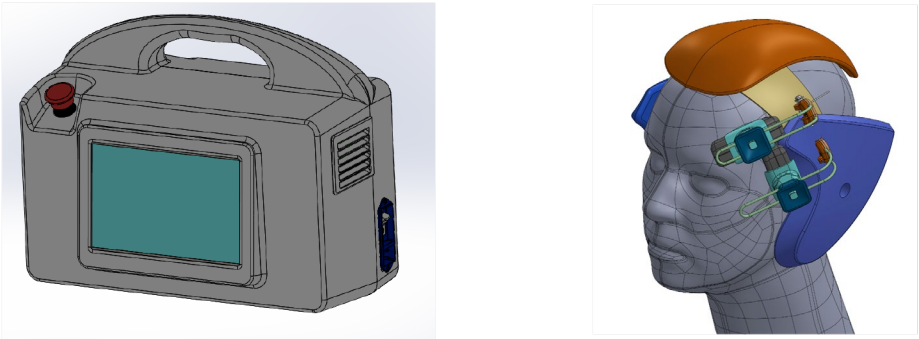
Openwater believes that these outputs have inherent interpretive value and can be independently used by the clinical user when displayed as part of the Openwater Headset operation. Of note, CBF and CBV measurements are key parameters through which MR and CT perfusion scans provide data to clinicians during standard-of-care in-hospital work-up of stroke patients, and therefore these outputs may be similarly interpreted by clinicians when measured at the point-of-care using the headset device in clinical research settings. However, since the efficacy of these measurements have not been noted in disease states, Openwater proposed restrictions on the use of these measurements within the proposed Indications for Use, specifically, for use only in research settings. The evolution of Openwater Headset's indications beyond the one noted in Q211873 was seen by Openwater as beyond the scope of the breakthrough designation request and focused the submission on only on the capabilities of the proposed Openwater Headset to support the Openwater LVO Stroke Alert.

Openwater LVO Stroke Alert is an SaMD that operates within the console of Openwater Headset and does not require any external communication or internet connection. This software as a medical device takes the raw BVI and BFI waveform output from the Openwater Headset software and applies a proprietary algorithm comparing relative differences between measurements of the left and right hemispheres to provide a dichotomous output of either a positive finding, resulting in an "LVO Stroke Alert," or a

negative finding, resulting in an output of "Does not meet criteria for LVO Stroke Alert." The EMS reviewing this notification on screen would interpret the "LVO Stroke Alert" finding to route the patient to an EVT capable center or would follow normal routing workflows with the "Does not meet criteria for LVO Stroke Alert" finding. Interpretation of the BVI and BFI output of Openwater Headset is not necessary to utilize the findings by Openwater LVO Stroke Alert. However, the Openwater Headset's output may be used as appropriate by healthcare personnel utilizing the device to review the underlying blood flow information and any differential deficits in perfusion.

b. ***Section 2 of the submission contains information related to the device description for the Openwater Headset and the Openwater LVO Stroke Alert. However, from the information described in subsections 2.2 and 2.3, it is not clear how the Openwater Headset interfaces with the console and the Openwater LVO Stroke Alert to generate a notification and communicate that an LVO is suspected. Clarify how the information is transmitted from the Openwater Headset to the console and then to the Openwater LVO Stroke Alert for analysis of the data obtained from the Openwater Headset. In your response, also identify potential sources of device failure, including alert failure, associated with wireless or cellular connections related to data transmission.***

Openwater Headset consists of two components, a wearable headset and a console (Figure S-3). The wearable headset is physically connected to the console with a multipurpose cable. The cable houses copper wires and fiber-optic cables. The fiber-optic cables are used to transmit the laser light from the single laser in the console to the various headset locations. The cable also houses the low current power lines to power the cameras. High speed data lines are used by the cameras for configuration, image acquisition, and for the transmission of the image data from the headset to the console. All of the aforementioned cables are individually insulated. The Openwater Headset's wearable and console are a self-contained unit (no wireless transmission) and is intended for easy mobile use. The console has a display that includes a user interface to operate the device. The display shows the blood flow data as noted in Openwater's response to deficiency 1(a) above (see Figure S-2 for details).



(a) *(b)*

Figure S-3: Proposed form factor of the Openwater Headset (a) Console, (b) Wearable headset

The Openwater LVO Stroke alert is a software package that can be installed within the Openwater Headset's console. This package uses the Openwater Headset generated blood flow data to analyze the likelihood of an LVO. A block diagram of the various elements of Openwater Headset including Openwater LVO Alert is shown in Figure S-4. As shown in the figure, the two devices are located in the shared platform of the Openwater Headset console and the interface between the two devices is in software only. When the Openwater LVO Stroke Alert software package is installed, the Openwater Headset automatically shares the recorded blood flow data with Openwater LVO Stroke Alert and the subsequent LVO stroke alert finding will be displayed on the LCD screen of the console. There are no wireless or cellular paths of transmission for the data and all of the data is transmitted through physically wired means.

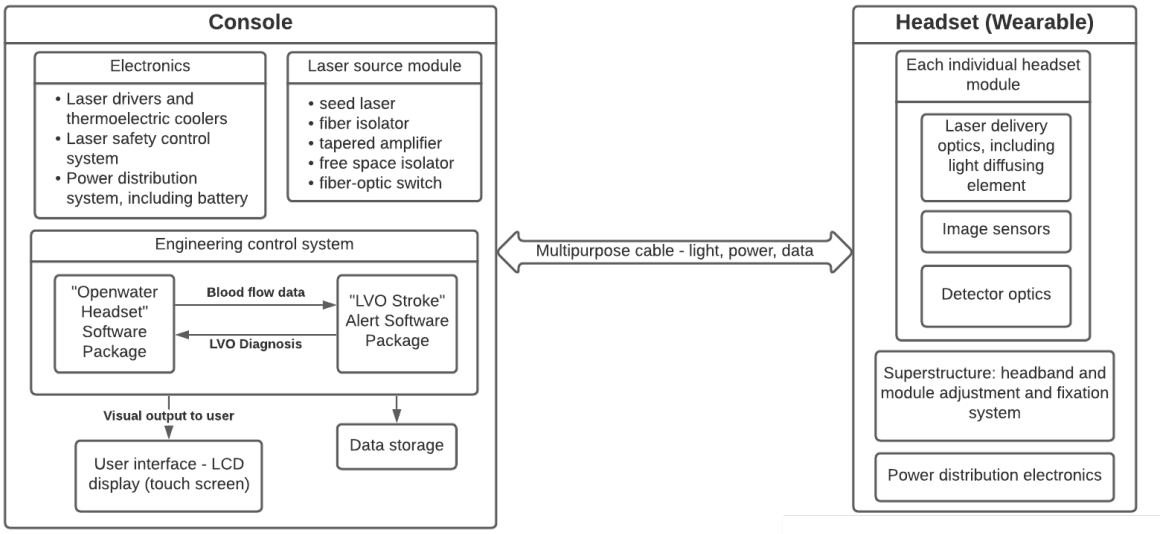


Figure S-4: Block diagram showing Openwater Headset with Openwater LVO Alert installed as a package or module

The sources of device failure are similar to that associated with such types of electronic devices, including hardware issues with the console, multipurpose cable, or wearable headset, software issues, and use errors. In addition, the device may fail to provide an alert if the device is not fitted correctly or is unable to perform its scan. A separate detailed discussion of the sources of variability in performance is discussed in Openwater's response to deficiency 1(c) below. The sources of device failure are mitigated through design controls and the use of verification and validation testing as well as human factors testing that ensures that the device is robust. Proposed testing to assess the effectiveness of the mitigations and to support a planned marketing submission for this device was discussed in Section 8 of Q211873. A brief discussion on the risks of the device and their mitigation is provided in Openwater's response to deficiency 3(b) as part of Table S-2. Additional details of the noted sources of failure and their risk assessment and risk mitigation strategy will be included as part of the premarket submission to support the Openwater Headset.

c. ***Section 2 provides an overview of the Openwater Headset and its use on subjects. However, it is not clear from this description how the device performance may be***

affected by various patient- specific characteristics across the intended patient population, such as skin pigmentation, size of forehead, hair length, and level of consciousness. Provide a discussion of these types of patient- specific factors, how these factors may affect device performance, and whether any mitigations have been applied to the design or envisioned device use to ensure adequate performance for the intended patient population. Also, evaluate whether there are other relevant factors related to expected use of the device once in clinical practice (e.g., from the intended use environment, sources of variability in the clinical user experience) that may affect its performance.

As part of product development, Openwater analyzed several factors that may affect device performance. Note that the current prototype device used in clinical studies is in the "wand" form factor and has to be manually applied at specific locations by the operator. Users in the clinical studies are instructed to use existing anatomical physical markers (midline, mid pupillary line, the eye sockets, ears, etc.) for proper placement of the wand device for each of the measurements. This is itself a source of variability that is mitigated by the development of a headset with a wearable form factor. Such a device would utilize fixed lasers and sensors and would speed up device placement for a scan.

Table S-1: Sources of variability and their mitigations

Source of variability	**Discussion/Mitigations**
Placement as affected by head size, forehead size, facial symmetry	The proposed design of the wearable component of Openwater Headset includes wand elements that can be individually adjusted to ensure optimal placement for each patient (see Figure S-3 for proposed design of the wearable). Once each module is in the optimal location, each one can be individually secured in place. Each of the modules will have visual cues to aid in the adjustment to the optimal anatomical location for each patient relative to their unique anatomy (such as the midpupillary line).
Forehead curvature	The Headset modules have a self-conforming mechanism to conform to the patient's unique surface curvature.
Movement	Once the Headset is placed on the head, it will be secured to the head with a fixation strap. Along with being locked once they are in the optimal position, the individual modules will be biased with spring force to make contact with the head. These design elements ensure that the laser and sensors make good contact with the head and any minor movement by the patient does not affect the measurements.
Body position and Level of consciousness	The device requires no active patient interaction and thus the patient's level of consciousness does not affect the measurements. The wearable headset is placed on the front of the head and is secured using straps. Thus, the patient body position causes no interference in how the headset can be installed or used. As such, neither the body position nor the level of consciousness should not be a determining factor in the use of the device.

Table S-1: Sources of variability and their mitigations

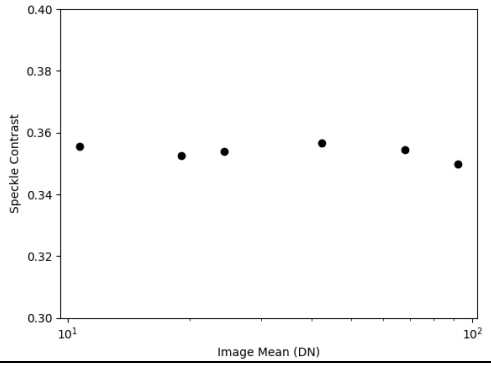
Source of variability	**Discussion/Mitigations**
Skin tone	Skin tone should have minimal effect on Openwater LVO Alert's algorithms for various reasons: • The algorithms operate by comparing intrapatient measurements. Specifically it compares relative differences between measurements of the left and right hemispheres of the same individual. Physiological differences which contribute to interpatient variability are not expected to influence these intrapatient hemispheric comparisons. • The first step in calculating the blood flow index by Openwater Headset is to calculate the speckle contrast. The speckle contrast is calculated by dividing the standard deviation of pixel values on the image sensor by the mean value of the pixels. If the amount of light hitting the sensor changes by some fraction (e.g. due to increased absorption of the light by the skin), both the standard deviation and the mean have the same relative change, and their quotient (i.e. the contrast), does not change. In an experiment to simulate the effect of a thin absorbing layer, Openwater performed the following experiment: a variable neutral density filter was used to reduce the amount of detected light over a 10x range when measuring a tissue simulating phantom. As can be seen in the figure below, standard deviation of the speckle contrast values is less than 0.6% of the mean over the entire range of intensities 

Table S-1: Sources of variability and their mitigations

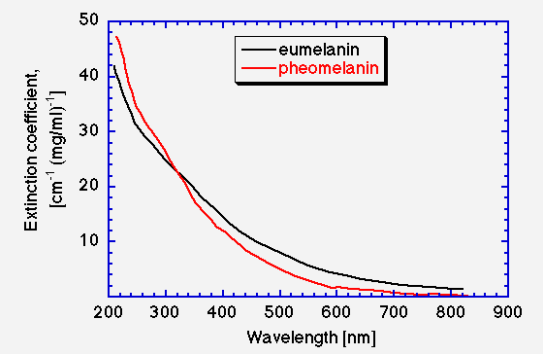
Source of variability	**Discussion/Mitigations**
	• Pulse oximetry, which uses relative absorption of light at 660 and 940 nm to determine oxygen saturation, is sensitive to skin tone because the absorption of light by melanin differs between those wavelengths. Unlike pulse oximetry, Openwater Headset operates at a single wavelength (785 nm) where the absorption of light by melanin is quite small (Jacques 1991) (see chart below showing the extinction coefficient of eumelanin and pheomelanin at various wavelengths (Jacques n.d.)). When the absorption due to skin tone at this wavelength was calculated by Openwater, the differences between various skin tones was minimal. 
Hair	Hair may be a source of interference. By design, hair length should not affect readings as the device is intended to be utilized in front of the hairline on the forehead and temple overlying the frontal lobe and temporal lobe (i.e., underlying ICA and MCA vascular distributions of interest for anterior LVO assessment). The Headset will additionally include physical features to mitigate the risk of stray hair coming into contact and affecting the measurement. Device labeling will instruct the operator to pull the patient's hair under the headband portion of the headset such that the operator can sweep and hold the hair under the headband and away from the forehead. The positioning of each of the modules is visible to and adjustable by the operator to avoid placement on hair. The modules can be temporarily lifted from the skin without altering the position to aid the operator in removing stray hair. Finally, in the case that hair is still obscuring either the laser light or the image's sensors, the Headset software will verify for each scan that the sensors detected a sufficient amount of light. In the case that insufficient light is detected, it will instruct the operator to make the necessary adjustments and repeat the scan.

Table S-1: Sources of variability and their mitigations

Source of variability	**Discussion/Mitigations**
Environmental	The Headset is designed to withstand the range of temperature and humidity conditions in the intended use operating environment and these specifications will be verified and validated as part of the normal product development and design control process. Ambient light could be a source of interference, but the design of the laser probes and the sensors are spring loaded to ensure they make good contact with the head surface. Additionally, the Openwater Headset includes an 800 nm hard coated broadband band-pass interference filter in the light detection optics that blocks all light in the visible spectrum. Band-pass filters transmit only the target range of wavelengths in the spectrum to pass through, while blocking all light with wavelengths above or below the band. The band-pass filter in the Openwater Headset has a bandwidth of 50 nm and OD (optical density) average greater than 4.0 outside the band-pass range.
Sweat	As shown in Figure 5 of the Q211873 submission, the absorption of light by water is very low through wavelengths up to around 900 nm. This is a key reason for the spectral window from 650 - 950 nm where near-infrared light can penetrate to depths of many centimeters, including transcranially through bone and soft tissue (with high water content). As such, any sweat should not be a source of interference for the device measurements.
Patient physiological differences: Blood pressure, vascular stiffness, age-related factors	Openwater Headset takes measurements on both the left and right side of the brain and one of the key features that Openwater LVO Alert's algorithm utilizes is the difference in the flow between the left and right side of the brain. Patient specific anatomical factors such as blood pressure, vascular stiffness, and age related factors will apply to both sides of the brain, and thus a difference between the left and right side of the brain, regardless of these factors, can still be assessed by the algorithm.

2. ***To meet Breakthrough Device designation criterion #1 as defined by section 515B(b)(1) of the FD&C Act (21 U.S.C. 360e-3(b)(1)), you need to demonstrate a reasonable expectation that the proposed device could provide for more effective diagnosis or treatment of the target condition compared to current available methods. Although the submission contains summaries of preliminary evidence collected from phantom testing, animal studies, and healthy subjects, additional evidence is needed to characterize the performance of the Openwater Headset and Openwater LVO Stroke Alert software algorithm in the intended use population of patients suspected of having a stroke located in a LVO in comparison to alternative available methods to meet Breakthrough Device designation criterion #1. We request that you address the***

following to support a reasonable expectation of the potential for clinical success of your device and that the subject device could provide for more effective diagnosis or treatment of the target condition in comparison to current available methods of diagnosis of a stroke with an LVO:

a. ***Section 1 of the submission provides information discussing the benefits of a pre-hospital LVO stroke alert in improving clinical outcomes. Additionally, ambulances outfitted with computed tomography (CT) scanners are mentioned as an alternative to the proposed device. However, the submission does not contain any discussion or provide data to show how the preliminary performance of the Openwater LVO Stroke Alert software algorithm and Openwater Headset compares to the performance of CT scans conducted in ambulances or to other existing methods of evaluating these patients in the pre-hospital setting, such as various validated stroke scales, or how the subject device compares to existing methods of diagnosis of stroke in the hospital setting. Therefore, provide performance data to demonstrate that the speed, safety, sensitivity, and specificity of the subject device is better than available alternative methods of assessment and diagnosis of stroke patients with an LVO (i.e., confirmed presence or absence of an LVO based on computed tomography angiography (CTA) scans or other types of imaging modalities). This preliminary evidence should demonstrate the ability of the subject device to distinguish between hemorrhagic and ischemic strokes as well as other neurological conditions which may present with overlapping symptoms as suspected strokes.***

Openwater LVO Stroke Alert is a tool to assist healthcare professionals in alerting the presence of an anterior large vessel occlusion stroke primarily in pre-hospital settings to optimize routing workflows given that time to treatment is the most critical factor in neuroprotection. As was the subject of the recent STAIR consensus conference (STAIR Stroke Treatment Academic Industry Roundtable, n.d.), there is a significant unmet need for a point-of-care prehospital stroke LVO detection diagnostic as no viable alternative currently exists for the vast majority of EMS stroke evaluations. Clinical experts have outlined the current pre-hospital "dilemma reveals the critical need for a prehospital tool to identify mechanical thrombectomy candidates" in light of "the absence of a 'brain electrocardiogram,' to correctly select LVO patients." (Abergel, 2020). Openwater LVO Stroke Alert focuses on this need and is not intended to replace standard of care for in-hospital evaluation of strokes.

While there are no alternatives that are part of the pre-hospital standard of care, the following methods are utilized to address this problem, albeit with limited success:

- Prehospital stroke scores: There are stroke visual assessments that are used to score and classify whether a patient potentially has a stroke, but these have limited efficacy in determining an anterior LVO. While safe to administer, these stroke scales have shown poor sensitivity in actual practice, as low as 38% in some studies (Nguyen et al., 2021) and additionally suffer from particularly poor specificity as low as 20% in some studies (English et al., 2018). They further suffer from their highly variable nature, with poor objectivity across different EMS users. Even when the stroke score is indicative of an ischemic stroke, the score has poor differentiation between an

anterior LVO stroke that is refractory to tissue plasminogen activator (tPA) and requires urgent transport to an EVT-capable stroke center, and a non LVO stroke that requires urgent infusion of tPA and thus direct transport to the closest stroke center. As such, the Openwater LVO Stroke Alert would offer significantly improved speed and efficacy in identifying an anterior LVO as compared to prehospital stroke scores (see Figure S-5 for additional performance of this device).

- Mobile Stroke Units (MSU): In hospital settings, a Computed Tomography (CT) scan would be the gold standard to determine the presence of an anterior LVO and as noted in Q211873 submission, efforts have been made to develop "mobile stroke units" that outfit ambulances with CT imaging devices to detect the presence of LVO and the need for emergent transport for endovascular therapy (Czap 2020). While MSUs have been available for over a decade to utilize pre-hospital CT scans, there are only a total of 20 MSU programs currently available in the US, which represents <0.01-0.02% coverage of all US ambulances responding to prehospital stroke assessments, with several studies outlining the prohibitive cost to scaling this solution to a larger number of patients especially in rural areas and globally (Calderon 2018). Even in the exceedingly rare situation where an MSU is available to make a pre-hospital CT scan feasible, 911 alerts to EMS only transmit to MSUs if there is a known likelihood of stroke at the time of dispatch, and in most cases, this is not known until further clinical workup ensues and transport time then becomes key thereby making additional MSU evaluation difficult in most cases. In addition, when MSUs are dispatched, they are always dispatched in addition to the standard ambulance transport because more than 80% of the 911 alerts that do include MSUs do not eventually result in an MSU transport and instead require routine EMS transport (Parker SA 2020).

  Furthermore, and perhaps most importantly, a key distinction is that MSUs are being used to evaluate patients who may potentially be eligible to receive intravenous tPA, whereas the unmet clinical need is for a prehospital diagnostic device with high specificity and sensitivity for LVO, which is refractory to tPA. Thus the intended usage of the proposed Openwater device is to facilitate clinical interpretations that can expedite the transport of these LVO patients to endovascular-capable centers, which is distinct and not competitive with the goals of MSUs.

  Comparatively, the proposed Openwater device would be safer to administer given the use of a Class I laser compared to the radiative effects of a CT scan. The device would also be faster to use with a scan completed in about 5 minutes compared to a MSU workup that takes as much as 37 ± 10 minutes (Parker SA 2020). The proposed Openwater device is significantly more portable and cost-effective compared to MSUs, thus enabling wider deployment and accessibility. The preliminary evidence of performance (discussed below) indicate that the Openwater LVO Stroke Alert would compare favorably with standard of care CT and MR analyses.

Preliminary evidence of Openwater LVO Stroke Alert supports the reasonable expectation of the potential for technical and clinical success. As discussed in Section 3 of Q211873 and as summarized in Section 3.4, the core technology has been evaluated in N>50 phantom experiments, N>30 preclinical animal studies, and N>70 human measurements across LVO ischemic stroke, non-LVO other ischemic stroke, intracranial hemorrhagic (ICH) stroke, and healthy controls with and without experimentally-induced vessel occlusions. Key findings that support reasonable expectation for success include:

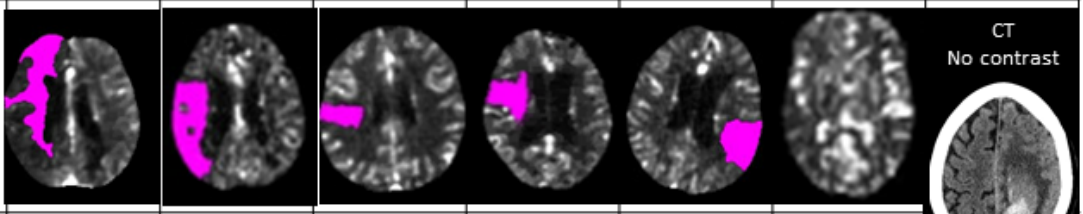
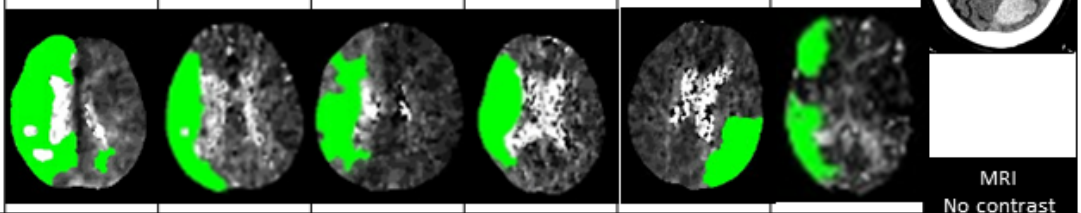
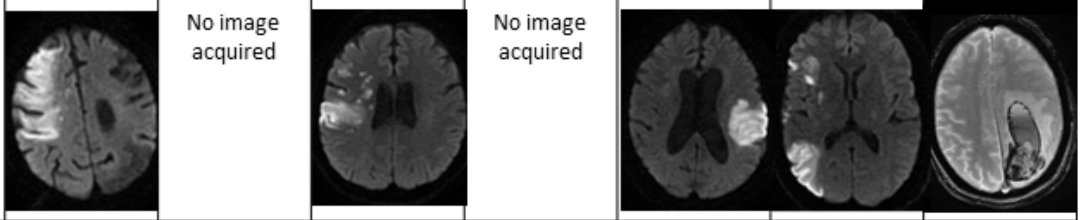
- Phantom testing: confirming depth of interrogation to over 30mm below the surface, with resolution to detect 1-2mm/s change in blood flow rates, validating BFI and BVI algorithms to clinically-relevant parameters and confirming 100% accuracy in detecting experimental obstruction of blood flow.
- Preclinical animal model testing: confirming noninvasive, transcranial ability to detect minor reductions in cerebral blood flow (well below thresholds of complete obstruction) in animal models of inhaled gas challenges and hypercapnia, as well as 100% accuracy in classifying experimental MCA occlusions using a BFI-based threshold.
- Clinical testing: confirming ability to measure human blood flow changes throughout the cardiac cycle, with high resolution ability to detect minor changes in flow rates during normal systolic and diastolic phases (Figure 14 in Q211873). Confirmed 100% accuracy in detecting experimental obstruction of human large vessel flow through induced flow arrest of the brachial artery (Figure 13 in Q211873) and external carotid artery circulation (Figure 15 in Q211873). Confirmed ability to detect transcranial regional CBF and CBV changes in human ischemic stroke correlated with gold standard CT and MR perfusion measurements in human stroke patients, with ability to confirm location of stroke on the basis of differential BFI and BVI (Figure 16 in Q211873).

To demonstrate the preliminary evidence of the efficacy of Openwater LVO Stroke Alert, a more detailed analysis of the clinical data compared to CT and MRI scans is presented in Figure S-5. This analysis includes additional clinical data acquired in Openwater's human LVO feasibility studies since the Q211873 submission. The figure displays the standard of care CT and MR imaging as well as Openwater data on patients with LVO strokes and non-LVO strokes. The figure includes the salient CT and MR slices, salient BVI and BFI measurements from these patients, and the classification results by Openwater LVO Stroke Alert. As shown in the figure, the Openwater device classified 100% of the LVO strokes accurately (N=4), classified 100% all the non-LVO strokes as such (N=3, with one ICH and two non LVO ischemia), and 100% of the controls (N=30) as not LVO. While the algorithm utilizes several features and is in continued development, the bottom of Figure S-5 shows the key factors utilized in the classification that demonstrates good specificity of the features.

Though this analysis is based on a small sample size, Openwater believes that with the bench data noted above and the preliminary human clinical evidence shown in Figure S-5, there is strong preliminary evidence that demonstrate the ability of the subject device to distinguish between LVO strokes, hemorrhagic strokes, other non-LVO ischemic

strokes, as well healthy controls. To demonstrate reasonable expectation that the proposed device can function as intended through demonstrated technical success, Openwater has prioritized initial clinical data collection to enroll subjects with LVO strokes and other forms of ischemic and hemorrhagic strokes that may also have changes in blood flow and blood volume on gold standard MR or CT imaging as compared to healthy controls. As part of the continued development and validation of Openwater LVO Stroke Alert, described in more detail in Section 8.2.2 of the submission, Openwater will prospectively confirm specificity and sensitivity of the algorithm against all LVO stroke mimics in support of the planned marketing submission for this device, following similar procedures as other recent FDA-approved LVO AI software (DEN170073 Viz.AI ContaCT) cleared for detecting LVO stroke using blood flow feature data. Openwater intends to expand on this data, as noted in the Data Development plan in Q211873, Section 9 and would welcome the opportunity to partner with the FDA to assess key factors, as appropriate through the sprint discussions that are part of the breakthrough devices program.

Openwater believes the device meets all requirements of the Breakthrough Device designation criterion #1 as defined by section 515B(b)(1) of the Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 360e-3(b)(1)), having demonstrated reasonable expectation that the proposed device can function as intended through demonstrated technical and clinical data and that the device could provide for more effective diagnosis of the anterior LVO ischemic strokes compared to current available methods. Openwater is further encouraged by the breakthrough device designation granted by the FDA to another manufacturer independently pursuing a device to address this problem of identifying LVO strokes in the prehospital setting (namely, Forest AlphaStroke, utilizing neuronal electrical activity that may change in the presence of a vascular obstruction).

	LVO				Other Stroke		
Diagnosis	Right ICA occlusion	Right M1 occlusion	Right ICA occlusion	Right ICA occlusion	Left M2 inferior occlusion	Right M3 frontal occlusion	Left ICH
Age / Sex	75 y/o female	77 y/o male	61 y/o female	95 y/o female	75 y/o female	47 y/o male	75 y/o female
NIHSS	23	15	16	17		15	15
CTP CBF							
CTP Tmax							
MRI DWI		No image acquired		No image acquired			
LVO Stroke Alert Output	Yes	Yes	Yes	Yes	No	No	No
BFI L vs. R Amplitude	-0.11	-0.10	-0.11	-0.026	-0.018	0	0.063
BVI L vs. R Mean	29	16	16	56	-107	3.5	16

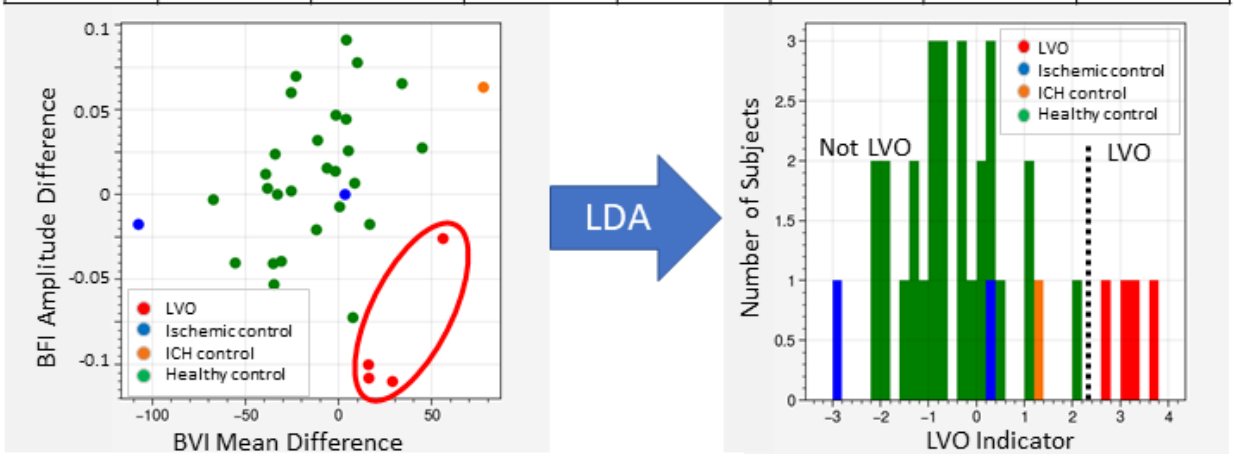


Figure S-5: Analysis by Openwater LVO Stroke Alert compared to standard of care CT and MR

b. ***Section 2.3 discusses the Openwater Headset-only operation procedures and specifies a total duration of less than 5 minutes. From the information provided, it is not clear what steps are included in the total time of use. Provide information specifying the procedure time associated with operation of the Openwater Headset including, but not limited to, headset placement, scan time, readjustment, and any subsequent scanning attempts while incorporating anticipated use scenarios, including worst-case use conditions. Additionally, provide a discussion of any potential risks associated with device use, including whether there is a potential for delay in care due to device utilization, and how you intend to mitigate these risks.***

The Openwater Headset is expected to take about 5 minutes from the start of set up to completion of the assessment. The 5 minute duration includes powering on the device, navigating to the proper LCD display screen, securing the headset onto the head, adjusting the headset location for accuracy, as well as the duration of the scan itself. As the scan duration itself is expected to take 30 seconds or less, if the first attempt fails and a 30 second readjustment and rescan is needed, it should add no more than a minute. The LCD screen will have visual cues to help the user position the device successfully on the first attempt. Before the scan, the device will also run a test to evaluate if any of the headset modules are not properly flush with the patient's skin. There may be a learning curve for new users where the entire process takes longer than 5 minutes, but apart from that Openwater expects the total duration to be less than 5 minutes.

Openwater's risk assessment for this procedure is summarized in Table S-2 below and the typical risk is for a short delay in care due to device utilization of about 5-10 minutes.

Table S-2: Summary of risks associated with device use

Hazard	**Hazardous Situation**	**Harm**	**Mitigations**
Device does not turn on or provide an analysis output	Patient with stroke needing immediate assessment of type of stroke to optimize routing decisions.	Delay in care	Labeling instructs HCP to revert to the current standard of care protocol if device analysis is not available.
User misinterprets the results of the displayed parameters	Misinterpretation leads to a false positive LVO diagnosis, causing incorrect routing to either an EVT-capable center or to the standard of care routing to the closest stroke center.	Delay in care	Applying human factors and usability engineering to the design of the console user interface.

Table S-2: Summary of risks associated with device use

Hazard	Hazardous Situation	Harm	Mitigations
Interference between the headset and the head (e.g., hair) blocks light transmission and/or detection.	Patient with stroke needing immediate assessment of type of stroke to optimize routing decisions and the assessments are not available or delayed.	Delay in care	Device includes algorithms to detect that the measurement is inappropriate for analysis and instructs user to address the issue and re-attempt the scan. If this repeatedly recurs the onscreen instructs HCP to revert to the current standard of care protocol.
Improper headset fit or inaccurate headset installation	Inaccurate measurement leading to a false positive LVO alert, causing unnecessary routing to CSC	Patient without an LVO transferred to a comprehensive stroke center instead of the closest center leading to delay in care	Headset and labeling provide visual cues and instructions on how to properly situate the sensor modules for an effective scan.
System malfunction	Inaccurate LVO diagnosis, causing unnecessary routing to CSC	Patient without an LVO transferred to a comprehensive stroke center instead of the closest center leading to delay in care	Design controls to ensure reliable operation of hardware and software in emergency situations
Laser power is too high	Laser light delivered to patient is over the MPE (maximum permissible energy)	Skin burns (minor or major) Eye damage (temporary or permanent)	The device constantly verifies the correct laser parameters are being delivered (such as power, pulse width, etc.), otherwise an interlock will turn off the laser. The diffusing element on the laser delivery module is physically captured, and thus cannot fall out. Note that the device uses a Class 1 laser and the likelihood of skin or ocular eye risks are negligible.

c. ***Section 3.3 contains preliminary clinical data in healthy human subjects to demonstrate the feasibility of cerebral blood flow measurements utilizing near infrared spectroscopy (NIRS), diffuse optics, and speckle contrast of the wand-based prototype device. However, it is not clear if there is any data generated from use of the Openwater Headset. Provide a comparison of the wand-based prototype to the proposed Openwater Headset design that justifies how the data collected using the prototype is representative of the Openwater Headset, characterizing how the differences in design may affect the observed results. Alternatively, provide performance data as requested in deficiency #2.a. using the current version of the Openwater Headset and Openwater LVO Stroke Alert.***

Openwater Headset is an optimized version of the current wand prototype. As noted in Section 3.3 of Q211873, all reported data were produced using Openwater's wand prototype that incorporates Openwater's core hardware laser technology and associated software algorithms. Openwater Headset uses these same core laser technologies and algorithms, and therefore these are direct technical and performance testing data of the core technology involved in the proposed Openwater Headset. During the use in current clinical studies, the wand is positioned directly over and held steady on the vascular distributions of interest. To complete one scan, the operator repeatedly positions the wand at specific points of interest and record the blood flow information. With the proposed new design and as outlined in Section 2.1 of Q211873, Openwater Headset can be thought of as multiple Openwater wands that can record multiple points of interest without having the operator move the unit. This design change is intended to result in the reduction of placement time, the reduction of scanning time (as the various interrogation locations can be scanned without repositioning the device), and in the reduction of motion artifacts. As previously noted, there is no change in core laser technology between Openwater wand and headset designs. As such, the data collected using the prototype is considered to be representative of the proposed Openwater Headset.

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