Introduction

Openwater is proposing to introduce the Openwater LVO Stroke Alert, which a noninvasive early notification system to quickly identify patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery. The device was first presented to FDA in Q211873 and after that review, FDA noted that additional clinical performance data to "*demonstrate a reasonable expectation that the proposed device could function as intended thereby demonstrating technical success and could provide for more effective diagnosis or treatment of the target condition compared to current available methods*." In Q211873/S001, Openwater presented additional clinical performance data from a feasibility study.

On September 20, 2023, FDA issued an AIRQ letter noting several concerns regarding the proposed device. A clarification meeting to understand specific Agency concerns was held on September 25, 2023. While the discussion helped clarify several Agency comments in Q211873/S001 AIRQ letter, a key concern regarding the proposed device and its use emerged. Specifically, the FDA noted that though LVO patients may benefit from endovascular therapies, the need for intravenous recombinant tissue plasminogen activator (tPA) in patients with acute ischemic stroke is essential and that there needs to be a discussion on the risks of delay in administering tPA.

In Openwater's response below, the Agency concerns have been split into 4 separate topics, namely (see Table 5 for details on how Openwater mapped the concerns noted in Q211873/S001 AIRQ to these topics):

1. Performance level for pre-hospital assessment of LVO
2. Performance of proposed device compared to CT/MR
3. Currently available technologies
4. Routing decisions and risks related to delaying thrombolytic therapy

In the following sections, each aspect of the FDA concern is noted verbatim in bold text, followed by Openwater's response. Note that topic #4 above is at the core of the need for the proposed device and is thus discussed first.

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Response to Q211873/S001 AIRQ Letter

FDA Concern: Routing decisions and risks related to delaying thrombolytic therapy
There would have to be evidence that the use of the Openwater LVO Stroke Alert to triage patients to a more remote hospital for endovascular therapy could result in increased benefit and show that patients who could have been treated earlier with thrombolytic therapy did not fare worse when compared to outcomes of patients transported according to the current methodology to make triage decisions. To be more effective than current available diagnosis of stroke occlusion location in the clinic and hospital and other settings per your proposed IFU and satisfy Breakthrough Device criterion #1 as defined by Section 515B(b)(1) of the Federal FD&C Act [21 U.S.C. 360e-3(b)(1)], we request that you provide clinical performance data that demonstrates more accurate diagnosis of stroke occlusion location for all types of stroke or conditions that mimic stroke using the Openwater LVO Stroke Alert compared to current methods as described above.

Rapidly identifying and routing acute ischemic stroke (AIS) patients to hospitals/stroke centers so that they can receive intravenous recombinant tissue plasminogen activator (tPA) is standard clinical practice and improves long-term functional outcome. Additionally, in the subset of AIS patients with a large vessel occlusion of the internal carotid artery or proximal middle cerebral artery, endovascular therapy (EVT) offers an opportunity to recanalize large arteries and thereby dramatically improve long-term functional outcome. Faster access to EVT is associated with more favorable outcome,[Goyal et al., 2016, Noorian 2021, Adeoye et al. 2022, Pajor et al. 2023] so a wide range of system-based interventions have been implemented to reduce endovascular treatment times. Unfortunately, a minority of centers offer EVT, so there is a critical need to get patients to an endovascular capable centers as soon as possible without negatively impacting access to intravenous tPA.

Current prehospital routing guidelines for AIS LVO and its impact on non-LVO AIS
The current American Heart Association (AHA) recommendations for routing patients suspected of LVO (using stroke severity scales) is to follow the "Mission: Lifeline" algorithm [Jauch et al 2021], which is shown in Figure 1. The AHA algorithm recommends direct transport to an endovascular capable center for patients suspected of LVO under certain conditions, noting that "*when several hospital options exist within similar travel times, EMS should seek care at the facility capable of offering the highest level of stroke care*" [Jauch et al 2021]. As can be seen in Figure 1, the routing incorporates various including last-known-well time, the time before the patient will be ineligible for thrombolytics, and assessment of time to a CSC to optimize the routing decision for the patient.

This "Mission: Lifeline" algorithm is supported by large body of peer-reviewed research. For example, Schlemm et al. modeled various geographic scenarios for routing and found that "*patients with acute ischemic stroke with suspected large vessel occlusion should be redirected to a CSC if the additional delay to intravenous thrombolysis (IVT) is <30 minutes in urban and 50 minutes in rural settings*". In another large study performed in the Chicago area, it was observed that "*implementation of a prehospital transport policy for comprehensive stroke center triage in Chicago was associated with a significant, rapid, and sustained increase in EVT rate for patients*

with AIS without deleterious associations with thrombolysis rates or times." [Kass-Hout et al 2021].

While faster routing for LVO patients improves endovascular treatment times and post-EVT outcomes, there is strong evidence that optimization of this routing does not negatively impact the timing of intravenous thrombolytics for AIS patients without LVO. Multiple groups have reported tPA treatment times before and after implementing a regional stroke routing strategy. This is helpful because it represents the experience of large region rather than that of a single hospital. Fortunately, routing strategies that incorporate bypassing the nearest stroke center in favor of endovascular capable center for select patients does not impact the time to intravenous thrombolytics for non-LVO AIS patients while improving time to EVT [Cabal et al 2021, Mohamad 2016]. Another analysis found that when restricting direct transfer to a CSC within 20 miles found, no non-LVO AIS patient was deprived of thrombolytic therapy nor had a measurable delay. In fact, routing this short distance may improve thrombolytic treatment time because CSCs have faster door-to-needle times [Mueller-Kronast et al 2019].

Essentially, the AHA recommended "Mission: Lifeline" algorithm "*seeks to balance the impact of triage recommendations, including the benefits of rapid, early access to EVT for patients with suspected LVO with the potential harm of delayed initiation IV alteplase*" [AHA 2020], and note that "*given the known impact on outcomes of every 15-minute delay of intravenous alteplase, the known impact of delays to thrombectomy, and the anticipated delays in transport for thrombectomy in eligible patients originally triaged to a nonendovascular center, the Mission: Lifeline algorithm is a reasonable approach.*" [Adeoye et al. 2022, Jauch et al 2021].

Prehospital methods used to assess AIS LVO and their challenges

All EMS routing decisions currently rely on pre-hospital stroke severity scales targeted at the recognition of the presence of stroke (e.g., Cincinnati Prehospital Stroke Scale (CPSS) and the Los Angeles Prehospital Stroke Screen) and identifying patients with a high probability of LVO using scales such as the Rapid Arterial Occlusion Evaluation (RACE) and the Los Angeles Motor Assessment (LAMS). However, there is urgent need for improved assessment of LVO since these scales have low sensitivity and subjective variability in pre-hospital settings [Duvekot et al. 2021, Nguyen et al. 2020]. The current AHA/ASA guidelines note that "*further research is needed to establish the most effective prehospital stroke severity triage scale, which may be one of the published scales or a novel scale or device.*" [Adeoye et al. 2022]

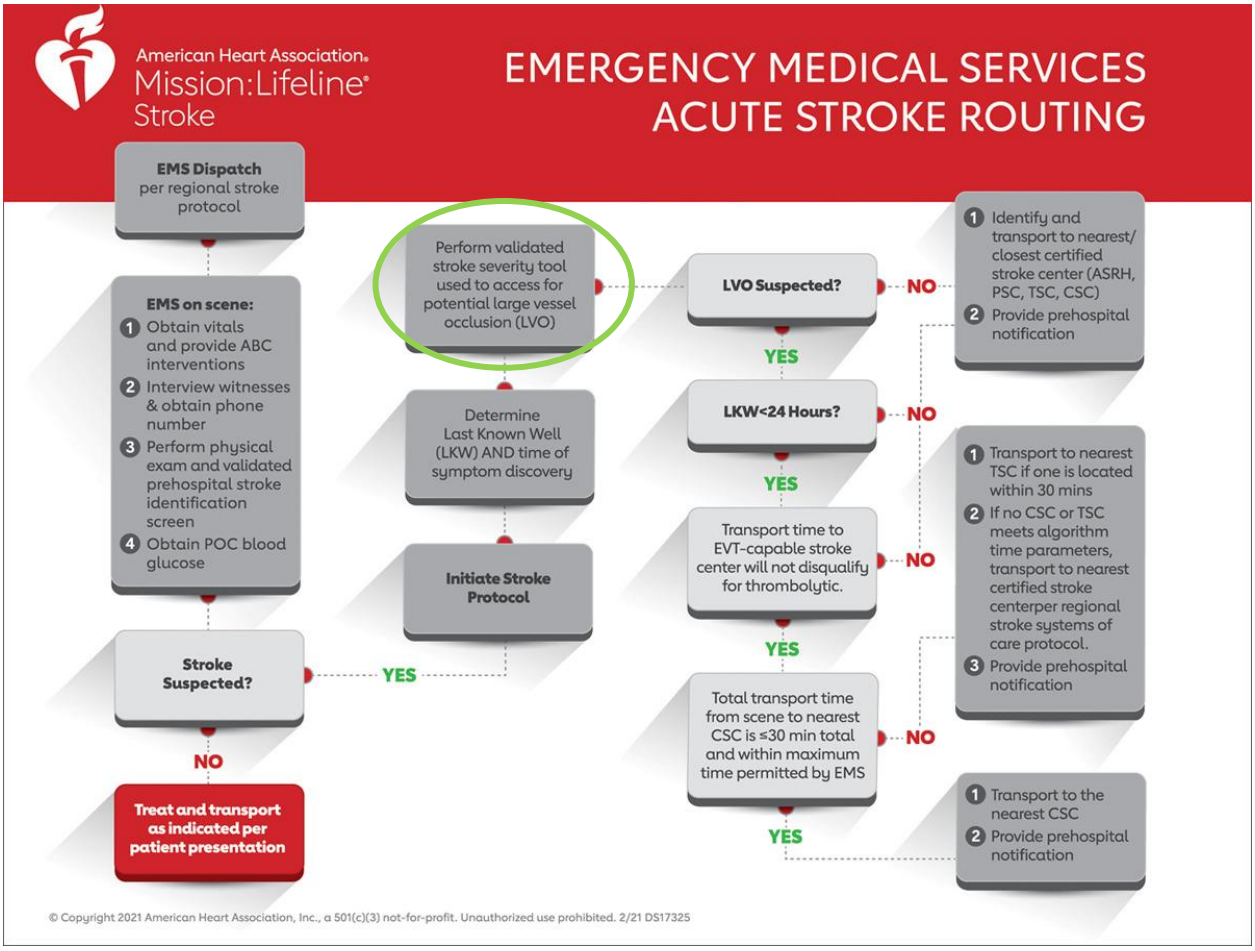

Figure 1: Mission: Lifeline Stroke AIS/LVO Routing Algorithm [Jauch et al 2021]

While there is still "*substantial uncertainty concerning the optimal acceptable additional transport time threshold*" [Schlemm 2020], and "*further research is needed to establish travel time parameters for hospital bypass in cases of prehospital suspicion of LVO*" [Adeoye et al. 2022], there is a clear need for optimizing routing decisions, based on patient and local geographic conditions, using an objective assessment of the patient. Openwater's LVO Stroke Alert is specifically designed to address these concerns by performing an assessment of LVO quickly and objectively to identify patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery. Currently, RACE, LAMS, CPSS, and other stroke scales are evaluated as part of the step highlighted with a green circle in Figure 1 as the current standard of care routing algorithms to help determine the optimal routing for the patient. The proposed device is intended to augment these assessments but not to replace them. The proposed device is not intended to automatically route LVO patients to an EVT-capable center but allow the EMS personnel to consider this information as part of their initial workup to optimize routing. As such, proposed device will not create new routing practices, but rather refine current routing practices. Indeed, as more research and information becomes available, the AHA/ASA recommendations and guidelines will be updated to refine the routing recommendations, and the availability of an objective tool with improved performance, as compared to current pre-hospital stroke scales, will help facilitate the implementation of the updated routing algorithms.

As such, Openwater believes that the proposed device, Openwater LVO Stroke Alert, satisfies the criteria necessary for Breakthrough Designation, as set forth in 515B(b) of the FD&C Act. Openwater LVO Stroke Alert is being developed to enable Emergency Medical Services (EMS) personnel to perform an objective assessment on-site to identify specific patients suspected of LVO stroke for the purpose of improving routing decisions to speed up access to endovascular therapy and reperfusion. Openwater is aware of at least one other technology (Forest AlphaStroke) that is being independently pursued to address the problem of identifying LVO strokes in a prehospital setting, which was recently included in FDA's Breakthrough Device program (Forest Devices, 2021). Openwater's approach has the advantage of directly measuring blood flow to characterize the presence of occlusion, instead of relying on indirect assessments of neuronal activity from surface electrical recording technologies.

FDA Concern: Performance level for pre-hospital assessment of LVO
The proposed indications for use (IFU) of the Openwater LVO Stroke Alert in the Breakthrough Device request (Q211873/S001) is: "*Openwater LVO Stroke Alert is indicated for use as an early notification system to identify patients suspected of large vessel occlusion (LVO) in the anterior circulation. This software as a medical device (SaMD) utilizes data from Openwater Headset in adult patients. Openwater LVO Stroke Alert is intended to be used in hospitals, clinics, and in pre-hospital settings*." The Breakthrough Device designation requires that you must provide scientific evidence to meet criterion #1 as defined by Section 515B(b)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act [21 U.S.C. 360e-3(b)(1)] to generate a reasonable expectation that the subject device could provide for more effective diagnosis or treatment of the target condition compared to current usual care methods and thus demonstrate clinical success. The feasibility study data provided in the Q211873/S001 submission does not demonstrate that the Openwater LVO Stroke Alert has both better sensitivity and specificity to distinguish LVO stroke compared to stroke caused by small or medium vessel occlusions, stroke mimics, or intracranial hemorrhage when used in the pre-hospital setting by emergency medical services (EMS) compared to the current clinical assessment tools. For example, the specificity of the Openwater LVO Stroke Alert is comparable or slightly less than the RACE (Rapid Arterial Occlusion Evaluation) and LAMS (Los Angeles Motor Scale) assessments performed in the pre-hospital setting, while the sensitivity is higher. Both sensitivity and specificity are important outcomes to show that the subject device is a better diagnostic assessment tool compared to the current assessments used in the pre-hospital setting because sensitivity demonstrates that the device can accurately identify the true LVO strokes, whereas specificity is important for the device to accurately distinguish LVO strokes from other clinical diseases or conditions, such as stroke mimics, intracranial hemorrhage, or small and medium vessel occlusion strokes.

As FDA noted above, pre-hospital stroke scores can match either the sensitivity or the specificity of the Openwater LVO Stroke Alert. However, Openwater believes that there are currently no pre-hospital stroke assessments or devices that can match <u>both</u> sensitivity and specificity of the proposed device together. For instance, in the performance assessment provided in Q211873/S001 (shown as Table 1 below), both RACE and LAMS have a specificity comparable to the Openwater device but have significantly lower sensitivity. Similarly, the NIH stroke scale can match the sensitivity of the Openwater device but has significantly lower specificity. This

difference is also reflected in the ROC curves provided in Q211873/S001 (see Figure 2 below). Practically, a healthcare professional using both the NIHSS and RACE can get contradictory information and would not know which score is more appropriate for the patient when routing decisions are being made in a pre-hospital setting. Table 2 shows a comparative analysis of one pre-hospital stroke scale, RACE versus the Openwater device for detecting LVO in the feasibility study (note that Openwater can perform this analysis for the other scores as part of the response to Q211873 AIRQ). In the 52 cases when a subject had an LVO, RACE was able to determine the presence only in 21 cases, while the Openwater device correctly detected LVO in 42 subjects. On the flip side, both RACE and the Openwater device had comparable performance when a subject did not have an LVO (Table 3). Note that this comparative performance assessment includes several non-LVO strokes including hemorrhagic strokes, non-LVO ischemic strokes, and stroke mimics (Table 4)

Table 1 also shows the likelihood ratios of the Openwater LVO Stroke Alert and the stroke scales. A higher positive likelihood ratio[1] indicates that the presence of LVO is more likely when a test is positive, and a lower negative likelihood ratio[2] indicates that the presence of LVO is less likely when the test indicates a negative for a patient. As can be seen in Table 1, the Openwater LVO Stroke Alert is significantly superior to improving the post-test likelihood of detecting the presence or absence of an LVO.

In the Q211873/S001 AIRQ clarification meeting held on September 25, 2023, FDA noted concerns regarding the device not providing an output for certain patients. As was noted by Openwater in the meeting, the proposed device is still in its development phase and the data was collected as part of feasibility studies. During the study, Openwater noted that the headset contact with subjects was suboptimal leading to the no analysis output error. Openwater then adjusted and optimized the device headset to improve subject contact that resulted in significant reductions in this error.

Given these considerations, Openwater believes that the proposed device, when compared to currently available pre-hospital stroke assessment tools, will be able to better assist in pre-hospital assessment of LVO.

[1] A positive likelihood ratio, or LR+, is the probability that a positive test would be expected in a patient divided by the probability that a positive test would be expected in a patient without a disease".
https://www.ncbi.nlm.nih.gov/books/NBK557491/

[2] A negative likelihood ratio or LR-, is "the probability of a patient testing negative who has a disease divided by the probability of a patient testing negative who does not have a disease. [ibid]

Table 1: Performance Characterization of Large Vessel Occlusion Detection

Type of method	**Prediction Method**	**Sensitivity %**	**Specificity %**	**Positive Likelihood Ratio (LR+)**	**Negative Likelihood Ratio (LR-)**	**Positive Predictive Value (PPV %)**	**Negative Predictive Value (NPV %)**
Hospital stroke scores	NIHSS ≥ 6	79	50	1.6	0.42	54	76
	NIHSS ≥ 10	53	76	2.2	0.62	62	69
	RACE ≥ 5	39	82	2.3	0.75	61	65
	LAMS ≥ 4	38	84	1.8	0.76	57	64
Openwater LVO Stroke Alert		81	80	3.9	0.24	72	88

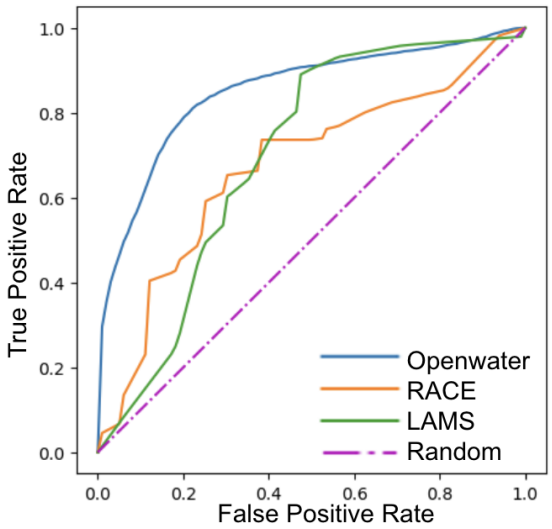

Figure 2: ROC curves for the various assessed methods

Table 2: Performance Characterization when a subject has LVO (52 subjects)

	RACE	Openwater
Predicted as LVO	21	42
Predicted as not LVO	31	10

Table 3: Performance Characterization when a subject does not have an LVO (85 subjects)

	RACE	Openwater
Predicted as LVO	13	17
Predicted as not LVO	71	66

Table 4: Subjects in Feasibility Study

Subject Type	Count
LVO	68
ICA	13
M1	28
M2	15
Tandem (M1/M2)	12
Ischemic Stroke (Non-LVO)	36
Hemorrhagic Stroke	15
Stroke Mimics	39

FDA Concern: Performance of proposed device compared to CT/MR
Furthermore, diagnostic imaging using computed tomography (CT) or a magnetic resonance (MR) scanner is used for the diagnosis of stroke upon presentation to the clinic or hospital and you have not provided any scientific evidence in the Q211873/S001 submission for the use of your device in the hospital and clinical settings and that it offers better diagnosis of stroke than CT or MR imaging. The feasibility study data shows that the use of the Openwater LVO Stroke Alert with the Openwater Headset has 81% sensitivity and 80% specificity to diagnose LVO stroke compared to CT or MR imaging modalities. These results indicate that the subject device does not have the same or better sensitivity and specificity of diagnosing the site of vessel occlusion compared to the current imaging modalities for the proposed indicated use in the clinic and hospital settings to satisfy Breakthrough Device criterion #1 as defined by Section 515B(b)(1) of the Federal FD&C Act [21 U.S.C. 360e-3(b)(1)].

Openwater notes that the Openwater LVO Stroke Alert is only intended for pre-hospital assessments to quickly identify patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery so that improved routing decisions can be made. The device is not intended to replace or be comparable to current imaging modalities used in a clinic or hospital settings. In other words, the device is not intended to change or replace any of the current in-hospital workflows but to optimize the workflow in routing patients to an appropriate stroke center in acute settings.

FDA Concern: Currently available technologies
The current available methods in the pre-hospital phase include stroke ambulances, telemedicine, trained emergency medical technicians (EMTs), and protocols that take into account current traffic delays, hospital capability to treat rapidly, stroke onset time, and other factors. In some areas, there are even attempts to transport interventionists to the stroke patient.

As noted in Q211873 and in Q211873/S001, endovascular therapy in patients with anterior LVO have demonstrated significant clinical improvements in both recanalization rates and clinical outcomes in five randomized clinical trials [MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT]. Clinical trials have demonstrated that the average time from hospital arrival to arterial access to begin endovascular treatment (“door to groin” time) can be improved

by 50 minutes when there is a pre-hospital notification that the patient is being transferred [Goyal et al., 2016]. There is a need to better detect large vessel occlusions in the prehospital setting in order to reduce the time to thrombectomy [Noorian 2021, Adeoye et al. 2022, Pajor et al. 2023]. As noted in the Agency's comments above, this need has led to significant active research in several areas. However, the methods used are experimental and currently not standard of care. For instance, mobile stroke units are only available to a very small minority of the public, and significant investments in mobile stroke units have been scaled back due to the high cost.

With the exception of mobile stroke units capable of performing CT angiography, the methods to identify LVO in a prehospital setting currently rely primarily on clinical examination-based scales, which enable EMS personnel to detect stroke. Their performance has been compared in several recent studies [Duvekot et al. 2021, Nguyen et al. 2020] and while these scales tend to have high specificity (80%-93%), their sensitivity is low (38%-62%). Furthermore, a recent analysis shows that while the scales are good at identifying subjects with severe symptoms, there is a need for methods that can better identify LVO in subjects with moderate symptoms, as these subjects are more common and the performance of the stroke scales in this population is worse [Goyal et al. 2021]. Finally, studies have observed that there is subjectivity to these scores which leads to inconsistency when performed by EMTs in a pre-hospital setting [Kim et al. 2017].

Openwater believes that the Openwater LVO Stroke Alert can address these concerns by performing an assessment of LVO quickly and objectively to identify patients suspected of large vessel occlusion of the internal carotid artery or proximal middle cerebral artery.

Breakthrough Designation Criteria Summary

An updated summary of the breakthrough designation criteria is presented below that incorporates Agency concerns noted in the Q211873/S001 AIRQ letter. Openwater would welcome the opportunity to partner with the Agency through the Breakthrough Device Program interactions to further refine and enhance the current standard of care routing algorithms.

Criterion	**Satisfies criterion?**	**Justification summary**
1. Device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions.	Yes	• Acute Ischemic Stroke (AIS) with a large vessel occlusion (LVO) of the internal carotid artery or proximal middle cerebral artery is a life-threatening and irreversibly debilitating condition that meets all requirements for Criterion 1. • Endovascular therapy (EVT) for LVO offers an opportunity to recanalize large arteries and thereby dramatically improve long-term functional outcome. • Unfortunately, a minority of centers offer EVT, so there is a critical need to get patients to an endovascular capable centers as soon as possible without negatively impacting access to intravenous tPA. AHA/ASA provide guidelines to optimize EMS routing decisions to ensure LVO patients get rapid access to EVT. • While faster routing for LVO patients improves endovascular treatment times and post-EVT outcomes, there is strong evidence that optimization of this routing does not negatively impact the timing of intravenous thrombolytics for AIS patients without LVO. • Pre-hospital detection of LVO currently rely on subjective stroke scales like RACE and LAMS that tend to have high specificity (80%-93%) but low sensitivity (38%-62%). • The Openwater device provides the potential for more effective diagnosis and treatment of anterior LVO stroke because it quickly (within 5 minutes) and objectively identifies such strokes in a pre-hospital acute setting with a sensitivity of 81% and a specificity of 80% (in early feasibility studies).
2. Device meets one of the components of the criterion, listed below:		
A. Device represents breakthrough technology;	Yes	There are no prehospital methods to objectively determine the presence of anterior LVO stroke.

Criterion	Satisfies criterion?	Justification summary
		The proposed device utilizes blood flow and volume data detected through breakthrough technology. The device can significantly help EMS make improved routing decisions for stroke patients and can help mitigate the life-threatening or irreversibly debilitating conditions by reducing the inherent delays in the current standard-of-care workflows.
B. No approved or cleared alternatives exist;	No	Efforts have been made to develop "mobile stroke units" that outfit ambulances with Computed Tomography (CT) imaging devices to detect the presence of LVO and the need for emergent transport for endovascular therapy but are limited due to cost and availability and thus are not standard of care (SOC). Current standard of care attempts to optimize routing protocols to account for delays but are the availability of an objective and accurate assessment of LVO would significantly help the workflow optimization.
C. Device offers significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long term clinical efficiencies; or	Yes	The standard of care requires routing to a closest hospital to get a CT scan often at a hospital not capable of providing endovascular therapy, which can result in >2hrs of transfer time delays. Alternatively, the methods use subjective pre-hospital stroke scales to optimize routing decisions to implement the AHA Mission: Lifeline acute stroke routing protocols. The Openwater solution provides significant advantages over these existing options in that it can be quickly and easily operated by EMS personnel in a pre-hospital acute setting to objectively assess a patient. The device can also enable notification of transport for the receiving hospital to be able to prepare in advance for a potential LVO stroke patient in transport as well as assist EMS transport protocols to endovascular therapy capable stroke centers.
D. Device availability is in the best interest of patients.	Yes	Availability of the device is in the best interest of patients, as a prehospital notification can save 50 minutes on average in workflow times per SWIFT PRIME and better routing can potentially reduce significant delays to transfer patients to comprehensive stroke centers. Improving stroke-related workflow is critical, as delays of 50 minutes to >2 hours are often the difference

Criterion	Satisfies criterion?	Justification summary
		between good functional neurological outcome and severe disability or death from LVO stroke.

Citations

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Mapping FDA Concerns in Q211873/S001 AIRQ to Topics

Table 5: Topics discussed in this response based on FDA concerns noted in Q211873/S001 AIRQ

Topic	Agency Concern
1. FDA Concern: Performance level for pre-hospital assessment of LVO	The proposed indications for use (IFU) of the Openwater LVO Stroke Alert in the Breakthrough Device request (Q211873/S001) is: "*Openwater LVO Stroke Alert is indicated for use as an early notification system to identify patients suspected of large vessel occlusion (LVO) in the anterior circulation. This software as a medical device (SaMD) utilizes data from Openwater Headset in adult patients. Openwater LVO Stroke Alert is intended to be used in hospitals, clinics, and in pre-hospital settings*." The Breakthrough Device designation requires that you must provide scientific evidence to meet criterion #1 as defined by Section 515B(b)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act [21 U.S.C. 360e-3(b)(1)] to generate a reasonable expectation that the subject device could provide for more effective diagnosis or treatment of the target condition compared to current usual care methods and thus demonstrate clinical success. The feasibility study data provided in the Q211873/S001 submission does not demonstrate that the Openwater LVO Stroke Alert has both better sensitivity and specificity to distinguish LVO stroke compared to stroke caused by small or medium vessel occlusions, stroke mimics, or intracranial hemorrhage when used in the pre-hospital setting by emergency medical services (EMS) compared to the current clinical assessment tools. For example, the specificity of the Openwater LVO Stroke Alert is comparable or slightly less than the RACE (Rapid Arterial Occlusion Evaluation) and LAMS (Los Angeles Motor Scale) assessments performed in the pre-hospital setting, while the sensitivity is higher. Both sensitivity and specificity are important outcomes to show that the subject device is a better diagnostic assessment tool compared to the current assessments used in the pre-hospital setting because sensitivity demonstrates that the device can accurately identify the true LVO strokes, whereas specificity is important for the device to accurately distinguish LVO strokes from other clinical diseases or conditions, such as stroke mimics, intracranial hemorrhage, or small and medium vessel occlusion strokes.
2. FDA Concern: Performance of proposed device compared to CT/MR	Furthermore, diagnostic imaging using computed tomography (CT) or a magnetic resonance (MR) scanner is used for the diagnosis of stroke upon presentation to the clinic or hospital and you have not provided any scientific evidence in the Q211873/S001 submission for the use of your device in the hospital and clinical settings and that it offers better diagnosis of stroke than CT or MR imaging. The feasibility study data shows that the use of the Openwater LVO Stroke Alert with the Openwater Headset has 81% sensitivity and

	80% specificity to diagnose LVO stroke compared to CT or MR imaging modalities. These results indicate that the subject device does not have the same or better sensitivity and specificity of diagnosing the site of vessel occlusion compared to the current imaging modalities for the proposed indicated use in the clinic and hospital settings to satisfy Breakthrough Device criterion #1 as defined by Section 515B(b)(1) of the Federal FD&C Act [21 U.S.C. 360e-3(b)(1)].
3. FDA Concern: Currently available technologies	The current available methods in the pre-hospital phase include stroke ambulances, telemedicine, trained emergency medical technicians (EMTs), and protocols that take into account current traffic delays, hospital capability to treat rapidly, stroke onset time, and other factors. In some areas, there are even attempts to transport interventionists to the stroke patient.
4. FDA Concern: Routing decisions and risks related to delaying thrombolytic therapy	There would have to be evidence that the use of the Openwater LVO Stroke Alert to triage patients to a more remote hospital for endovascular therapy could result in increased benefit and show that patients who could have been treated earlier with thrombolytic therapy did not fare worse when compared to outcomes of patients transported according to the current methodology to make triage decisions. To be more effective than current available diagnosis of stroke occlusion location in the clinic and hospital and other settings per your proposed IFU and satisfy Breakthrough Device criterion #1 as defined by Section 515B(b)(1) of the Federal FD&C Act [21 U.S.C. 360e-3(b)(1)], we request that you provide clinical performance data that demonstrates more accurate diagnosis of stroke occlusion location for all types of stroke or conditions that mimic stroke using the Openwater LVO Stroke Alert compared to current methods as described above.