Contrast Enhanced Characterization of Liver Lesions – A Phase III Clinical Trial

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Early Clinical Trials

- Numerous clinical trials involving ultrasound contrast agents (UCAs) were performed in the 1990s
- Albunex™ (Mallinckrodt Medical, Inc., St. Louis, MO) was the first UCA to gain FDA approval in 1994
  - Approved only for echocardiographic applications (cardiac chamber opacification and endocardial border definition)
  - No longer being marketed

Early UCA Clinical Trials

- Early clinical trials for radiologic applications were designed to compare the accuracy of contrast-enhanced ultrasound imaging (CEUS) to contrast-enhanced CT (CECT) as a gold standard
  - These trials failed to lead to FDA approval
  - Lack of approval was often related to difficulties in comparing CEUS findings to CECT results

Problems related to using CECT as the gold standard in CEUS clinical trials

- **False positive CEUS studies:** If CEUS identified a liver mass that was not detected with CECT then CEUS was considered wrong
- **False negative CEUS studies:** If a liver mass was identified on both modalities, to confirm that it was the same mass the two lesions had to be within 2 cm of each other. If not, it was assumed that CECT was correct

Current Status of UCAs in the USA

- Two UCAs are currently FDA approved for echocardiography applications
  - Optison® (GE Healthcare) was approved in 1997
  - Definity® (Lantheus Medical Imaging) was approved in 2001
- Imagent® (Alliance Pharmaceutical Corp.) was approved in 2002 but is not being marketed

The AIUM Ultrasound Contrast Agent Task Force

- In 2007 the U.S. FDA approached the AIUM to request that the organization develop recommendations for future CEUS clinical trials
- The AIUM convened an *Ultrasound Contrast Agent Task Force* comprised of physicians, engineers and sonographers who had extensive UCA expertise
- The Task Force developed an outline that described what they considered the critical components of CEUS clinical trials
The AIUM Ultrasound Contrast Agent Task Force

• The report described appropriate end points for assessment of UCA efficacy for liver lesion characterization
  - The recommendations emphasized that CEUS should be compared to conventional (non-contrast) US

• The report included recommendations to ensure uniformity between centers and enhance reproducibility of CEUS results
  - detailed examination procedures
  - equipment criteria
  - training guidelines

The AIUM statement on the use of US contrast agents:

“…the lack of availability of contrast-enhanced ultrasound in the United States hinders the delivery of optimal diagnostic imaging to our patients, resulting in an adverse impact on clinical care.”

JUM, June 2007

The FDA accepted the Task Force’s concepts in principal and in June ’07 the recommendations were published in the Journal of Ultrasound in Medicine

The AIUM Ultrasound Contrast Agent Task Force

2007: The Black Box Warning

• In October, 2007 the FDA imposed a black box warning on Definity and Optison that highlighted the risk of “serious cardiopulmonary reactions” within 30 minutes of administration

• Mandated 30 minute monitoring period after UCA administration in all patients

• Listed multiple new contraindications:
  - Worsening or clinically unstable heart failure
  - Acute myocardial infarction or acute coronary syndrome
  - Serious ventricular arrhythmia or high risk for arrhythmias due to QT prolongation
  - Respiratory failure
  - Severe emphysema, pulmonary emboli, or other conditions that cause pulmonary hypertension

Complications vs Pseudocomplications

• Complications after any medical procedure may be attributable to the procedure itself or may be due to the underlying disease (“pseudocomplication”)

• Major cardiac events, including death, are relatively common in patients who are sick enough to warrant invasive testing

• Echocardiography is the procedure of choice (and often the only diagnostic procedure possible) in critically ill patients
  - Common indications for echocardiographic evaluation include “hypotension,” “shock,” “status post cardiac arrest,” and “tamponade.”

• It is important to differentiate between association and causation; without knowledge of the ambient event rate, any incremental risk of contrast agents cannot be known

• A study of “complications” that occurred 24h before to 72h after cardiac catheterizations found an event rate of 0.81% before the procedure and 0.81% in post-procedure

Perspectives re: the risk of UCAs

• Even if all of the reported events were related to UCA administration (which is unlikely, because a significant proportion must be attributable to pseudocomplications), it would indicate an ~ 1:500,000 risk of death

• To put this number in proper perspective:
  - The mortality rate for diagnostic coronary angiography is ~1:1,000, and the risk of myocardial infarction or death with exercise treadmill testing is approximately 1:2,500
  - The lifetime risk of fatal malignancy after stress single-photon emission CT or radionuclide ventriculograms is estimated at 1:1,000 to 1:10,000

• Despite these finite risks of serious complications, coronary angiography, exercise testing, and nuclear scintigraphic examinations are performed without trepidation, and with good reason - all allow early diagnosis and treatment of coronary artery disease - the primary cause of death in the U.S.

FDA Cardiovascular-Renal Advisory Panel

• In June, 2008 the FDA convened a meeting of its Cardiovascular and Renal Drug Advisory Committee to review the safety of UCAs
  - This meeting demonstrated the FDA’s willingness to be more open to additional discussions re: the future of UCAs
  - Included representatives from the cardiac and radiologic communities as well as UCA manufacturers

• Attendees had an opportunity to discuss how they could work together to:
  - Convince the FDA to revise the Black Box Warning; and
  - Encourage companies to submit clinical trial proposals to the FDA for non-cardiac applications of UCAs

- Retrospective, 13 sites (January 1, 2001-September 30, 2007)
- 66,164 doses of Definity and 12,219 doses of Optison (5% of transthoracic/28% stress)
- Severe adverse reactions in 8 patients (0.01%)
- Anaphylactoid reactions in 4 patients (0.006%)
- No deaths
- No SAE in hospitalized patients

**Conclusion:** The incidence of severe adverse reactions to UCAs is lower than, or similar to that reported for contrast agents commonly used in other cardiac imaging tests


May 2008: FDA Revised Product Labeling
- The October 2007 “black box” product label changes were substantially revised in May, 2008
- The original “Contraindications” were changed to “Warnings”
- Mandated 30 minute monitoring period following contrast administration only in patients with pulmonary hypertension or critically ill

Other developments
- Recently published data regarding toxic renal effects from the use of MRI contrast agents (e.g. gadolinium)
- Issues related to excessive ionizing radiation exposure from overuse of CT imaging
- The FDA has recently initiated several programs designed to reduce unnecessary radiation exposure from medical imaging examinations
  - Primary focus is on CT, nuclear medicine and fluoroscopy

**These recent developments have helped to advance the utilization of both conventional ultrasound as well as CEUS around the world**

Current status of UCAs
- In Europe, Asia and many other regions around the world UCAs are approved for general radiologic applications
- Numerous post-approval investigations have shown that compared to CECT, CEUS is more cost-effective and safe
- There is an abundance of peer-reviewed scientific articles that support these findings

European Guidelines for the Use of Contrast Enhanced Ultrasound (2008 Update): Liver
- Focal liver disease has evolved into the single most important application of CEUS (outside echocardiography)
- Marked improvement over conventional US in both the detection and characterization of focal liver lesions
- CEUS provides real-time data (compared to the intermittent nature of CECT)
- CEUS is equal to, or exceeds CECT in diagnostic accuracy

**Renewed interest in UCAs**
As a result of the concerted and collaborative efforts by the AIUM and it’s Ultrasound Contrast Agent Task Force and the International Contrast Ultrasound Society (ICUS) there has been renewed interest by the UCA industry to initiate new clinical trials that will lead to FDA approval of UCAs for non-cardiac applications
Definity

• Since its release in 2001, more than 2 million cardiac patients have received Definity

• Lantheus Medical Imaging (N. Billerica, MA) has shown an interest in seeking approval for a non-cardiac application from the FDA for their agent Definity®

GE Healthcare

• GE Healthcare (Buckinghamshire, England) has indicated that they have renewed interest in moving forward with clinical trials designed to gain FDA approval for non-cardiac applications
  – The time frame for these investigations has not been disclosed

SonoVue

• Bracco (Milan, Italy) began selling SonoVue in Europe in 2001
  – More than 1 million vials have been shipped

• Bracco is planning several clinical trials in Europe to support expanded applications for SonoVue including:
  – Myocardial perfusion
  – Guiding prostate biopsy procedures
  – Monitoring cancer treatment

SonoVue

• Bracco has initiated two multicenter clinical trials this year to collect data for a regulatory submission of SonoVue to the U.S. FDA
  – Bracco was in the final stages of a regulatory submission for SonoVue in 2007, but withdrew the application after the FDA’s black box warnings were imposed on Definity and Optison

• CEUS clinical trial for liver lesion characterization
  – Patient recruitment has begun

SonoVue clinical trials (BR1-128 / BR1-130)*

CHARACTERIZATION OF FOCAL LIVER LESIONS WITH SONOVUE®-ENHANCED ULTRASOUND IMAGING:
A PHASE III, INTRAPATIENT COMPARATIVE STUDY VERSUS UNENHANCED ULTRASOUND IMAGING USING HISTOLOGY OR COMBINED IMAGING/CLINICAL DATA AS TRUTH STANDARD

SonoVue clinical trials: Study Design

• Phase III, Multicenter, Open Label, Nonrandomized Study
• Investigational sites in USA, Canada and China
• Training subjects
  – Up to 10 subjects will be enrolled at each site for the characterization of FLLs as training cases
  – Data on training subjects will be included in safety analysis only
• Efficacy subjects
  – 156 efficacy subjects will be enrolled to obtain 140 evaluable subjects (~84 subjects with a malignant lesion)
Unique Characteristics of the SonoVue Trials

The BR1-128 and -130 trials are the first to be consistent with these key documents:


SonoVue clinical trials: Enrollment Expectations

- Efficacy Subjects
  - Enrollment is competitive
  - Minimum of 12 subjects/site
  - Maximum of 30 subjects/site
  - Enrollment
    - First patient enrolled: September 2009
    - Enrollment completion: September 2010 (estimated)

SonoVue clinical trials: Truth Standard

- Met protocol requirements for truth standard
- Histology/Pathology
  - Yes
  - No
- Inadequate truth standard
  - FLL < 1cm
  - FLL > 1cm
- Follow for 6 Months
  - Yes
  - No
- * For HCC > 2 cm only CE-CT or CE-MRI is required

SonoVue clinical trials: BR1-128 Site Status

- 17 sites contacted
  - 1 USA site declined participation
  - 14 USA sites remain
  - 2 China sites planned
  - Actively enrolling sites (n=6)
    - Barr, Goldberg, Grant, Mattrey, Robbin, Tublin

SonoVue clinical trials: BR1-128 Sites (N= 14)

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<th>Institution</th>
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<tr>
<td>Goldberg</td>
<td>UC Philadelphia, PA</td>
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<tr>
<td>Sun</td>
<td>UCSF, San Francisco, CA</td>
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<tr>
<td>Grant</td>
<td>UC, Los Angeles, CA</td>
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<tr>
<td>Tublin</td>
<td>U of Pittsburgh, Pittsburgh, PA</td>
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<td>Robbin</td>
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<td>Sun</td>
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<td>Mattrey</td>
<td>UCSD, San Diego, CA</td>
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<td>McCahan</td>
<td>UC Davis Sacramento, CA</td>
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<td>Di Salvo</td>
<td>U of Pittsburgh, Pittsburgh, PA</td>
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SonoVue clinical trials: BR1-130 Site Status

- 21 sites contacted
  - 5 sites declined participation (3 in USA, 2 in Canada)
  - 12 North American sites remain
  - 3 China sites planned
SonoVue clinical trials: BR1-130 Sites (N=12)

Investigator

Acar
University Hosp
Cleveland, OH

Bhush
Ochsner Clinic
New Orleans, LA

Chong
UNC
Chapel Hill, NC

Cronan
Rhode Island
Providence, RI

Fletcher
Vanderbilt
Nashville, TN

Investigator

Haystead
Stanford
Palo Alto, CA

Lane
Univ MD
Baltimore, MD

Quiroz
Froedert
Milwaukee, WI

Lane
Univ MD
Baltimore, MD

Investigator

Kim
Toronto General
Toronto

Milot
Sunnybrook
Toronto

Conclusions

• Practitioners in numerous disciplines have come together to educate the FDA relative to its approval process and the FDA appears to be listening
  – As a result, a FDA Phase III trial for liver lesion characterization has been initiated
• Within the next several years UCAs will become available for non-cardiac applications
• The routine use of UCAs will improve patient care through more accurate and cost-effective diagnoses of a variety of abnormalities