# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

| | |
|---|---|
| Device Generic Name: | Test for Esophageal Varices |
| Device Trade Name: | HepQuant SHUNT® Liver Diagnostic Test |
| Device Procode: | SIO |
| Applicant's Name and Address: | HepQuant LLC<br>8110 E. Union Avenue, Suite 750<br>Denver, CO 80237 |
| Date(s) of Panel Recommendation: | None |
| Premarket Approval Application (PMA) Number: | P220016 |
| Date of FDA Notice of Approval: | June 18, 2026 |

## II. INDICATIONS FOR USE

The HepQuant SHUNT® Liver Diagnostic Test is designed for the quantitative detection of 13C-cholate and d4-cholate in human serum from blood samples collected after the intravenous administration of 13C-cholate and the oral ingestion of d4-cholate. The assay generates a Disease Severity Index (DSI) score from the clearance of 13C-cholate and d4-cholate. Sample analysis is conducted by the HepQuant Analytical Test Laboratory.

A DSI score below the validated threshold can be used in patients with compensated cirrhosis (Child Pugh Class A), age 22 years or older, undergoing screening or surveillance for esophageal varices to identify those patients unlikely to have large esophageal varices. The DSI score aids in identifying patients unlikely to require esophagogastroduodenoscopy (EGD) at the time of testing.

The HepQuant SHUNT® Liver Diagnostic Test is not a stand-alone test and should be used in conjunction with other clinical and laboratory findings.

## III. CONTRAINDICATIONS

1. The test should not be administered to patients who have a known sensitivity or allergy to albumin or any other HepQuant SHUNT® Kit component.

2. The test should not be administered in patients with severe gastroparesis or in patients who have had upper bowel resection.

## IV. WARNINGS AND PRECAUTIONS

The limitations, warnings and precautions can be found in the HepQuant SHUNT® Liver Diagnostic Test labeling.

## V. DEVICE DESCRIPTION

The HepQuant SHUNT® Liver Diagnostic Test is a dual-cholate clearance test involving the administration of two non-radioactive isotope-labeled compounds (13C-cholate and d4-cholate). d4-cholate is administered orally and 13C-cholate is administered intravenously with a human serum albumin excipient. Blood samples are collected via an indwelling intravenous catheter at baseline and five time points (5, 20, 45, 60, and 90 minutes) over the 90-minute period following administration and processed to serum at the clinical collection sites. Serum samples are shipped to the HepQuant Analytical Test Laboratory where samples are inspected for integrity, quality and volume prior to undergoing extraction. The extract is measured using a high-performance liquid chromatography (HPLC) system and a liquid chromatography-tandem mass spectrometry (LC-MS/MS) instrument. Applied Biosystems Analyst Software (Version 1.7) is used to determine the concentrations of 13C-cholate and d4-cholate present in the extract. The cholate concentrations are used to generate a disease severity index (DSI) score using HepQuant software (TQ Data Template Version 0 and DSI Data Template Version 2). A DSI score below the validated threshold can be used to identify patients with Child Pugh Class A cirrhosis, 22 years of age or older, unlikely to have large esophageal varices (LEVs).

The HepQuant SHUNT® Liver Diagnostic Test consists of:

- A test kit containing 13-cholate IV formulation in 1M $NaHCO_3$, d4-cholate oral formulation in 1M $NaHCO_3$, 25% human serum albumin, materials needed to process and ship the blood samples, instructions for use, and test requisition form. Additional materials needed for test administration, blood sampling and processing are required, but not provided.
- LC-MS/MS instrument, HPLC system, reagents and software needed to quantitate cholate concentrations in the serum samples and generate a DSI score.

Please refer to the instructions for use for additional details of the components of the test.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no alternative in vitro diagnostic devices that can identify patients unlikely to have LEVs. Esophagogastroduodenoscopy (EGD) is the gold standard for identification of esophageal varices in patients with Child Pugh Class A cirrhosis and is used as part of the current standard of care. If no varices are found on initial EGD, EGD should be repeated every 2-3 years (depending on whether there is ongoing liver injury or associated conditions). EGD may be avoided in patients with a liver stiffness measurement (LSM) of <20 kPa and platelet count >150,000/µL who have a very low probability (<5%) of having high-risk varices (i.e., Baveno VI criteria). This alternative has its own advantages and disadvantages. A patient should fully discuss this alternative with his/her physician to select the method that best meets expectations and lifestyle.

## VII. MARKETING HISTORY

The HepQuant SHUNT® Liver Diagnostic Test has not been marketed in the United States or any foreign country.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the test administration process:

- Test compounds: Allergic reaction to cholate compounds, allergic reaction to human serum albumin.
- Indwelling IV catheter: Pain with placement of the catheter, thrombosed vein, hematoma.
- Phlebotomy: Localized pain, bruising, occasional lightheadedness, fainting, infection at the site.
- Fasting before the test: dizziness, headache, stomach discomfort, fainting.

For the specific adverse events that occurred in the clinical study, please see Section X.D.1 below.

For a discussion of the potential adverse effects associated with an erroneous test result, please see Section X.IV.C below.

## IX. SUMMARY OF NON-CLINICAL STUDIES

### A. Laboratory Studies

#### 1. Precision/Reproducibility

Precision study with patient samples

The precision performance of the HepQuant SHUNT® Liver Diagnostic Test was established according to CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition. Native human serum samples from intended use patients were pooled to create three sample sets (with six time points each: T0, T5, T20, T45, T60, T90) with DSI scores across the low (DSI 10), medium (DSI 20), and high (DSI 30) DSI score range. Two additional patient pools representing the high ends of the 13C-cholate (High 13C) or d4-cholate (High d4) ranges were evaluated. Sample pools were run in duplicate in each run, two runs per day for 19 days for a total of 76 measurements using the AB Sciex API 4500 LC-MS/MS. One replicate for the High d4 sample was excluded due to a pipetting error. The data was analyzed for repeatability, between-run, between-day, and within-laboratory variability and is summarized in the tables below (Tables 1-3).

Table 1. 13C-cholate

| Sample | N | Mean | Within-Run | | Between-Run | | Between-Day | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| High 13C | 76 | 10 | 0.2 | 2.0 | 0.2 | 1.8 | 0.0 | 0.5 | 0.3 | 2.7 |
| High d4 | 75 | 3.6 | 0.1 | 2.5 | 0.0 | 0.7 | 0.0 | 0.0 | 0.1 | 2.6 |
| T5 DSI 10 | 76 | 6.0 | 0.1 | 1.5 | 0.1 | 0.9 | 0.1 | 0.9 | 0.1 | 2.0 |
| T5 DSI 20 | 76 | 7.7 | 0.1 | 1.5 | 0.1 | 1.1 | 0.0 | 0.6 | 0.1 | 1.9 |
| T5 DSI 30 | 76 | 6.9 | 0.1 | 1.8 | 0.0 | 0.7 | 0.1 | 2.0 | 0.2 | 2.7 |
| T20 DSI 10 | 76 | 1.4 | 0.1 | 5.5 | 0.0 | 1.0 | 0.0 | 0.0 | 0.1 | 5.6 |
| T20 DSI 20 | 76 | 1.7 | 0.0 | 1.7 | 0.0 | 0.6 | 0.0 | 1.0 | 0.0 | 2.0 |
| T20 DSI 30 | 76 | 3.0 | 0.1 | 2.3 | 0.0 | 1.0 | 0.0 | 1.3 | 0.1 | 2.9 |
| T45 DSI 10 | 76 | 0.6 | 0.0 | 2.2 | 0.0 | 0.7 | 0.0 | 1.3 | 0.0 | 2.6 |
| T45 DSI 20 | 76 | 0.8 | 0.0 | 1.8 | 0.0 | 0.6 | 0.0 | 1.5 | 0.0 | 2.4 |
| T45 DSI 30 | 76 | 1.8 | 0.0 | 1.7 | 0.0 | 1.5 | 0.0 | 2.0 | 0.1 | 3.0 |
| T60 DSI 10 | 76 | 0.4 | 0.0 | 2.0 | 0.0 | 0.2 | 0.0 | 1.2 | 0.0 | 2.3 |
| T60 DSI 20 | 76 | 0.5 | 0.0 | 1.5 | 0.0 | 0.8 | 0.0 | 1.1 | 0.0 | 2.0 |
| T60 DSI 30 | 76 | 1.4 | 0.0 | 2.2 | 0.0 | 0.0 | 0.0 | 1.4 | 0.0 | 2.7 |
| T90 DSI 10 | 76 | 0.3 | 0.0 | 1.9 | 0.0 | 0.9 | 0.0 | 1.1 | 0.0 | 2.4 |
| T90 DSI 20 | 76 | 0.3 | 0.0 | 1.8 | 0.0 | 0.0 | 0.0 | 1.6 | 0.0 | 2.4 |
| T90 DSI 30 | 76 | 0.9 | 0.0 | 2.0 | 0.0 | 1.5 | 0.0 | 1.5 | 0.0 | 2.9 |

Table 2. d4-cholate

| Sample | N | Mean | Within-Run | | Between-Run | | Between-Day | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |
| High 13C | 76 | 0.1 | 0.0 | 6.0 | 0.0 | 4.2 | 0.0 | 0.0 | 0.0 | 7.3 |
| High d4 | 75 | 7.6 | 0.2 | 2.8 | 0.0 | 0.0 | 0.1 | 0.7 | 0.2 | 2.9 |
| T5 DSI 10 | 76 | 0.1 | 0.0 | 4.6 | 0.0 | 2.7 | 0.0 | 3.3 | 0.0 | 6.3 |
| T5 DSI 20 | 76 | 0.1 | 0.0 | 3.2 | 0.0 | 2.8 | 0.0 | 1.5 | 0.0 | 4.5 |
| T5 DSI 30 | 76 | 0.1 | 0.0 | 3.8 | 0.0 | 0.0 | 0.0 | 2.6 | 0.0 | 4.6 |
| T20 DSI 10 | 76 | 0.8 | 0.0 | 5.4 | 0.0 | 1.4 | 0.0 | 0.0 | 0.0 | 5.5 |
| T20 DSI 20 | 76 | 2.3 | 0.0 | 1.6 | 0.0 | 0.7 | 0.0 | 1.4 | 0.1 | 2.2 |
| T20 DSI 30 | 76 | 2.8 | 0.1 | 2.4 | 0.0 | 1.0 | 0.0 | 1.4 | 0.1 | 2.9 |
| T45 DSI 10 | 76 | 0.7 | 0.0 | 1.7 | 0.0 | 0.2 | 0.0 | 2.6 | 0.0 | 3.2 |
| T45 DSI 20 | 76 | 1.4 | 0.0 | 1.6 | 0.0 | 0.6 | 0.0 | 2.1 | 0.0 | 2.7 |
| T45 DSI 30 | 76 | 3.8 | 0.1 | 1.8 | 0.0 | 1.2 | 0.1 | 1.8 | 0.1 | 2.8 |
| T60 DSI 10 | 76 | 0.5 | 0.0 | 1.9 | 0.0 | 1.1 | 0.0 | 2.7 | 0.0 | 3.5 |
| T60 DSI 20 | 76 | 0.8 | 0.0 | 1.7 | 0.0 | 0.0 | 0.0 | 2.4 | 0.0 | 3.0 |
| T60 DSI 30 | 76 | 3.2 | 0.1 | 1.9 | 0.0 | 0.0 | 0.0 | 1.3 | 0.1 | 2.3 |
| T90 DSI 10 | 76 | 0.2 | 0.0 | 2.6 | 0.0 | 0.4 | 0.0 | 4.8 | 0.0 | 5.5 |
| T90 DSI 20 | 76 | 0.5 | 0.0 | 2.3 | 0.0 | 0.0 | 0.0 | 2.8 | 0.0 | 3.6 |
| T90 DSI 30 | 76 | 2.2 | 0.0 | 2.0 | 0.0 | 1.0 | 0.0 | 1.7 | 0.1 | 2.8 |

Table 3. DSI

| Sample | N | Mean | Within-Run | | Between-Run | | Between-Day | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | CV(%) | SD | CV(%) | SD | CV(%) | SD | CV(%) |
| DSI 10 | 76 | 14.6 | 0.2 | 1.5 | 0.1 | 0.7 | 0.2 | 1.4 | 0.3 | 2.1 |
| DSI 20 | 76 | 24.2 | 0.1 | 0.5 | 0.1 | 0.3 | 0.2 | 0.9 | 0.3 | 1.1 |
| DSI 30 | 76 | 37.8 | 0.1 | 0.3 | 0.1 | 0.4 | 0.2 | 0.6 | 0.3 | 0.8 |

Precision study with controls – Assessment of repeatability

Six control samples were prepared in pooled normal human serum and spiked with the indicated amounts of both 13C-cholate and d4-cholate. Each sample was assayed in replicates of ten in one run. The data was analyzed for repeatability and is summarized in the following table (Table 4).

Table 4.

| Analyte | Spiked Concentration (µM) | Repeatability %CV |
|---|---|---|
| 13C-cholate | 0.1 | 5.7% |
| | 0.3 | 2.9% |
| | 0.8 | 1.6% |
| | 2.5 | 1.2% |
| | 7.5 | 1.4% |
| | 10 | 2.4% |
| d4-cholate | 0.1 | 2.9% |
| | 0.3 | 2.3% |
| | 0.8 | 1.0% |
| | 2.5 | 2.5% |
| | 7.5 | 2.8% |
| | 10 | 2.6% |

Precision study with controls – Assessment of precision across replicates, runs and days

Six control samples were prepared in pooled normal human serum and spiked with the indicated amounts of both 13C-cholate and d4-cholate. Each sample was assayed in replicates of two per run, with two runs per day over 20 days for a total of 80 measurements per sample. A single reagent lot was used. The data was analyzed for mean and %CV across the dataset. The results are summarized in the following table (Table 5).

Table 5.

| Analyte | Mean spiked Concentration (µM) | %CV |
|---|---|---|
| 13C-cholate | 0.1 | 6.3% |
| | 0.3 | 2.5% |
| | 0.7 | 2.6% |
| | 2.5 | 2.3% |
| | 7.6 | 5.3% |
| | 10 | 2.3% |
| d4-cholate | 0.1 | 4.7% |
| | 0.3 | 5.9% |
| | 0.7 | 2.4% |
| | 2.5 | 2.5% |
| | 7.6 | 2.5% |
| | 10 | 4.2% |

Extraction reproducibility study

An extraction reproducibility study was conducted using pooled native patient serum samples at three levels of 13C-cholate and three levels of d4-cholate. Each sample underwent five extractions over five days using two operators and one lot of reagent. The within-run, between operator, between day, and overall reproducibility of the extraction process is shown below (Table 6).

Table 6.

| Sample | N | Mean (µM) | Within-Run | | Between-Operator | | Between-Day | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | CV(%) | SD | CV (%) | SD | CV(%) | SD | CV(%) |
| 13C-Low | 50 | 1.0791 | 0.0161 | 1.5 | 0.0100 | 0.9 | 0.0000 | 0.0 | 0.0190 | 1.8 |
| d4-Low | 50 | 0.6771 | 0.0096 | 1.4 | 0.0075 | 1.1 | 0.0070 | 1.0 | 0.0140 | 2.1 |
| 13C-Medium | 50 | 5.0212 | 0.0768 | 1.5 | 0.0277 | 0.6 | 0.0289 | 0.6 | 0.0866 | 1.7 |
| d4-Medium | 50 | 4.2394 | 0.0836 | 2.0 | 0.0677 | 1.6 | 0.0268 | 0.6 | 0.1108 | 2.6 |
| 13C-High | 50 | 9.7391 | 0.1775 | 1.8 | 0.0000 | 0.0 | 0.0915 | 0.9 | 0.1997 | 2.1 |
| d4-High | 50 | 6.6124 | 0.2211 | 3.3 | 0.0793 | 1.2 | 0.0934 | 1.4 | 0.2528 | 3.8 |

**2. Linearity**

Linearity

The linearity performance of the HepQuant SHUNT® Liver Diagnostic Test was established in a linearity study according to CLSI EP06 2nd Edition. In the study, for each analyte (13C-cholate, d4-cholate), a high concentration pool was prepared from patient samples and supplemented with spiked analyte. A blank concentration pool was prepared from patient samples not containing the cholate analytes. A dilution series of 11 samples (ranging from 0.1 to 12 µM) was created by intermixing the high and low pools in various proportions. Each sample was analyzed using the AB Sciex API 4500 LC-MS/MS with four replicates. Data were analyzed using weighted linear regression. The results of the regression are shown below (Table 7) and support the claimed analytical measuring interval (AMI) for both analytes as shown below.

Table 7.

| Analyte | Regression equation | Claimed AMI |
|---|---|---|
| 13C-cholate | Y = 1.006X – 0.003 | 0.1 to 10 µM |
| d4-cholate | Y = 0.982X + 0.429 | 0.1 to 9 µM |

Sample Dilution

If the d4-cholate concentration exceeds the upper limit of the AMI, the sample is invalid (with the exception of the 5-minute sample, for which the 13C-cholate and d4-cholate concentrations may be imputed). If the 13-cholate concentration exceeds the upper limit of the AMI, the sample can be manually diluted 1:5 once using double charcoal stripped human serum and rerun. If the final 13C-cholate concentration (after taking into account the dilution factor) exceeds the upper limit of the extended measuring interval (i.e., 20 µM), then the sample is invalid (with the exception of the 5-minute sample, for which the 13C-cholate and d4-cholate concentrations may be imputed).

A dilution study was conducted according to CLSI EP34 Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking to support a single 1:5 manual dilution of samples with 13C-cholate concentrations that exceed the upper limit of AMI. In the study, human serum samples were spiked with 10, 15 and 20 µM 13C-cholate concentrations and diluted 1:5 with double charcoal-stripped human serum. Each diluted sample was assayed in replicates of 12. The results of the study are shown below (Table 8).

Table 8.

| Spiked 13C-cholate concentration (µM) | Measured concentration (µM) | % Recovery |
|---|---|---|
| 10 | 9.6 | 96.0% |
| 15 | 15.8 | 105.3% |
| 20 | 20.1 | 100.5% |

**3. Detection Limit/Analytical Sensitivity**

The limit of quantitation (LoQ) for the HepQuant SHUNT® Liver Diagnostic Test was established following the recommendations in CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition. Five low level samples containing 13C-cholate and d4-cholate were prepared from pooled patient serum samples. Each sample was tested in replicates of three per run, one run per day over three days using two reagent lots on one instrument for a total of 45 replicates per lot. The LoQ was determined based on a total error goal of 18%. The study supports an LoQ of 0.1 µM for 13C-CA and 0.1 µM for d4-CA.

**4. Assay Cut-off**

A DSI score below 18.3 can be used to identify patients with compensated cirrhosis (Child Pugh Class A), 22 years of age or older, undergoing screening or surveillance for esophageal varices, unlikely to have LEVs.

## 5. Assay Reportable Range

The analytical measuring interval for 13C-cholate is 0.1 to 10 µM.
The analytical measuring interval for d4-cholate is 0.1 to 9 µM.

The concentrations of 13C-cholate and d4-cholate are not reported, but are used in the calculation of Disease Severity Index (DSI). The validated DSI range is 6.7 to 42.1.

## 6. Analytical Specificity/Interference

Interference with endogenous and exogenous substances

Interference testing was conducted according to CLSI EP07 Interference Testing in Clinical Chemistry, 3rd Edition and CLSI EP37 Supplemental Tables for Interference Testing in Clinical Chemistry, 1st Edition. Five endogenous substances and fifteen exogenous substances, representing the most commonly used medications by patients with chronic liver disease (CLD), were selected for testing. Pooled patient samples containing 13C-CA and d4-CA at the low end (0.1-1 µM) and high end (8-10 µM) of the assay measuring intervals were spiked with the potentially interfering substances (test samples) and compared to the corresponding control samples without the potentially interfering substances. Each sample was tested in replicates of five. The test results show that the observed bias between the test and control samples across replicates was within 6.4% for all exogenous and endogenous compounds tested. The table below (Table 9) shows the concentrations of the substances tested.

Table 9.

| Substance | Tested concentration (mg/dL) |
|---|---|
| Atenolol | 0.90 |
| Atorvastatin | 0.08 |
| Ezetimibe | 0.002 |
| Fenofibrate | 4.50 |
| Glimepiride | 0.16 |
| Glipizide | 0.30 |
| Insulin | 0.0002 (30 mU/L) |
| Liraglutide | 0.02 |
| Metformin | 1.20 |
| Metoprolol | 0.15 |
| Pioglitazone | 0.48 |
| Pravastatin | 0.02 |
| Propranolol | 0.10 |
| Rosuvastatin | 0.01 |
| Simvastatin | 0.01 |
| Bilirubin (conjugated) | 40 |
| Bilirubin (unconjugated) | 40 |
| Cholesterol, total | 400 |
| Hemoglobin | 1000 |
| Triglycerides, total | 1500 |

## 7. Carryover

For each instrument run, analyte-free methanol samples are assayed for the presence of measurands to monitor for possible carryover. The results must be below a predefined threshold for run acceptance.

A study was conducted to assess whether there was significant well to well sample carryover of the analytes. In the study, an instrument run was conducted with duplicates of a methanol sample assayed following the highest calibrator on each of 20 days for a total of 40 carryover measurements. The results showed that for each of the methanol samples, the measurand concentrations were less than 20% of the LoQ for 13C-cholate and d4-cholate to support that carryover is not likely to affect the performance of the test.

## 8. Traceability

The assays for 13C-cholate and d4-cholate are metrologically traceable to qualified reference materials.

### 9. Stability

Sample stability

A sample stability study was conducted to support the labeling claims that samples may be stored at collection sites at ambient temperature for up to 5 days after collection prior to shipping the samples to the HepQuant Analytical Test Laboratory. The samples should be tested within 14 days of sample collection. In the study, samples containing low, medium, or high levels of 13C-cholate and d4-cholate were tested fresh and after storage for up to 14 days at -80°C, 40°C or 50°C. The results of the study showed that the cholate concentrations were stable up to 14 days at these temperatures.

The sponsor also provided sample stability data to support the stability of stored samples used in the pivotal clinical study and analytical studies.

## B. Animal Studies

Not applicable.

## C. Additional Studies

Spike and recovery studies

The analytical accuracy of the HepQuant SHUNT® Liver Diagnostic Test was demonstrated in four studies, which are described below. The studies were conducted using recommendations from CLSI C62-A, Liquid Chromatography-Mass Spectrometry Methods; Approved Guideline.

*Spike and recovery with clinical study samples*

A spike and recovery study was conducted with patient samples collected during the pivotal clinical study. In this study, four sample pools were prepared from the serum of intended use patients that contained both 13C-cholate and d4-cholate prior to spiking. Each of the four patient sample pools was spiked with 13C-cholate- and d4-cholate-containing solutions to concentrations of 2.0, 4.0, and 6.0 µM. The standards for spiking were prepared from high purity materials using gravimetric and volumetric methods and were prepared in charcoal stripped serum to create the spiking solutions. As a reference to determine recovery, each of the four patient sample pools was spiked with the same volume of charcoal stripped serum without analyte. Each of the 16 spiked samples was assayed in replicates of five for both analytes on the AB Sciex API 4500 LC-MS/MS. For each sample at each concentration, the recovery was calculated as the percent (%) bias between the mean sample concentration and the mean reference sample concentration. The results are summarized below (Table 10).

Table 10.

| | 13C-cholate | | d4-cholate | |
|---|---|---|---|---|
| Sample | Spiked concentration (µM) | Mean % bias | Spiked concentration (µM) | Mean % bias |
| 1 | 2 | 3.4% | 2 | 4.6% |
| | 4 | 6.4% | 4 | 6.4% |
| | 6 | 10.0% | 6 | 9.5% |
| 2 | 2 | 6.5% | 2 | 3.6% |
| | 4 | 4.4% | 4 | 3.3% |
| | 6 | 4.0% | 6 | 2.7% |
| 3 | 2 | 6.2% | 2 | 6.2% |
| | 4 | 7.2% | 4 | 7.6% |
| | 6 | 4.0% | 6 | 3.3% |
| 4 | 2 | 2.9% | 2 | 0.9% |
| | 4 | 0.0% | 4 | 0.3% |
| | 6 | 1.4% | 6 | 1.3% |

*Spike and recovery study with diseased liver patient samples*

A spike and recovery study was conducted with diseased liver patient samples representative of native patient samples from the intended use population. In the study, three samples with low (0.15 µM), medium (5 µM), and high (9 µM) concentrations of both 13C-cholate and d4-cholate were prepared by spiking standards of each analyte into pooled serum from intended use patients that was free of the analytes. Each of the three samples was assayed in triplicates per run, two runs per day over four days for a total of 24 measurements using the AB Sciex API 4500 LC-MS/MS. Each sample was analyzed individually for the measured analyte concentration and compared against the spiked concentration as a percent (%) bias. The results are summarized below (Table 11).

Table 11.

| Analyte | Spiked concentration (µM) | Mean recovered concentration (µM) | Mean % Bias | Minimum % Bias | Maximum % Bias |
|---|---|---|---|---|---|
| 13C-cholate | 0.15 | 0.151 | 0.64% | -1.3% | 3.3% |
| | 5 | 5.030 | 0.60% | -2.8% | 3.9% |
| | 9 | 9.100 | 1.11% | -2.5% | 5.1% |
| d4-cholate | 0.15 | 0.149 | -0.58% | -3.3% | 3.3% |
| | 5 | 4.998 | -0.04% | -2.6% | 4.5% |
| | 9 | 8.985 | -0.17% | -4.0% | 2.7% |

*Spike and recovery with control samples over one run*

A spike and recovery study was conducted with control samples. In the study, six control samples were prepared in pooled normal human serum and spiked with the indicated amounts of both 13C-cholate and d4-cholate. Each sample was assayed in replicates of 10 in one run. The data was analyzed for mean percent (%) bias against the spiked concentration, and are summarized in the table below (Table 12).

Table 12.

| Spiked concentration (µM) | 13C-cholate Mean % bias | D4-cholate Mean % bias |
|---|---|---|
| 0.1 | 7.0% | 8.1% |
| 0.25 | 2.0% | 3.8% |
| 0.75 | -4.5% | 0.9% |
| 2.5 | 0.6% | -1.8% |
| 7.5 | 3.7% | 1.2% |
| 10.0 | 0.7% | 1.5% |

*Spike and recovery with control samples over multiple runs and days*

A spike and recovery study was conducted with control samples. In the study, six control samples were prepared in pooled normal human serum and spiked with the indicated amounts of both 13C-cholate and d4-cholate. Each sample was assayed in duplicates per run, two runs per day over 20 days for a total of 80 measurements for each analyte. Each sample was analyzed individually for the measured analyte concentration and compared against the spiked concentration as a percent (%) bias. The mean % bias across all replicates was calculated and summarized below (Table 13).

Table 13.

| Spiked concentration (µM) | 13C-cholate Mean % bias | D4-cholate Mean % bias |
|---|---|---|
| 0.1 | 7.4% | 9.9% |
| 0.25 | 2.3% | 3.1% |
| 0.75 | -1.9% | -0.9% |
| 2.5 | -1.0% | 1.4% |
| 7.5 | 1.1% | 1.3% |
| 10.0 | 1.0% | 0.6% |

*Chemistry, manufacturing and controls for 13C-cholate and d4-cholate*

Chemistry, manufacturing and controls information for the sterile 13C-cholate solution for intravenous injection and the sterile d4-cholate solution for oral ingestion was reviewed. This included information regarding chemistry and composition, manufacturing, and methods and acceptable limits used to ensure the identity, strength,

quality, and purity of the cholate substances and cholate products. The reviewed information supports the identity, strength, quality, and purity of the cholate substances and cholate products used in the HepQuant SHUNT® Liver Diagnostic Test. In addition, information supporting the safety of administering 13C-cholate through intravenous injection and d4-cholate through oral ingestion was reviewed and found acceptable. See also Section X.D.1 below regarding the safety results from the clinical study.

Albutein-25®
Albutein-25® is a human serum albumin solution administered with 13C-cholate. Safety information for Albutein-25® was reviewed under approved Biologics License Application (BLA) 102478 and supports its safe use as part of the HepQuant SHUNT® Liver Diagnostic Test. See also Section X.D.1 below regarding the safety results from the clinical study.

## X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

A multicenter, prospective clinical study (The SHUNT-V Study for Varices) was conducted to establish a reasonable assurance of safety and effectiveness of the HepQuant SHUNT® Liver Diagnostic Test for identifying patients undergoing screening or surveillance for esophageal varices who are unlikely to have LEVs and unlikely to require EGD at the time of testing. The study was performed in the U.S. under IDE #G180098. Data from this clinical study were the basis for the PMA approval decision.

A summary of the clinical study is presented below.

### A. Study Design

This multicenter, prospective clinical study enrolled subjects between February 4, 2019 and December 2, 2020. There were 23 investigational sites that enrolled at least one subject. 367 subjects were screened for the study and 306 of these subjects were enrolled in the study based on the inclusion and exclusion criteria shown below.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the study was limited to patients who met the following inclusion criteria:
   - Adults 21 years of age or older with Child-Pugh class A cirrhosis who were scheduled, or in the process of being scheduled, for EGD for screening or surveillance of esophageal varices.
   - Subjects may or may not have had prior endoscopy.
   - Adequate peripheral venous access for IV catheter.
   - Ability to take oral dose of d4-cholate.
   - Ability to hold morning doses of medications for the 90-minute duration of the HepQuant SHUNT® Liver Diagnostic Test.
   - Signed and dated informed consent.

- Stated willingness to comply with all study procedures and availability for the duration of the study.

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- Unable to absorb oral cholate (e.g., underlying severe gastroparesis or having undergone extensive small bowel resection, conditions or postoperative state that could impair the absorption of the oral d4-cholate).
- Known hypersensitivity to any of the components of the HepQuant SHUNT® Liver Diagnostic Test.
- Acute hepatitis, acute liver failure, or acute on chronic liver failure (i.e., acute aggravation of a chronic condition).
- Acute drug-induced liver disease.
- Noncirrhotic causes for portal hypertension and varices.
- Ongoing active alcoholic hepatitis (AH).
- Child-Pugh class B or C (Note: subjects with Child-Pugh B were enrolled according to the study protocol but excluded from the final validation dataset).
- Dialysis.
- Active infection or febrile illness within the last month.
- Documented history of large esophageal or gastric variceal hemorrhage (VH).
- Documented history of treatment of varices.
- HCC beyond Milan or University of California San Francisco criteria.
- Thrombosis of main portal vein.
- Liver transplant recipient.
- Pregnancy.
- Women who were breastfeeding.
- Serious intercurrent medical or surgical illness, such as acute myocardial infarction, acute cerebral hemorrhage, sepsis, or other immediate life-threatening illness.
- *Nil per os* (NPO; nothing by mouth) status (per physician order).

2. Follow-up Schedule
   Enrolled subjects underwent one-time testing with the HepQuant SHUNT® Liver Diagnostic Test prior to EGD. The majority of subjects underwent EGD after the HepQuant SHUNT® Liver Diagnostic Test within 42 days (with ten subjects undergoing EGD from 48 to 182 days after the HepQuant SHUNT® Liver Diagnostic Test). Subjects underwent follow up examinations within 30 days of the administration of the HepQuant SHUNT® Liver Diagnostic Test. Adverse events (AEs) and complications were recorded at all of these visits.

3. Clinical Endpoints

With regards to safety, AEs, serious adverse events (SAEs) and subject-reported outcomes from a self-reported subject tolerability survey were recorded at the visits.

With regards to effectiveness, the primary objective of this study was to validate the DSI of $\leq$ 18.3 for identifying subjects with chronic liver disease, undergoing screening or surveillance for esophageal varices, who are unlikely to have LEVs.

## B. Accountability of PMA Cohort

A total of 306 subjects were enrolled in the study: 297 subjects had HepQuant SHUNT® Liver Diagnostic Tests performed, 282 subjects had EGDs performed, and 280 subjects had both HepQuant SHUNT® Liver Diagnostic Tests and EGDs performed. A total of 85 subjects were excluded from the final primary analysis due to limited data in certain populations (n=37) or invalid HepQuant SHUNT® Liver Diagnostic Test (n=48; an invalid test rate of 17.1%). The reasons for exclusion are shown in the table below (Table 14). Some subjects had more than one exclusion reason, so the subcategory counts in the table do not sum to the total number excluded.

Table 14.

| Reason for exclusion from primary analysis | N |
|---|---|
| Limited data in certain populations: | **37** |
| • Subjects with Child-Pugh B cirrhosis | 30 |
| • Subjects with pre-cirrhotic fibrosis | 4 |
| • Subjects with unknown Child Pugh class | 3 |
| Invalid test result | **48** |
| • Quality control failure | 16 |
| • Calibrator failure | 11 |
| • Blood samples drawn outside pre-specified sampling windows | 9 |
| • D4-cholate concentration did not peak by 90 minutes | 6 |
| • Incorrect sample time point order suspected | 3 |
| • Oral dose was not administered | 2 |
| • Inadequate blood sampling | 1 |
| • Infiltration at the intravenous catheter site | 1 |
| • Sample contamination | 1 |
| • Baseline sample was collected after the cholate dose was administered | 1 |

The final clinical validation dataset included 195 subjects aged 23-85 years with Child Pugh Class A cirrhosis with evaluable HepQuant SHUNT® Liver Diagnostic Tests.

## C. Study Population Demographics and Baseline Parameters

The demographics and baseline parameters of the primary analysis population (n=195) are shown in the table below (Table 15). The data is presented as mean ± standard deviation or as the number of subjects with a certain characteristic (percentage of subjects out of total number of subjects). Limited data are available in non-White populations.

Table 15.

| | Overall (n=195) | LEVs Absent (n=172) | LEVs Present (n=23) |
|---|---|---|---|
| Age (years) | 61.5 ± 10.4 | 61.6 ± 10.7 | 61.1 ± 8.4 |
| Sex, male | 95 (48.7%) | 83 (48.3%) | 12 (52.2%) |
| Sex, female | 100 (51.3%) | 89 (51.7%) | 11 (47.8%) |
| BMI, $kg/m^2$ | 33.1 ± 7.1 | 33.2 ± 7.1 | 32.2 ± 6.6 |
| BMI < 25 $kg/m^2$ | 26 (13.3%) | 21 (12.2%) | 5 (21.7%) |
| BMI >25 $kg/m^2$ | 169 (86.7%) | 151 (87.8%) | 18 (78.3%) |
| BMI >30 $kg/m^2$ | 124 (63.6%) | 108 (62.8%) | 16 (69.6%) |
| No Diabetes | 93 (47.7%) | 81 (47.1%) | 12 (52.2%) |
| Diabetes | 102 (52.3%) | 91 (52.9%) | 11 (47.8%) |
| White | 187 (95.9%) | 164 (95.4%) | 23 (100.0%) |
| Black | 7 (3.6%) | 7 (4.1%) | 0 (0.0%) |
| Asian | 1 (0.5%) | 1 (0.6%) | 0 (0.0%) |
| Other | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hispanic | 21 (10.8%) | 20 (11.6%) | 1 (4.4%) |
| Non-Hispanic | 174 (89.2%) | 152 (88.4%) | 22 (95.7%) |

## D. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the 297 subjects that had HepQuant SHUNT® Liver Diagnostic Tests performed. A total of 40 subjects (13.5%) reported 75 AEs during the course of the clinical trial. Of the 40 subjects who reported AEs, 11 subjects (3.7%) had 17 AEs that were determined to be related to the HepQuant SHUNT® Liver Diagnostic Test (i.e., adverse device effects, ADE). These adverse device effects and number of subjects affected (some subjects had more than one ADE) are shown in the table below (Table 16). None of the reported AEs related to the HepQuant SHUNT® Liver Diagnostic Test were considered moderate or severe.

Table 16.

| Adverse device effects | Number of subjects (% of total subjects) |
|---|---|
| Infusion site bruising | 5 (1.7%) |
| Catheter site bruise | 3 (1.0%) |
| Infusion site pain | 1 (0.3%) |
| Upper abdominal pain | 1 (0.3%) |
| Diarrhea | 1 (0.3%) |
| Contusion | 1 (0.3%) |
| Pain in extremity | 1 (0.3%) |
| Flushing | 1 (0.3%) |

2. Effectiveness Results

The analysis of effectiveness was based on 195 evaluable patients with Child Pugh A cirrhosis. The effectiveness results are shown below (Tables 17-18).

Table 17.

| | EGD – LEVs present | EGD – LEVs absent | Total |
|---|---|---|---|
| DSI > 18.3 | 23 (true positive) | 117 (false positive) | 140 |
| DSI ≤ 18.3 | 0 (false negative) | 55 (true negative) | 55 |
| Total | 23 | 172 | 195 |

Table 18.

| | Estimate | 95% confidence interval |
|---|---|---|
| Sensitivity | 100.0% | 85.2% to 100.0% |
| Specificity | 32.0% | 25.1% to 39.5% |
| Positive likelihood ratio (PLR) | 1.47 | 1.33 to 1.63 |
| Negative likelihood ratio (NLR) | 0 | 0 to 0.45 |
| Positive predictive value (PPV) | 16.4% | 10.7% to 23.6% |
| Negative predictive value (NPV) | 100.0% | 93.5% to 100.0% |
| Prevalence | 23/195 = 11.8% | |

The negative predictive value (NPV) point estimate of the HepQuant SHUNT® Liver Diagnostic Test is 100.0% (with 95% confidence intervals (CIs) of 93.5% to 100.0%) and the negative likelihood ratio (NLR) point estimate is 0 (with 95% CIs of 0 to 0.45). The results show that DSI ≤ 18.3 can effectively identify patients with Child Pugh Class A cirrhosis who are unlikely to have LEVs. The positive predictive value (PPV) point estimate of the HepQuant SHUNT® Liver Diagnostic Test is low at 16.4% (with 95% CIs of 10.7% to 23.6%) such that healthcare providers should follow the standard of care for patients with DSI > 18.3.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: age, sex and race. No meaningful differences were observed. However, the study was not specifically powered for these subgroups, some of which had small sample sizes.

4. Pediatric Extrapolation

Not applicable. The HepQuant SHUNT® Liver Diagnostic Test is intended for use in adults 22 years of age and older.

## XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 27 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

## XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Clinical Toxicology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The clinical study showed that the HepQuant SHUNT® Liver Diagnostic Test has an NPV point estimate of 100.0% (with 95% CIs of 93.5% to 100.0%) and NLR point estimate of 0 (with 95% CI of 0 to 0.45) using a cutoff of DSI 18.3 in a cohort of 195 subjects with Child Pugh Class A cirrhosis. The results show that DSI $\leq$ 18.3 can effectively identify patients with Child Pugh Class A cirrhosis who are unlikely to have LEVs. The PPV point

estimate of the HepQuant SHUNT® Liver Diagnostic Test is low at 16.4% (with 95% CIs of 10.7% to 23.6%) such that healthcare providers should follow the standard of care for patients with DSI > 18.3.

The analytical performance studies support that the HepQuant SHUNT® Liver Diagnostic Test can quantitatively measure 13C-cholate from 0.1 to 10 µM and d4-cholate from 0.1 to 9 µM in serum samples and consistently report accurate DSI results.

The results from both the analytical and clinical studies support the use of the HepQuant SHUNT® Liver Diagnostic Test to identify patients with Child Pugh Class A cirrhosis, undergoing screening or surveillance for esophageal varices, who are unlikely to have LEVs and unlikely to require EGD at the time of testing when used in conjunction with other clinical and laboratory findings.

## B. Safety Conclusions

The risks of the test are based on analytical performance testing as well as data collected in a clinical performance study conducted to support PMA approval as described above. Additionally, chemistry, manufacturing and controls for 13C-cholate and d4-cholate and safety information for Albutein-25 was considered. The HepQuant SHUNT® Liver Diagnostic Test involves administering d4-cholate orally and 13C-cholate intravenously with a human serum albumin excipient and collection of multiple blood samples via an indwelling intravenous catheter over a 90-minute period. In the clinical study, 3.7% of the safety set population experienced mild adverse events related to the administration of the HepQuant SHUNT® Liver Diagnostic Test. The chemistry, manufacturing and controls information for the 13C-cholate and d4-cholate and safety information for Albutein-25 supports safe use of these components of the test in the intended use population. The analytical and clinical performance testing was determined to be adequate to mitigate the risks of erroneous results from the test.

## C. Benefit-Risk Determination

Assessment of benefit

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. At present, there is no FDA authorized test for identifying patients with Child Pugh Class A cirrhosis who are unlikely to have LEVs. Based on the current standard of care, patients with Child Pugh Class A cirrhosis undergo EGD for screening and surveillance of LEVs. EGD is an invasive procedure that carries inherent risks, including complications associated with anesthesia. The HepQuant SHUNT® Liver Diagnostic Test, therefore, may fill an unmet medical need in identifying patients unlikely to have LEVs, allowing these patients to not require EGD (at the time of testing). Moreover, the HepQuant SHUNT® Liver Diagnostic Test is a noninvasive test compared to the invasive EGD procedure.

Assessment of risk

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Risks associated with the use of the test include the following:

- Risks associated with the test administration process:
  - Test compounds: Allergic reaction to cholate compounds, allergic reaction to human serum albumin.
  - Indwelling IV catheter: Pain with placement of the catheter, thrombosed vein, hematoma.
  - Phlebotomy: Localized pain, bruising, occasional lightheadedness, fainting, infection at the site.
  - Fasting before the test: dizziness, headache, stomach discomfort, fainting.
- Incorrect test results: False negative and false positive results
  - False negative test result: A false negative test result could lead a clinician to incorrectly conclude that a patient is unlikely to have LEVs and not send the patient for screening EGD, which could have adverse clinical outcomes. If the patient is not sent for EGD, identification of high-risk varices would be missed, preventing the opportunity for appropriate treatment and management to prevent variceal hemorrhage and subsequent complications, including bacterial infection and death.
  - False positive test result: A false positive test result could lead a clinician to incorrectly conclude that a patient cannot be ruled out as unlikely to have LEVs and send the patient for screening EGD, which would have minimal adverse outcomes. Sending the patient for EGD would carry the risks of the current standard of care, which are the risks associated with the EGD procedure.

Assessment of benefit-risk

The safety profile of the test, as demonstrated in the clinical study, supports the conclusion that administration of the HepQuant SHUNT® Liver Diagnostic Test exposes subjects to minimal risk. To further minimize risk, the test will be administered by healthcare professionals with appropriate experience/expertise who will undergo onboard training prior to conducting the test.

The risks of false negative and false positive results are mitigated by the analytical and clinical performance studies, which support that the HepQuant SHUNT® Liver Diagnostic Test consistently generates accurate results. In addition, the product labeling includes an indications for use and limitations that make clear who the test should and should not be used in, instructions for how to conduct the test (as validated in the performance studies), and the analytical and clinical performance that can be expected for the test.

Patient perspectives

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

Conclusion regarding benefit-risk

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for the use of the HepQuant SHUNT® Liver Diagnostic Test when used in accordance with the indications for use.

### D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this test when used in accordance with the indications for use. The data from the analytical and clinical performance studies support the safety and effectiveness of the HepQuant SHUNT® Liver Diagnostic Test to identify patients with Child Pugh Class A cirrhosis, undergoing screening or surveillance for esophageal varices, who are unlikely to have LEVs and unlikely to require EGD at the time of testing, when used in conjunction with other clinical and laboratory findings.

## XV. CDRH DECISION

CDRH issued an approval order on June 18, 2026.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

## XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XVII. REFERENCES

Not applicable.