PRECISION V

Prospective, Randomised, Multi-centre Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by DEBDOX™ with DC Bead™

PRECISION V Trial Design

- **Control arm of conventional transarterial chemoembolisation (cTACE) with doxorubicin**
- **200 patients (100 per arm)**
- **23 European centres in Austria, France, Germany, Greece, and Switzerland**
- **Patients receive up to 3 treatments (baseline, 2 and 4 months)**
- **Follow-up period: 6 months**

Patient Demographics

Characteristics	DC Bead® (n=102)	cTACE (n=110)
Age Mean (±sd)	67.3 years (±9.1)	67.4 years (±8.8)
Sex (Male/Female)	79/14	95/13
Aetiology (HepC/HepB/Alcohol/Other)	22/16/43/21	18/18/57/25
Okuda (I/II)	79/14	103/5
BCLC (A/B/C)*	24/69/0	29/79/0
No. Lesions Median (range)	2.8 (1-20)	3.8 (1-50)
Sum Longest Diameter Mean (±sd)	88.9mm (±52.1)	89.2mm (±59.3)
Liver Involvement Mean (range)	16.1% (<10-50)	16.1% (<10-50)

*BCLC Classification according to tumour stage (Llovet et al Lancet 2003)

Product, Dose and Technique Guidelines

DEBDOX™ with DC Bead™

- **2 x 2ml vials of DC Bead™ (total 4ml) loaded at 37.5mg/ml for total dose of 150mg**
- **1 vial of 300-500µm followed by 1 vial of 500-700µm**

cTACE

- **Doxorubicin dose of 50-75mg/m² to maximum of 150mg**
- **Physician preference for embolic**

Technique for both groups

- **Unifocal tumours treated with selective segmental chemoembolisation**
- **Microcatheter could be used**
- **Bilobar disease: both lobes treated within a 3-week period**
- **Embolisation to stasis in 2nd or 3rd order branches**
- **DC Bead™ group: additional Bead Block™ could be used**

DCBead™

DC Bead™ DEBDOX™ Bibliography

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Drug-Eluting Bead Therapy in Primary and Metastatic Disease of the Liver
Carter S and Martin RCG. HPB Oxford 11 (2009): 541-550

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DC Bead™ Important Information

Indication: DC Bead™

- DC Bead is primarily intended as an embolic agent for the treatment of malignant hypervascularised tumour(s). DC Bead is compatible with doxorubicin, which can be loaded prior to embolisation and then, as a secondary action, elute a local, controlled and sustained dose to the tumour after embolisation.

This product and/or all indications may not be available in your territory.
DC Bead is not cleared by the FDA for sale or distribution in the USA.
For full instructions for use, please refer to: www.biocompatibles.com/dcbead-ifu

Cautions: DC Bead™

- Embolisation with DC Bead should only be performed by a physician with appropriate interventional occlusion training in the region intended to be embolised
- Do not use if the vial or packaging appear damaged
- Ensure that DC Bead is an appropriate size for the intended vasculature
- Consider upsizing to a larger size of DC Bead in the presence of AV shunts or if angiographic evidence of embolisation does not appear quickly during delivery
- Consideration should be given to Tc99m-MAA scanning if there is suspicion of AV shunting
- Exceeding a loading dose of 37.5mg doxorubicin per 1ml DC Bead may lead to some systemic distribution of doxorubicin and related side effects

Potential Complications: DC Bead™

- Undesirable reflux or passage of DC Bead into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds
- Non-target embolisation
- Pulmonary embolisation
- Ischaemia at an undesirable location
- Capillary bed saturation and tissue damage
- Ischaemic stroke or ischaemic infarction
- Vessel or lesion rupture and haemorrhage
- Neurological deficits including cranial nerve palsies
- Vasospasm
- Death
- Recanalisation
- Foreign body reactions necessitating medical intervention
- Infection necessitating medical intervention
- Clot formation at the tip of the catheter and subsequent dislodgement causing arterial thromboembolic sequelae

DC Bead™ Ordering Information:

Label Colour and Size	100-300µm	300-500µm	500-700µm
Volume of Beads	2ml	2ml	2ml
Product Code	DC2V103	DC2V305	DC2V507

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BTG

There are no limits to where our ideas will take us.

Imagine where we can go.

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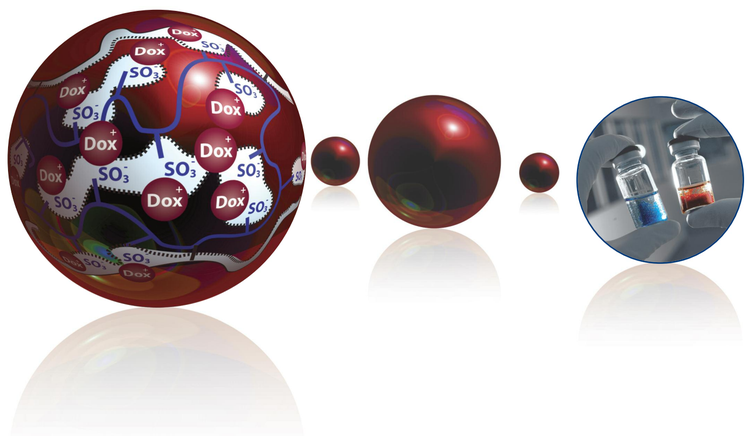
DCBead™

DEBDOX™ for Hepatocellular Carcinoma

Greater tolerability
Increased efficacy

for more patients



BTG

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Imagine where we can go.

DC Bead™

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Increased efficacy
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PRECISION V

Prospective, Randomised, Multi-centre Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by DEBDOX™ with DC Bead™

"We believe that these results show that DC Bead™ is a better treatment than conventional TACE. An improved response with significantly lower toxicity is unusual for a new cancer therapy."

PRECISION V Publication Committee

Professor Johannes Lammer, Vienna
Professor Katarina Malagari, Athens
Professor Alban Denys, Lausanne
Professor Riccardo Lencioni, Pisa
Professor Frank Pilleul, Lyon
Professor Anthony Watkinson, Exeter
Professor Thomas Vogl, Frankfurt

PRECISION V Conclusions[5]

- **DEBDOX™ with DC Bead™ is well tolerated, efficacious and reproducible**
- **There is a significant reduction in liver toxicity with DEBDOX™ with DC Bead™**
- **There is a significant advantage of DEBDOX™ with DC Bead™ in more advanced patients – those with more compromised liver function, poorer performance status, bilobar disease and recurrent disease – greater response, greater disease control and improved safety**
- **Currently AASLD guidelines do not recommend chemoembolisation for Child B and ECOG 1 patients. The PRECISION V data show that these patients can now be safely treated with DEBDOX™ with DC Bead™**

DC Bead™ is an embolic Drug-Eluting Bead capable of loading and releasing in a controlled manner high doses of chemotherapeutic agents.[1]

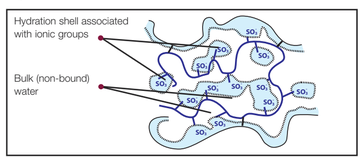
DC Bead™ Indication for Use

DC Bead™ is CE-marked and is intended to be loaded with doxorubicin for the purpose of:

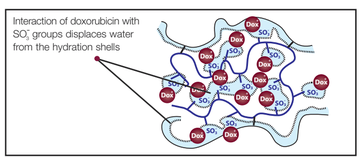
- Embolisation of vessels supplying malignant hypervascularised tumour(s)
- Delivery of a local, controlled, sustained dose of doxorubicin to the tumour(s)
- Doxorubicin maximum dose of 37.5mg/ml and 150mg per treatment with 4ml DC Bead™

Interaction of Doxorubicin With DC Bead™ Sulphonate Groups

Hydrated Beads



Loaded Beads

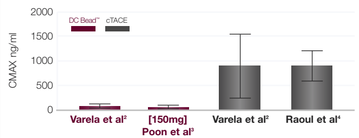


DC Bead™ Presentation

- Novel N-fil technology sulphonate modified hydrogel polymer
- Blue tinted to aid visualisation
- Delivered as vials containing 2ml Beads in 6ml saline
- Precise calibration to achieve an accurate level of embolisation

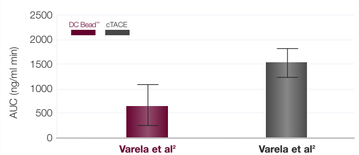
Systemic Exposure – Peak Concentration (Cmax)

DEBDOX™ vs Conventional TACE



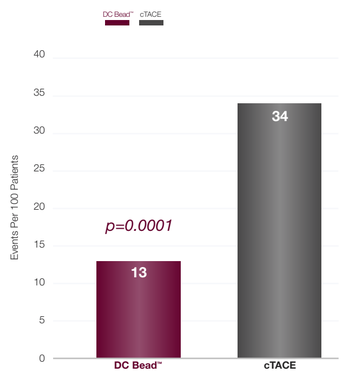
Total Systemic Exposure – Area under the Curve (AUC)

DEBDOX™ vs Conventional TACE



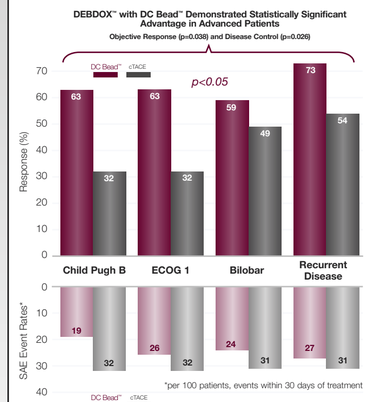
DC Bead™ was shown by Varela et al[2] to deliver a more targeted release of doxorubicin to the tumour, with greater consistency. Patients experienced a substantial reduction in both peak concentration and total systemic exposure to doxorubicin.

Doxorubicin-Related Side Effects



In the PRECISION V clinical trial, patients who received DEBDOX™ with DC Bead™ had a significant (p<0.001) reduction in doxorubicin-related systemic adverse events, despite receiving 30% more doxorubicin.

Response and Adverse Events – Advanced Disease

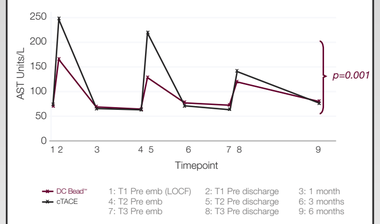


DC Bead™ improved response in all treated patients. More Advanced Patients demonstrated a significant improvement (p<0.05). DC Bead™ patients experienced fewer treatment-related side effects compared to the control group.

	DC Bead™ Response (%)			cTACE Response (%)		
Classification	DC	OR	CR	DC	OR	CR
Child Pugh B	63	44	25	32	21	16
ECOG 1	63	63	37	32	29	14
Bilobar	59	49	17	49	40	13
Recurrent Disease	73	55	27	54	31	15

DC = Disease Control OR = Objective Response CR = Complete Response

Liver Enzyme Levels (AST)[6]



Liver Enzyme Levels (ALT)[6]

The elevation of liver enzyme levels after each of the three treatments was significantly less in patients receiving DC Bead™, demonstrating that DEBDOX™ with DC Bead™ is less toxic to healthy liver.

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6. PRECISION V Clinical Study Final Results. Data on file at BTG International Ltd.