A Novel Inherently Radiopaque Bead for Transarterial Embolization to Treat Liver Cancer – A Pre-clinical Study

Rafael Duran,¹² Karun Sharma,³ Matthew R Dreher,¹ Koorosh Ashrafi,¹ Sahar Mirpour,¹ MingDe Lin,⁶ Ruediger E Schernthaner,¹² Todd R Schlachter,¹² Vania Tacher,¹ Andrew L Lewis,⁵ Sean Willis,¹ Mark den Hartog,⁷ Alessandro Radaelli,⁷ Ayele H Negussie,⁵ Bradford J Wood,⁸ Jean-François H Geschwind¹²

1. Russell H Morgan Department of Radiology and Radiological Science, Division of Vascular and Interventional Radiology, Johns Hopkins Hospital, Baltimore, MD, USA
2. Department of Diagnostic Radiology and Imaging Science, Yale University School of Medicine, New Haven, CT, USA
3. Department of Diagnostic Imaging and Radiology, Children’s National Medical Center, Washington, DC, USA
4. Biocompatibles Inc (a BTG International group company), Oxford, CT, USA
5. Biocompatibles UK Ltd, a BTG International group company, Farnham, Surrey, United Kingdom
6. U/S Imaging and Interventions (UII), Philips Research North America, Briarcliff Manor, NY, USA
7. iXR, Philips Healthcare, Best, The Netherlands
8. Center for Interventional Oncology, Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD, USA

A clinical need exists to directly visualise embolic materials. However, previous imageable bead prototypes did not receive widespread adoption due to handling and administration challenges arising from their:
- Increased density
- Aggregation potential
- Insufficient imaging visibility

**DC Bead LUMI™** have been developed using the same chemistry as DC Bead™ with the addition of covalently bonded radiopaque moiety to provide a high degree of inherent radiopacity, equivalent to that of soluble iodinated contrast agents
- DC Bead LUMI™ are more dense than DC Bead™ and require suspension in 100% contrast for delivery
- During administration, DC Bead LUMI™ are not discernable from the contrast media they are suspended in, but become visible as they accumulate in the vessel and contrast clears (In-vitro testing suggests visibility in vessels ≥0.4mm with X-ray single-shot)*
- DC Bead LUMI™ are visible on all X-ray modalities, with CBCT offering the greatest visibility and X-ray single-shot offering better visibility than fluoroscopy
- DC Bead LUMI™ may offer intra-procedural benefits in terms of endpoint determination, discovery of regions of under-treatment and identification of non-target embolisation
- DC Bead LUMI™ may offer post-procedural benefits in terms of optimising post-procedure patient care and informing future treatment strategies

*Early clinical experience suggests LUMI may be visible in smaller diameter vessels

**Study Design**

**Bench-testing experiments**
- DC Bead™ vs DC Bead LUMI™
- DC Bead LUMI™ radiopaque drug-eluting beads – developed based on the DC Bead™ platform – were compared to DC Bead™ for the following:
  - Bead size and distribution
  - Equilibrium water content (EWC)
  - Density
  - X-ray attenuation
  - Iodine distribution (micro-CT)
  - Suspension (settling times in contrast)
  - Catheter deliverability
  - In-vitro penetration depth
- Image analysis was performed by two experienced board-certified interventional radiologists

**In-vivo experiments - VX2 liver tumour model**
- N=15
- VX2 tumour model used in left lobe (tumour grown to about 2cm)
- Three randomised groups:
  1. DC Bead™ + soluble contrast medium (iodixanol, 320 mgI/ml)
  2. DC Bead LUMI™ + soluble contrast medium (iodixanol, 320 mgI/ml)
  3. DC Bead LUMI™ + dextrose* (dextrose in water 50%)

* Dextrose was chosen as a radiolucent alternative to contrast, providing higher viscosity and density (specific gravity: 1.17) and allowing for a better suspension than saline

- Image analysis was performed by six experienced board-certified interventional radiologists
- Imaging modalities included
  - Fluoroscopy
  - X-ray single-shot
  - CBCT

**Key Messages:**

DC Bead LUMI™ are inherently radiopaque and have been developed to improve on the limitations of previous imageable bead prototypes. They offer several advantages in terms of:

- Improved visibility during and after embolisation procedures
- Enhanced ability to determine embolic endpoint and identify under-treated or non-target embolised regions
- Potential for optimising post-procedural care and informing future treatment strategies

DC Bead LUMI™ may offer both intra-procedural and post-procedural benefits, making them a promising tool for transcatheter embolisation treatments.

**Background**

A clinical need exists to directly visualise embolic materials. However, previous imageable bead prototypes did not receive widespread adoption due to handling and administration challenges arising from their:

- Increased density
- Aggregation potential
- Insufficient imaging visibility

**Objective**

To characterise DC Bead LUMI™ in terms of:

- Physico-mechanical properties
- Deliverability
- Imaging visibility in a rabbit VX2 liver tumour model

**Background Objective**

DC Bead LUMI™ have been developed using the same chemistry as DC Bead™ with the addition of covalently bonded radiopaque moiety to provide a high degree of inherent radiopacity, equivalent to that of soluble iodinated contrast agents

- DC Bead LUMI™ are more dense than DC Bead™ and require suspension in 100% contrast for delivery
- During administration, DC Bead LUMI™ are not discernable from the contrast media they are suspended in, but become visible as they accumulate in the vessel and contrast clears (In-vitro testing suggests visibility in vessels ≥0.4mm with X-ray single-shot)*
- DC Bead LUMI™ are visible on all X-ray modalities, with CBCT offering the greatest visibility and X-ray single-shot offering better visibility than fluoroscopy
- DC Bead LUMI™ may offer intra-procedural benefits in terms of endpoint determination, discovery of regions of under-treatment and identification of non-target embolisation
- DC Bead LUMI™ may offer post-procedural benefits in terms of optimising post-procedure patient care and informing future treatment strategies

*Early clinical experience suggests LUMI may be visible in smaller diameter vessels
A clinical need exists to directly visualise embolic materials. However, previous imageable bead prototypes did not receive widespread adoption due to handling and administration challenges arising from their:

- Increased density
- Aggregation potential
- Insufficient imaging visibility

To characterise DC Bead LUMI™ in terms of:

- Physico-mechanical properties
- Deliverability
- Imaging visibility in a rabbit VX2 liver tumour model

DC Bead LUMI™ have been developed using the same chemistry as DC Bead™ with the addition of covalently bonded radiopaque moiety to provide a high degree of inherent radiopacity, equivalent to that of soluble iodinated contrast agents.

- DC Bead LUMI™ are more dense than DC Bead™ and require suspension in 100% contrast for delivery
- During administration, DC Bead LUMI™ are not discernable from the contrast media they are suspended in but become visible as they accumulate in the vessel and contrast clears (*In-vitro* testing suggests visibility in vessels ≥0.4mm with X-ray single-shot)

During administration, neither DC Bead™ nor DC Bead LUMI™ could be distinguished from soluble contrast

- The visibility vanished quickly with DC Bead™, whereas DC Bead LUMI™ were still visible after contrast washout
- DC Bead LUMI™ with contrast significantly increased visibility on X-ray single shot compared to DC Bead™ with contrast in target and non-target arteries (p=0.0043)
- DC Bead LUMI™ demonstrated better visibility on CECT in target arteries (p=0.0238) with a trend for better visibility in non-target arteries (p=0.0519)

DC Bead LUMI™ with contrast significantly increased visibility on X-ray single shot compared to DC Bead™ with contrast in target and non-target arteries (p=0.0238)

- DC Bead LUMI™ demonstrated better visibility on CECT in target arteries (p=0.0238) with a trend for better visibility in non-target arteries (p=0.0519)
- DC Bead LUMI™ with dextrose were not sufficiently visible to monitor embolisation using fluoroscopy

- Progressive embolisation with DC Bead LUMI™ allows for better control of embolisation process
- DC Bead LUMI™ visibility was durable in vivo, lasting to at least 7 days

**Key Messages:**

- DC Bead LUMI™ visibility was durable in vivo, lasting to at least 7 days

**Table of Results**

<table>
<thead>
<tr>
<th>Property</th>
<th>DC Bead LUMI™ vs DC Bead™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core chemistry</td>
<td>Same (iodine added in place of blue dye)</td>
</tr>
<tr>
<td>Size distribution</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Penetration depth (mean)</td>
<td>Equivalent</td>
</tr>
<tr>
<td>EWC</td>
<td>Greater (60-72% vs 96%)</td>
</tr>
<tr>
<td>Density</td>
<td>Higher (1.21-1.36 g/cc vs ~1.05 g/cc)</td>
</tr>
</tbody>
</table>

**Radiopacity**

- Uniform distribution of iodine throughout the bead
- Improved visibility on X-ray single shot vs fluoroscopy

**Suspension**

- Higher density of DC Bead LUMI™ and viscosity of contrast influenced suspension
  - Equilibration of LUMI with 100% contrast provided a durable suspension
  - Dilution of contrast with saline greatly reduced suspension duration inversely proportional to bead size

**Catheter compatibility**

- Deliverable through standard microcatheters
  - Testing performed on Progreat™ and Renegade™
  - 70-110µm and 100-300µm deliverable through a 2.3Fr microcatheter

*Early clinical experience suggests LUMI may be visible in smaller diameter vessels

**Catheter Compatibility**

- Deliverable through standard microcatheters
  - Testing performed on Progreat™ and Renegade™
  - 70-110µm and 100-300µm deliverable through a 2.3Fr microcatheter

**Suspension**

- Higher density of DC Bead LUMI™ and viscosity of contrast influenced suspension
  - Equilibration of LUMI with 100% contrast provided a durable suspension
  - Dilution of contrast with saline greatly reduced suspension duration inversely proportional to bead size

**Catheter compatibility**

- Deliverable through standard microcatheters
  - Testing performed on Progreat™ and Renegade™
  - 70-110µm and 100-300µm deliverable through a 2.3Fr microcatheter

*Early clinical experience suggests LUMI may be visible in smaller diameter vessels
Study Limitations

The limitations of this study include the following:

- *In-vivo* radiopacity was evaluated in rabbits that have less attenuation than humans.
- Image quality degradation in rabbits is more problematic than in humans (higher rate of cardiorespiratory motion).
- No histological analysis of effect of DC Bead LUMI™ on tissue or of target vs non-target embolisation.

Key Messages:

DC Bead LUMI™ have been developed using the same chemistry as DC Bead™ with the addition of covalently bonded radiopaque moiety to provide a high degree of inherent radiopacity, equivalent to that of soluble iodinated contrast agents

- DC Bead LUMI™ are more dense than DC Bead™ and require suspension in 100% contrast for delivery
- During administration, DC Bead LUMI™ are not discernable from the contrast media they are suspended in, but become visible as they accumulate in the vessel and contrast clears (*In-vitro* testing suggests visibility in vessels ≥0.4mm with X-ray single-shot)*
- DC Bead LUMI™ are visible on all X-ray modalities, with CBCT offering the greatest visibility and X-ray single-shot offering better visibility than fluoroscopy
- DC Bead LUMI™ may offer intra-procedural benefits in terms of endpoint determination, discovery of regions of under-treatment and identification of non-target embolisation
- DC Bead LUMI™ may offer post-procedural benefits in terms of optimising post-procedure patient care and informing future treatment strategies

*Early clinical experience suggests LUMI may be visible in smaller diameter vessels.