Aims and objectives

Aim:
To compare the efficacy of orally-administered manganese chloride tetrahydrate CMC 001 and Gd-chelate-enhanced MR images for the evaluation of focal liver lesions.

Introduction:
MRI is an important modality for the detection and characterization of focal liver lesions (FLL), whether primary tumors, such as hepatocellular carcinoma, or secondary tumors, such as metastases. Although an unenhanced MR of the liver is superior to an unenhanced CT for this purpose, the use of intravenous contrast material with either modality significantly improves both the detection and characterization of FLL. Patients with renal insufficiency, however, are commonly referred for the evaluation of FLL and in this particular clinical scenario, and for different reasons, neither an iodinated agent for CT nor a gadolinium agent for MR are indicated.

The current MR imaging options of evaluating patients for FLL include: (a) an unenhanced MR, and (b) Feraheme, an iron-based blood pool agent. The latter option, however, is an off-label application of a drug indicated for the treatment of iron-deficiency anemia.

CMC 001 is a manganese-based orally-administered MR contrast agent that is taken up by hepatocytes with very little absorption and excretion by the kidney [1-7]. Because CMC 001 consists of manganese (II) chloride tetrahydrate combined with L-alanine and vitamin D3 as promoters of gastrointestinal absorption (Figure 2), it is efficiently taken up by hepatocytes after absorption from the gastrointestinal tract, predominantly in the small bowel.

From the liver, the manganese is excreted into the bile and eventually eliminated in the stool. The route of CMC 001 administration, uptake and excretion means that only minute amounts of the agent enter the systemic circulation and, as a result, there is minimal renal absorption and excretion. Due to the retention of CMC 001 in the hepatocytes and the paramagnetic properties of manganese, the contrast agent vividly enhances the liver parenchyma in MR imaging.

CMC 001 has been evaluated in six phase I and phase II clinical trials and in one study as part of a compassionate use program. Since these studies were done at different clinical sites, parameters for efficacy were not evaluated in a standardized fashion. A subset of these subjects with liver metastases and obviously without renal insufficiency, also underwent MRI with a gadolinium-based contrast agents [7].
The current blinded reader study was performed on the subset data collected from these studies to gain information about the efficacy of CMC 001 using a standardized methodology, particularly in comparison to a gadolinium-based MR contrast agent. All potential bias was removed by having the reads performed by a single reader, blinded to all patient parameters. The goal of this review was to provide guidance for planning future phase III studies.

**Hypothesis:**
The hypothesis for this study is that compared to Gd-enhanced MRI, CMC 001-enhanced MRI demonstrates similar efficacy in: (a) lesion detection, (b) lesion visualization or conspicuity and (c) lesion delineation.

**Images for this section:**

![T2-Pre](image1.png) ![T1-Post](image2.png)

**Fig. 1:** Figure 1: T2-weighted image pre-contrast and T1-weighted image post-contrast following the oral administration of CMC 001. Note the lobulated lesion in segment VII (arrow), which demonstrates high signal intensity on T2 and no excretion of contrast material on T1.
Fig. 2: The three components of CMC 001 include: (a) manganese chloride, the paramagnetic molecule, (b) L-alanine, and (c) vitamin D3. The latter two components facilitate gastrointestinal absorption.
Methods and materials

Methods and Materials:

**Subjects:**
The study consisted of a total of 49 subjects with liver metastases, including 23 men (47%) and 26 women (53%), with a mean age of 48 years (range 17-83 years). The study population included 27 patients from four Phase II or III clinical trials (26 patients with liver metastases and one healthy subject), as well as 22 patients with liver metastases who were studied as part of a compassionate use program.

**Inclusion Criteria:**

- All subjects with liver metastases who were included in early phase studies with CMC 001-enhanced MRI or
- All subjects with liver metastases who underwent CMC 001-enhanced MRI for compassionate use, and
- Have both CMC 001-enhanced MRI and Gd-enhanced MRI data available.

**Exclusion Criteria:**

- Imaging data of subjects who do not have both CMC 001-enhanced MRI and Gd-enhanced MRI data available for independent evaluation.

**Image acquisition:**

All studies consisted of pre-contrast and post-contrast-enhanced T1 & T2-weighted images acquired in the axial plane using FSE/TSE pulse sequences at 1.5 T as depicted in Table 1.

All patients underwent the oral administration of either 800 mg (n=3) or 1600 mg (n=46) of CMC 001. Post-contrast imaging was performed at 2.5-4.0 hours following complete oral intake of the contrast agent. A summary of the six different studies, four of which were multi-center, is shown in Table 2. Note that studies CMC-P001 and CMC-P010 were not included in this subset analysis since they were conducted in healthy subjects.

**Blinded Reads:**
All image sets were evaluated by a single reader, with fellowship training in abdominal imaging and more than 25 years of MRI experience. The reader was blinded to all patient information, the name and location of each institution, the indication for the study, scanner details, the CMC 001 dosage and the timing of the post-contrast examination. Four
separate reads were performed as described below. Note that Read 4 which included Gd-enhanced MRI was the basis for this subset analysis.

**Image Quality Technical Assessment:**
During each assessment, the Blinded Reader began by rating the overall quality of the image data. The electronic case report form (eCRF) provides three general quality categories: *Optimal, Sub-Optimal, and Not Readable*. If the Blinded Reader selected either *Optimal* or *Sub-Optimal*, the independent assessment was allowed to begin. If the Blinded Reader described the overall image quality as *Not Readable*, the Blinded Reader was not allowed to perform the assessment. An explanation as to why the image data are not evaluable was forced, either from selections provided or as free-text entered by the Blinded Reader.

The Blinded Reader was also asked whether artifacts were present, and if present, if there was a problem with the evaluation of the scans due to these artifacts. If yes, the Blinded Reader was asked to provide details within a free text comment field.

**Efficacy Criteria:**

*Lesion Detection*
As the primary efficacy variable, to demonstrate if CMC 001 demonstrates similar ability to detect liver metastases compared to Gd-enhanced MRI, each lesion up to a maximum of ten (10) lesions was evaluated and the Blinded Reader was asked to answer the following question: "Using the 5-point scale below, please rate your confidence in liver lesion detection using the images provided.

1: The lesion is detected with low confidence.
2: The lesion is detected with moderately low confidence.
3. The lesion is detected with moderate confidence.
4: The lesion is detected with moderately high confidence.
5: The lesion is detected with high confidence."

Diagnostic confidence is based on the information available from the MRI images, including;

- number of lesions
- lesion size
- visual evaluation of lesion(s)

The longest dimension of each lesion was measured (in mm).
**Lesion Visualization:**
To determine if CMC 001 demonstrates similar lesion visualization or conspicuity compared to Gd-enhanced MRI, each lesion up to a maximum of ten (10) lesions was evaluated and the Blinded Reader was asked to answer the following question:

"Using the 4-point scale below, rate your confidence in liver lesion visualization using the images provided.

1: Visualization of the lesion is poor.
2: Visualization of the lesion is fair.
3: Visualization of the lesion is good.
4: Visualization of the lesion is excellent."

**Lesion Margin Delineation:**
To determine if CMC 001 demonstrates similar delineation of the margins of a lesion compared to Gd-enhanced MRI, delineation of each lesion, up to a maximum of ten (10) lesions were evaluated and the Blinded Reader was asked to answer the following question:

"Using the 4-point scale below, rate your confidence in your ability to delineate the margins of the lesion using the images provided.

1: Delineation of the margins of the lesion is poor.
2: Delineation of the margins of the lesion is fair.
3: Delineation of the margins of the lesion is good.
4: Delineation of the margins of the lesion is excellent."

**Quantitative Measurements:**
Regions-of-interest (ROI) were measurements were drawn over a uniform and representative portion of each lesion for up to a maximum of ten lesions as well as the adjacent non-tumorous liver parenchyma, main portal vein and common bile duct on CMC 001-enhanced MR images in order to calculate the following parameters:

- signal-to-noise ratio (SNR)
- contrast-to-noise ratio (CNR)
- lesion-to-liver contrast ratio

**Statistical Methods:**
The statistical methods used to analyze both the qualitative and quantitative data is summarized in Table 3.
Table 2: Details of the six different clinical studies, the data of which was combined in the current study.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TITLE</th>
<th>CENTER</th>
<th>PHASE</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC-P001</td>
<td>The safety of CMC 001 in liver MRI in healthy volunteers</td>
<td>Gentofte University Hospital (Hellerup, Denmark) Copenhagen University Hospital (Hertlev, Denmark)</td>
<td>I</td>
<td>Healthy volunteer males.</td>
</tr>
<tr>
<td>CMC-P002</td>
<td>Evaluation and diagnostic quality of CMC 001 in liver MRI in subjects with known liver metastases</td>
<td>UMNC (Nijmegen, The Netherlands)</td>
<td>II (randomized, parallel group, open-label)</td>
<td>M &amp; F &gt;18 yrs with liver metastases verified by imaging technique other than that investigated</td>
</tr>
<tr>
<td>CMC-P003</td>
<td>Evaluation of the diagnostic efficacy of CMC 001 in liver MRI in subjects with liver metastases.</td>
<td>Charité-Universitätsmedizin (Berlin, Germany)</td>
<td>III (randomized crossover)</td>
<td>M &amp; F &gt;18 yrs with not more than 10 liver metastases</td>
</tr>
<tr>
<td>CMC-P004</td>
<td>Evaluation of the diagnostic quality of CMC 001 in liver MRI in subjects with liver metastases in comparison to Gd-BOPTA.</td>
<td>Karolinska Institutet, Karolinska University Hospital Huddinge (Stockholm, Sweden)</td>
<td></td>
<td>M &amp; F &gt;18 yrs with not more than 10 liver metastases</td>
</tr>
<tr>
<td>CMC-P005</td>
<td>Evaluation of the diagnostic efficacy of CMC 001 in MR cholangiography in subjects with suspected liver lesions.</td>
<td>Sahlgrenska University Hospital, Othenburg University (Gothenburg, Sweden)</td>
<td>II (randomized, parallel group, open-label)</td>
<td>M &amp; F &gt;18 yrs with suspected liver lesions as indicated by US or CT</td>
</tr>
<tr>
<td>CMC-P006</td>
<td>Evaluation of the imaging quality of CMC 001 in liver MRI in healthy volunteers.</td>
<td>Karolinska University Hospital Huddings (Stockholm, Sweden)</td>
<td>Single-center, double blind, randomized, crossover</td>
<td>Healthy M &amp; F &gt;18 yrs</td>
</tr>
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</table>

Table 1: Description of the four different read sessions.

<table>
<thead>
<tr>
<th>READ TYPE</th>
<th>SERIES INCLUDED</th>
<th>MINIMUM SCAN REQUIREMENTS FOR READ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read 1 (Pre-contrast alone)</td>
<td>Ax T1-Pre, Ax T2-Pre</td>
<td>Axial T1-weighted FSE/TSE sequence</td>
</tr>
<tr>
<td>Read 2 (Post-contrast alone)</td>
<td>Ax T1-CMC, Ax T2-CMC</td>
<td>CMC 001-enhanced: Axial T1-weighted FSE/TSE sequence</td>
</tr>
<tr>
<td>Read 3 (Combined Pre- + Post-contrast)</td>
<td>Ax T1-Pre, Ax T2-Pre, Ax T1-CMC, Ax T2-CMC</td>
<td>Axial T1-weighted FSE/TSE sequence &amp; CMC 001-enhanced: Axial T1-weighted FSE/TSE sequence</td>
</tr>
<tr>
<td>Read 4 (Gd-enhanced MRI)</td>
<td>Ax T1-Pre, Ax T1-Post-Gd, Ax T2-Pre, Ax T2-Post-Gd</td>
<td>MRI-enhanced with Gadolinium-based contrast agent: Axial T1-weighted FSE/TSE sequence</td>
</tr>
<tr>
<td>OBJECTIVE</td>
<td>TEST HYPOTHESIS</td>
<td>TEST</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>CMC-001 enhanced MRI demonstrates similar lesion detection and visualization compared to Gd-enhanced MRI</td>
<td>$H_0: \mu_D = 0$ vs. $\mu_D \geq 0$</td>
<td>Wilcoxon one sample rank sum test and the paired t-test.</td>
</tr>
<tr>
<td>CMC-001 demonstrates similar delineation of the margins lesions compared to Gd-enhanced MRI.</td>
<td>$\mu_D$ is the mean difference in the responses between CMC 001-enhanced and Gd-enhanced MR image evaluation</td>
<td>Non-visualization vs. good/excellent visualization (score $&gt; 3$)</td>
</tr>
</tbody>
</table>

Table 3

Max = 10 liver lesions
Results

Results:

Image Quality Assessment:
Overall, the image quality on pre-contrast plus CMC 001-enhanced MR images demonstrated optimal quality in 86% compared to 67% in Gd-enhanced MRI. This difference was statistically significant (p<0.0001)(Table 4). A breakdown of the various artifacts reveals that respiratory motion was the main artifact encountered with unenhanced plus CMC 001-enhanced MRI, while cardiovascular motion was the main artifact encountered with Gd-enhanced MRI (Table 5). This is likely due to the high signal intensity in the heart and blood vessels post-Gd administration.

Detection Confidence:
Overall, the confidence in lesion detection was high, with scores in the "moderately high-high confidence" category in 89% for both pre-contrast plus CMC 001-enhanced MRI and Gd-enhanced MRI (Table 6).

Confidence in Lesion Visualization:
There was no significant difference in confidence in lesion visualization comparing pre-contrast plus CMC 001-enhanced MRI to Gd-enhanced MRI (Table 7).

Lesion Margin Delineation:
There was no significant difference in delineation of the margins of malignant lesions comparing pre-contrast plus CMC 001-enhanced MRI to Gd-enhanced MRI (Table 8).

Quantitative Analysis:
Pre- and post-contrast signal intensity characteristics of the liver parenchyma and common bile duct (CBD) before and after the oral administration of 800 mg of CMC 001 is shown in Figure 3. Note that on T1-weighted images, the signal intensity of liver parenchyma slightly increases while the signal intensity of the CBD markedly increases post-contrast. On T2-weighted images, there was no significant change in the signal intensity of the liver parenchyma but a significant decrease in the signal intensity of the CBD post-contrast.

Pre- and post-contrast signal intensity characteristics of the liver parenchyma and common bile duct (CBD) before and after the oral administration of 1600 mg of CMC 001 is shown in Figure 4. Note that on T1-weighted images, the signal intensity of both liver parenchyma and the CBD markedly increases post-contrast. On T2-weighted images,
there was no significant change in the signal intensity of the liver parenchyma but a significant decrease in the signal intensity of the CBD post-contrast (Figure 5).

Images for this section:

Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>n</th>
<th>Optimal</th>
<th>Suboptimal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Image Quality</td>
<td>Pre + CMC 001</td>
<td>63</td>
<td>54 (86%)</td>
<td>9 (14%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>-enhanced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gd -enhanced</td>
<td>55</td>
<td>37 (67%)</td>
<td>18 (33%)</td>
<td></td>
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Table 5

<table>
<thead>
<tr>
<th>Artifact</th>
<th>Pre + CMC 001 -enhanced</th>
<th>Gd -enhanced</th>
</tr>
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<tbody>
<tr>
<td>• n</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>• Ascites Motion</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>• Respiratory Motion</td>
<td>21 (88%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>• Cardiovascular Motion</td>
<td>1 (4%)</td>
<td>19 (73%)</td>
</tr>
<tr>
<td>• Other</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Comparison</td>
<td>n</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td><strong>Confidence in Lesion Detection</strong></td>
<td>Pre + CMC 001 -enhanced</td>
<td>197</td>
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<tr>
<td></td>
<td>Gd-enhanced</td>
<td>170</td>
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</table>

Table 6

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>n</th>
<th>Poor – Fair</th>
<th>Good – Excellent</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confidence in Lesion Visualization</strong></td>
<td>Pre + CMC -enhanced</td>
<td>81</td>
<td>8 (10%)</td>
<td>73 (90%)</td>
<td>1.0000</td>
</tr>
<tr>
<td></td>
<td>Gd-enhanced</td>
<td>85</td>
<td>9 (11%)</td>
<td>76 (89%)</td>
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</table>

Table 7

<table>
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<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>n</th>
<th>Poor – Fair</th>
<th>Good – Excellent</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Lesion Margin Delineation</strong></td>
<td>Pre + CMC -enhanced</td>
<td>81</td>
<td>11 (14%)</td>
<td>70 (86%)</td>
<td>0.6676</td>
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<tr>
<td></td>
<td>Gd-enhanced</td>
<td>85</td>
<td>14 (16%)</td>
<td>71 (84%)</td>
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</table>

Table 8
Fig. 5: Axial images of the common bile duct following the oral administration of CMC 001 demonstrates low signal intensity on the T2-weighted image and high signal intensity on the T1-weighted image (arrows).
Conclusion

Conclusions:

This initial analysis with orally-administered manganese chloride tetrahydrate (CMC 001) demonstrates that when combined with pre-contrast images, there is similar image quality, as well as confidence in lesion detection and delineation compared to Gd-enhanced images. Post-contrast T1-weighted imaging with 1600 mg demonstrates significant enhancement of the liver parenchymal and CBD.

Personal information

References