NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** **and** **final stakeholder list** on the NICE website.

1. **Company submission** from Terumo:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. British Association for Study of the Liver-Hepatocellular Carcinoma UK

4. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York

5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Selective internal radiation therapy with QuiremSpheres™ for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

Document B

Company evidence submission

January 2024

File name	Version	Contains confidential information	Date
ID6376_ QuiremSpheres cost-comparison company evidence submission_[CON]_22Jan2024	**V1**	**Yes**	**22 January 2024**

Instructions for Companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) when a cost-comparison case is made as part of the single technology appraisal process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 100 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

In this template any information that should be provided in an appendix is listed in a box.

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation, as the technology is authorised for the treatment of all unresectable liver tumours. The proposed position in the treatment population is narrower than the marketing authorisation because:

- The published NICE technology appraisal guidance (TA688) for the comparator(s) specified in the NICE scope recommends the SIRT technology (SIR-Spheres and TheraSphere) for a subgroup of the population in the marketing authorisation, and therefore a cost-comparison case can be made only for this population: adults with unresectable advanced hepatocellular carcinoma.

Table 1. ***The decision problem.***

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	Adults with unresectable advanced hepatocellular carcinoma with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate	Adults with unresectable advanced hepatocellular carcinoma with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate	In line with the NICE final scope
Intervention	QuiremSpheres™	Selective Internal Radiation Therapy (SIRT) with QuiremSpheres™	It is in line with the scope. We are proposing a slight change of wording to be in line with TA688. We are awaiting NICE technical team feedback
Comparator(s)	• SIR-Spheres • TheraSphere	• SIR-Spheres • TheraSphere	In line with the NICE final scope
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival	The outcome measures to be considered include: • overall survival • progression-free survival	In line with the NICE final scope

	• time-to-progression • response rates • rates of liver transplant or surgical resection • adverse effects of treatment • health-related quality of life	• time-to-progression • response rates • rates of liver transplant or surgical resection • adverse effects of treatment • health-related quality of life	
Economic analysis	Cost-comparison	Cost-comparison	In line with the NICE final scope

B.1.2 Description of the technology being evaluated

In appendix C include the summary of product characteristics or information for use, and the UK public assessment report, scientific discussion or drafts.

Table 2. Technology being evaluated.

UK approved name and brand name	QuiremSpheres™
Mechanism of action	Selective internal radiation therapy (SIRT) is a treatment option for patients with unresectable liver tumours. During a SIRT procedure, microspheres loaded with a radionuclide (yttrium-90, here holmium-166) are administered into the hepatic artery. Since blood from the hepatic artery flows preferentially towards tumour tissue, most microspheres get trapped in the capillary bed of the tumour(s). This eventually results in higher dosages of radiation delivered to the tumour tissue than to the healthy liver tissue. Following lodging of the microspheres, tumour cell death is induced by local emission and absorption of high-energy beta radiation (1).
Marketing authorisation/CE mark status	CE Mark was first obtained in April 2015 under the Active Implantable Medical Device Directive (AIMDD). CE Mark under the Medical Device Regulation (MDR) has been obtained in April 2023 and will start being valid as of March 2024. QuiremSpheres™ is also registered with the MHRA.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	QuiremSpheres™ is indicated for the treatment of unresectable liver tumours (1)
Method of administration and dosage	For transarterial implantation of QuiremSpheres™ a catheter is inserted either via the femoral or the radial artery under x-ray guidance. QuiremSpheres™ is supplied as a patient-specific dose calculated during the pre-treatment work-up procedure which is aimed to ensure sufficient distribution of the radiation dose to the tumour tissue while keeping the normal liver tissue and extrahepatic deposition activity below the levels assumed to be sufficiently safe. QuiremSpheres™ is administered into the hepatic artery via a catheter of appropriate diameter, following the instructions stipulated in the IFU.

	Terumo supplies dedicated administration accessories (Delivery Set and Customer Kit) designed to facilitate handling of the product vial and maximize the operator's safety. QuiremSpheres™ microspheres can be visualized in-vivo with MRI and/or SPECT.
Additional tests or investigations	A work-up procedure with a surrogate marker(either ^{99m}Tc-MAA or QuiremScout™ as per IFU) needs to be performed before each SIRT procedure (regardless of the technology) to verify eligibility (1)
List price and average cost of a course of treatment	List price is £12000 The total costs of a SIRT procedure are estimated to be £20,510 (2)
Patient access scheme/commercial arrangement (if applicable)	A confidential PAS simple discount has been proposed for QuiremSpheres™ of [redacted], leading to a PAS price of [redacted]. It is being considered by NHS England.

B.1.3 Health condition and position of the technology in the treatment pathway

Hepatocellular carcinoma (HCC)

- Hepatocellular carcinoma (HCC) is the most common form of liver cancer in England (3). It is commonly associated with cirrhosis (scarring of the liver), which can be caused by viral infections such as hepatitis B or C, excessive alcohol intake, or other diseases that result in chronic inflammation of the liver.

- The most frequently used staging system of HCC in the UK and globally is the Barcelona Clinic Liver Cancer (BCLC) staging classification, which links the stage of the disease to a specific treatment strategy (4).

Current treatment options and clinical pathway of care

- The majority of patients with HCC in England present with advanced stage disease (BCLC C) (5, 6). This stage includes patients with metastatic spread, portal vein invasion and greater size and numbers of tumours. For years, tyrosine kinase inhibitors (TKI), such as sorafenib, were the standard choice for treatment of such patients.

- Alternative treatments have been developed, which currently replace or complement sorafenib (7). Other treatments approved by NICE include a combination of

Atezolizumab with bevacizumab (TA 666), as well as SIRT (TA 688). Other NICE evaluations are ongoing.

- In the NICE technology appraisal guidance from 2021 (TA688), SIRT with SIR-Spheres and TheraSphere (microspheres loaded with yttrium-90, Y90-SIRT) was identified as a cost-effective option, as compared to sorafenib, for treating patients with advanced HCC and Child–Pugh grade A liver impairment for whom conventional transarterial therapies (CTT) are inappropriate.

Unmet need

New SIRT technologies may provide for additional treatment options and flexibility of use for HCPs. Such technologies should:

- Have efficacy similar to that of Y90 SIRT

- Offer a similar safety profile

- Provide for improved imaging possibilities to. facilitate post-treatment dose evaluation. According to the Council Directive 2013/59/Euratom a quantifiable post-treatment dosimetry should be performed (8). Although the UK is no longer part of the EU and subject to the EURATOM directive, this consideration may be relevant. In line with that, dose verification with SPECT-CT, rather than PET-CT, currently used for Y-90 SIRT dose verification, offers more accuracy and flexibility of use in clinical settings depending on the available facilities.

- Provide for the ease of preparation and administration, thus reducing the burden on the hospital staff and improving operator's safety.

QuiremSpheres™

QuiremSpheres™ is intended for implantation into hepatic tumours by delivery via the hepatic artery for the treatment of patients with unresectable liver tumours.

QuiremSpheres™ consist of biocompatible poly-L-lactic acid (PLLA) microspheres containing holmium-166 (Ho-166), which is a high-energy beta-emitting isotope.

- Gamma radiation emitted by holmium-166 and its paramagnetic properties allows for visualization of the microspheres by means of SPECT or MRI, and therefore facilitates post-treatment evaluation.

Anticipated place of QuiremSpheres™ in therapy is equivalent to Y90-SIRT with SIR-Spheres and TheraSphere

- Based on clinical experts' input, all SIRT products may be regarded as a 'technical variant' of SIRT with clinically equivalent results. The medical devices differ by the isotope used, specific activity, microsphere material used and specific weight, but clinical accuracy is equivalent since the method of action (i.e., beta-emitting radiation) is the same for all SIRT products.

- The Dutch health technology assessment agency ("Zorginstituut") in the Netherlands defined QuiremSpheres™ as a technical variant of the existing Y-90 products, making the following statement: "Based on the many similarities between the two types of microspheres, the Healthcare Institute considers holmium-166 microspheres to be a technical variant of yttrium-90 microspheres"(9).

- NICE Interventional Procedure Programme considers that the place of QuiremSpheres™ in therapy is equivalent to the place of SIR-Spheres and TheraSphere. Indeed, all the IPGs published ((IPG 630, IPG 672) (10, 11) or in development (IPG GID-IPG10336) since 2015 (QuiremSpheres CE Mark) consider that SIRT can be provided by either of the 3 products available.

- The decision on the product choice can be left to the multidisciplinary tumour boards (MDTs) or interventional radiologists (IRs) based on a careful evaluation of their patients' needs.

Disease overview and epidemiology

Hepatocellular carcinoma (HCC) is the most common form of liver cancer in England. It is commonly associated with cirrhosis (scarring of the liver), which can be caused by viral infections such as hepatitis B or C, excessive alcohol intake, or other diseases that result in chronic inflammation of the liver. In England, between 2016 and 2018, on average 5,148 people were diagnosed with liver cancer every year, and there were 3,537 diagnoses of HCC. HCC accounted for 67% of diagnoses in men and 37% of diagnoses in women (3).

Treatment for HCC depends on the location and stage of the cancer, and how well the liver function is preserved. The most frequently used staging system in the UK is the BCLC staging classification, which links the stage of the disease to a specific treatment strategy (Figure 1) (4).

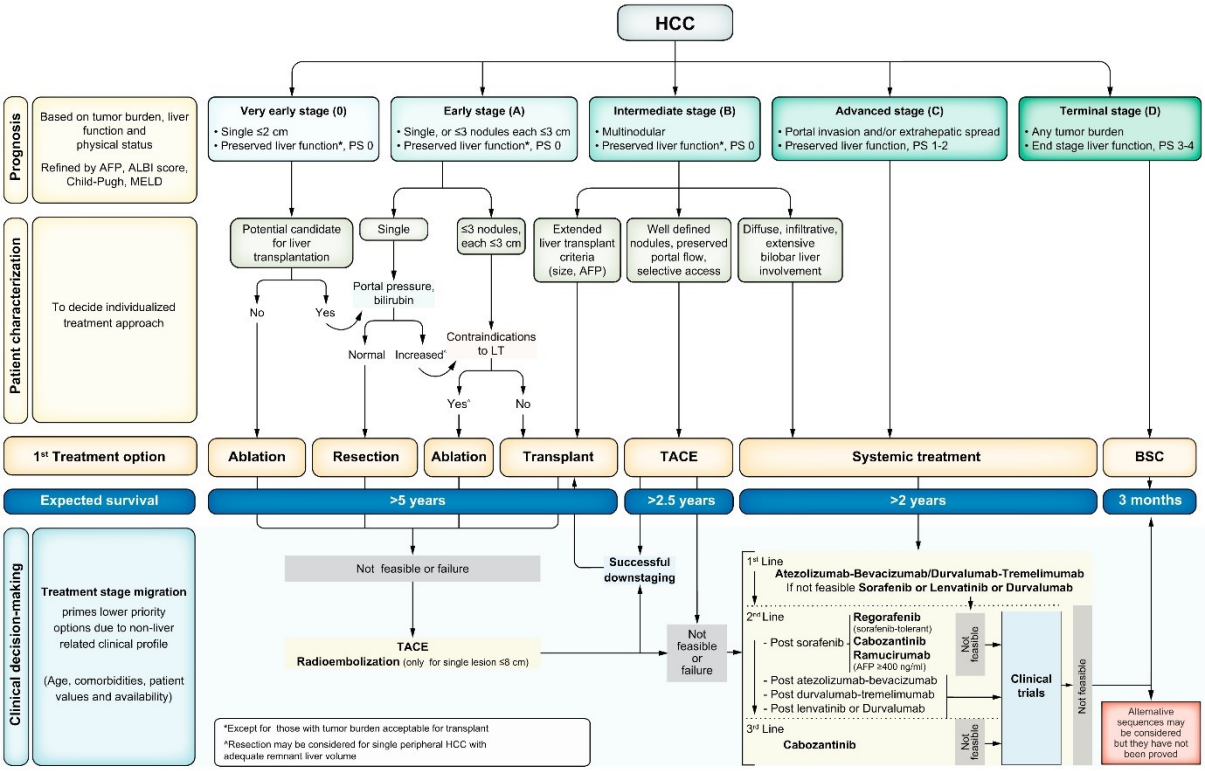

Figure 1. **The BCLC staging classification**.

Reproduced from (4).

In the early stage of the disease (0, A) curative treatments such as liver transplantation, resection, and ablation are considered. For patients with intermediate stage (B) HCC, TACE is currently considered as a standard treatment. This includes patients with compensated liver function and multifocal HCC without vascular invasion or extrahepatic spread. Unfortunately, the majority of patients with HCC in England present with advanced stage disease (C) (5, 6). This stage includes patients with metastatic spread, portal vein invasion and greater size and numbers of tumours. In the advanced stage, systemic treatments with multikinase inhibitors are available in first- (sorafenib, lenvatinib) and second-line (regorafenib) setting. Recently,

immunotherapies with or without vascular endothelial growth factor inhibitor bevacizumab have been positively evaluated in clinical studies, which changed the landscape of available treatments for this indication (7). Combinations such as atezolizumab + bevacizumab or tremelimumab + ipilimumab became first-line treatment options for the advanced stage HCC (4).

Despite these significant improvements, not all patients respond to systemic therapies, and few are 'downstaged' to surgical intervention. Additional therapeutic options are needed as stated in a recent UK guidance paper on SIRT for HCC: informing clinical practice for multidisciplinary teams in England by the team in Newcastle upon Tyne (12).

Clinical pathway of care, unmet need and place of QuiremSpheres™ in therapy

The place for SIRT in the clinical pathway of care depends on available evidence as compared to alternative treatments.

In the multiple technology appraisal guidance [TA688] evaluating all SIRT technologies (SIR-Spheres, TheraSphere and QuiremSpheres™) NICE considered SIR-Spheres and TheraSphere to be a cost-effective use of NHS resources and recommended both as options for treating advanced HCC for people with Child–Pugh grade A liver impairment for whom CTT is inappropriate (13). Currently, there are 2 Y90 SIRT devices available on the market (SIR-Spheres and TheraSphere).

The decision by NICE has been welcomed by the healthcare providers, patients and their advocacy groups. However, the absence of 'a guideline' presents a challenge, especially in centres where SIRT has not been accessible, and expertise is currently lacking.

Therefore, the team in Newcastle upon Tyne NHS Foundation Trust (NUTH) have audited their MDT practice and published a decision-making for SIRT based on 'real-world' patients in England (12).

Their recommendations can be found in the Figure 2.

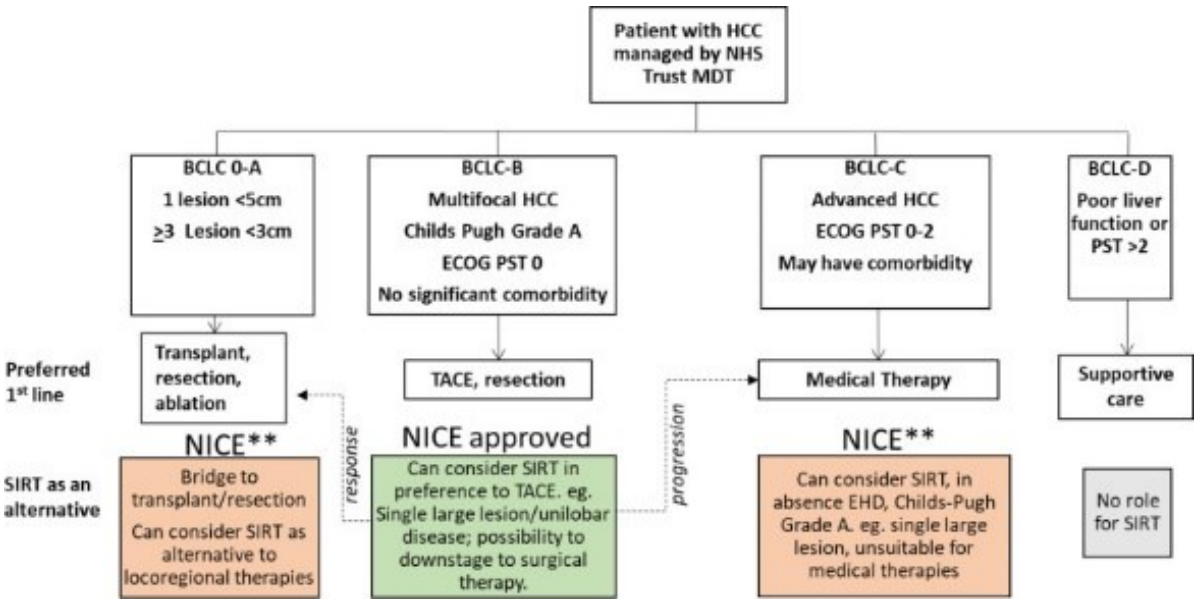

Figure 2. **Patient flow according to Newcastle upon Tyne NHS Foundation Trust (NUTH).**

The MDTs stage the patient, with the Barcelona clinic for liver cancer (BCLC) algorithm commonly used as a guide-aiding treatment selection by the MDT. The preferred first-line therapies for patients within each stage are shown. SIRT has been approved by the National Institute for Health and Care Excellence (NICE), as an alternative to transarterial chemoembolization (TACE) first line, typically used for BCLC-B patients, if an MDT considers SIRT a more suitable option (green box). For BCLC-B patients responding to or downstaged by SIRT, subsequent treatments for earlier stage disease may be considered (dotted line to left). For BCLC-B patients who progress post SIRT, medical therapies would be considered (dotted line to right). NICE advised that SIRT for patients with BCLC 0-A, or BCLC-C stage HCC (highlighted ** and shown in orange boxes) could be considered as an alternative to preferred first-line therapies within the setting of an expert MDT but offered subject to funding approval. Reproduced from (12).

Changes compared to previous assessment

In the initial assessment, limited evidence of QuiremSpheres™ was available for HCC. In the recent years, new evidence has become available that supports the efficacy of QuiremSpheres™ in the setting of HCC from prospective and retrospective non-comparative clinical studies that include the target patient population. Furthermore, a patient access scheme will be provided by Terumo to be able to reach similar costs than Y90-SIRT. As stated in the NICE TA688 review decision leading to this partial review, "*Depending on the level of PAS discount, QuiremSpheres™ could potentially be considered cost-effective*" (13).

Unmet need

New SIRT technologies may provide for additional treatment options and flexibility of use for HCPs. Such technologies should:

- Have efficacy similar to that of Y90 SIRT.
- Offer a similar safety profile.
- Provide for improved imaging possibilities to. facilitate post-treatment dose evaluation. According to the Council Directive 2013/59/Euratom a quantifiable post-treatment dosimetry should be performed (8). Although the UK is no longer part of the EU and subject to the EURATOM directive, this consideration may be relevant. In line with that, dose verification with SPECT-CT, rather than PET-CT, currently used for Y-90 SIRT dose verification, offers more accuracy and flexibility of use in clinical settings depending on the available facilities.
- Provide for the ease of preparation and administration, thus reducing the burden on the hospital staff and improving operator's safety.

Technical advantages of QuiremSpheres™ supporting the unmet need

- QuiremSpheres™ offer more flexibility for post-treatment evaluation. Ho-166 emits primary gamma photons (81 keV) that can be used for quantitative SPECT imaging. Furthermore, being a lanthanide, it can be imaged by high resolution magnetic resonance imaging (MRI), enabling the visualization of its distribution in the liver and quantification of the absorbed tumour dose. Y-90 SIRT is limited to either bremsstrahlung SPECT with a low spatial resolution or Y90-PET limited by the low count rate (only 32 decays per million via β+).
- The importance of post-treatment dosimetry is stated in the Council Directive 2013/59/Euratom:

  For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as

reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure. Although the UK is no longer part of the EU and subject to the EURATOM directive, this consideration may be relevant (8).

QuiremSpheres™ is the SIRT product facilitates adherence to this legislation, offering more flexibility for post-treatment dose verification.

QuiremSpheres™ is delivered as a patient-specific dose in a vial, which is ready to use and easy to operate. The activity delivered in a vial can be chosen with precision of up to two decimals. The vial can be optimally used with a dedicated Customer kit to maximize radiation safety and ease of operation.

The element holmium allows the HCPs to choose if they would like to evaluate QuiremSpheres™ distribution based on high resolution MR or SPECT based imaging, therefore providing for more flexibility in treatment verification.

Optimal use of NHS resources

- It is expected that QuiremSpheres™ will require the same NHS resources as other SIRT devices.

Radioactive precaution period

- Ho-166 has a half-life of 26.8 hours in contrast to 64.1 hours for Y-90. Therefore, in the unfortunate event of death or a medical intervention shortly after therapy, QuiremSpheres™ treated patients can be treated as non-radioactive within 15-20 days after treatment. For Y-90-treated patients this is 35-45 days calculated based on a tool of the Belgian radioprotection authority (14).

QuiremSpheres™

The therapeutic holmium microspheres (QuiremSpheres™) first received CE Mark in April 2015 under the Active Implantable Medical Device Directive (AIMDD). CE Mark under the Medical Device Regulation (MDR) has been obtained in April 2023 and is expected to be valid as of March 2024. QuiremSpheres™ is also registered with the MHRA.

QuiremSpheres™ is indicated for the treatment of unresectable liver tumours.

QuiremSpheres™ requires a work-up procedure with a surrogate marker (either ^{99m}Tc-MAA or QuiremScout as per IFU) for treatment planning before the administration (15, 16).
QuiremSpheres™ is intended for implantation into hepatic tumours by delivery via the hepatic artery for the treatment of patients with unresectable liver tumours.

The element holmium allows the physician to choose if they would like to evaluate QuiremSpheres™ distribution based on high resolution MR or SPECT based imaging. In study setting this is often combined to further cross-validate the two imaging modalities, but this is not a requirement in standard clinical practice.

Description of the technology

QuiremSpheres™ consist of biocompatible poly-L-lactic acid (PLLA) microspheres containing Ho-166, which is a high-energy beta-emitting isotope which also emits gamma radiation. The microspheres have a mean diameter of 30 micrometer (97% between 25 and 35 micrometers), which results in preferential lodging in the microvasculature in and around the tumor, maximizing tumor-killing effects and minimizing the effects on the healthy liver. The half-life of QuiremSpheres™ is 26.8 hours, which means that more than 90% of the radiation is delivered within the first 4 days following the implantation procedure.
The mode of action of QuiremSpheres™ is comparable to Y-90 based products – namely based on the emission of beta radiation. As described earlier, in addition to the emission of beta radiation, holmium is paramagnetic and ^{166}Ho emits primary gamma photons allowing accurate post-treatment verification even at a low concentration with high resolution. A detailed comparison of the main characteristics of QuiremSpheres™ and Y-90 microspheres is listed in Table 3 below.

Table 3. Characteristics of QuiremSpheres™, SIR-Spheres and TheraSphere.

Characteristics	QuiremSpheres™	SIR-Spheres	TheraSphere
Material	PLLA (biodegradable)	Resin (non-biodegradable)	Glass (non-biodegragable)
Isotope	Ho-166	Y-90	Y-90

Gamma radiation (visible on SPECT-CT)	81 keV (6.7%)	No	No
Visible on MRI	Yes	No	No
Half-life (h)	26.8	64.1	64.1
Product supplied	Patient specific vial Available in all increments with 2 decimals, highest flexibility No preparation needed	Mother vial Requires preparation of patient specific dose	Patient specific vial Available in 0.5 GBq increments between 3 GBq-20 GBq. No preparation needed

B.1.4 Equality considerations

No equality issues are presented by Terumo concerning the treatment of HCC or use of QuiremSpheres™ or SIRT in general.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

QuiremSpheres™, SIR-Spheres and TheraSphere are the 3 SIRT devices considered in the previous TA688 appraisal.

The comparative effectiveness of the 3 SIRT devices was uncertain, and it was assumed to be similar in the cost-effectiveness analysis.

In the committee's preferred analysis, SIRTs were less effective than sorafenib with an incremental quality-adjusted life years loss of 0.029 QALYs. In clinical trials, SIR-Spheres did not improve survival compared with sorafenib. However, the committee considered that

the adverse event profiles of SIRTs and sorafenib are different and people with HCC would welcome new treatment options. Compared with sorafenib, SIRTs may have fewer and more manageable adverse effects, which can improve quality of life. SIR-Spheres and TheraSphere were less costly than sorafenib and the estimated cost savings outweigh the loss of QALYs after taking into account the uncertainty associated with the clinical effectiveness. QuiremSpheres™ did not provide for cost-saving because of the price difference.

Therefore, the committee considered SIR-Spheres and TheraSphere to be a cost-effective use of NHS resources and recommended both as options for treating advanced HCC for people with Child–Pugh grade A liver impairment for whom CTT is inappropriate. Information on clinical outcomes and measures appraised in published NICE guidance for SIRT are presented in Table 4.

Table 4. Clinical outcomes and measures appraised in published NICE guidance for SIRT.

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
TA688	Median OS Median PFS	months	Yes	Yes	The committee concluded that it would consider the cost effectiveness of the 3 SIRTs by assuming they were equally effective, generalising the SIR-Spheres data to the other 2 SIRTs	The cost-effectiveness estimates for QuiremSpheres™ would be more uncertain than those for TheraSphere and substantially more uncertain than for SIR-Spheres
TA688	Tumour downstaging	Proportion of downstaged	No	No	The committee reconsidered downstaging after consultation and during its third	The proportion of people who have tumours that downstage, and the subsequent

					meeting. It concluded that downstaging may be an option for a small proportion of people with advanced HCC	outcomes, are uncertain
TA688	Safety	Adverse event rates and durations, all grades	Yes	Yes	SIRTs may have fewer and less severe adverse events than sorafenib and these have not been captured in the economic modelling.	
TA688	HRQoL	EORTC-QLQ-C30, mapped EQ-5D	Yes	Yes – critical assumption	The committee concluded that an adverse event-related QALY gain of 0.047 for SIRTs compared with sorafenib might be plausible and should be included in the base-case analysis.	The Committee concluded that there was high uncertainty associated with this estimate and the uncertainty was highest for QuiremSpheres™ because of its limited data

B.2.2 Resource use assumptions

The key resource use and preferred assumptions in TA688 are presented in Table 5.

Table 5. Committee-preferred model assumptions.

Model component	Description
Population	People with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, • For whom any conventional transarterial embolisation therapies (TAE, TACE, DEB-TACE) are inappropriate, • With or without macroscopic vascular invasion, without extrahepatic disease.
Intervention	• SIR-Spheres Y-90 resin microspheres • TheraSphere Y-90 glass microspheres • QuiremSpheres™ Ho-166 PLLA microspheres
Comparator	• Sorafenib
Analysis type	• Cost-effectiveness (cost-utility) analysis
Economic outcome	• Incremental cost per QALY gained, incremental net monetary benefit
Perspective	• NHS and PSS
Time horizon	• Lifetime (10 years)
Discount rate	• Annual rate of 3.5% applied to costs and QALYs

Table 6. Sources of input parameters for the base case economic model.

Model parameters	Evidence source
OS	*As per AG proposed base case*: Weibull fitted to pulled OS data from the SARAH and SIRveNIB trials for both SIR-Spheres (per protocol) and sorafenib (intention-to-treat).

	OS for patients who received work-up but were ineligible to receive SIRT use KM data from SARAH.
PFS	*As per AG proposed base case*: Weibull fitted to pulled PFS data from the SARAH and SIRveNIB trials for both SIR-Spheres and sorafenib.
Health utilities	*As per AG base case*: Utilities from SARAH trial data and applied by treatment class (SIRT/systemic therapy).
Proportion receiving SIRT	*As per AG base case*: Proportion receiving SIRT after work-up based on the full SARAH trial population. Number of administrations of SIRT based on the SARAH trial.
SIRT costs	*As per AG base case*: Acquisition cost: Sirtex CS, BTG CS, Terumo CS Work-up costs: BTG-elicited values from The Christie NHS Foundation Trust Procedure costs: NHS Reference costs 2017-18 *Additionally*: Equal administration costs for all SIRTs Imaging costs to be included for all SIRTs
Systemic therapies costs	*As per AG base case*: Sorafenib: BNF Dosing of sorafenib: SARAH trial *Additionally*: Duration of sorafenib: SARAH trial individual patient data

Subsequent treatment costs	*As per AG base case*: BNF, eMIT, TA555 (regorafenib)
AE costs	*As per AG base case*: AEs ≥5% of the population were modelled with rates drawn from the SARAH and REFLECT trials. Costs were drawn NHS Reference Costs, with cost categories based on NICE TA474, and 551.
Health state costs	*As per AG base case*: Sirtex survey of clinical experts and NHS reference costs 2017/18
Downstaging	*As per AG base case*: Not to be included because robust data are not available

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

- In appendix D describe the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.
- See section 3.1 of the user guide for full details of the information required in appendix D.

B.3.2 List of relevant clinical effectiveness evidence

Table 7. Clinical effectiveness evidence

Study	HEPAR Primary (17)
Study design	Multi-center, interventional treatment, non-randomized, non-comparative, early Phase II
Population	Unresectable intermediate and advanced HCC

Study	HEPAR Primary (17)
Intervention(s)	SIRT with QuiremSpheres™
Comparator(s)	None
Indicate if study supports application for marketing authorisation (yes/no)	No
Reported outcomes specified in the decision problem	The outcomes measured are: Adverse effects of treatment Response rates Overall survival Health-related quality of life
All other reported outcomes	Liver function based on hepatobiliary scintigraphy / Comparison of overall survival of responders and nonresponders

Study	RETOUCH (Manuscript submitted for publication)
Study design	Open label, prospective, non-randomized, single-center pilot study
Population	Unresectable early, intermediate, and advanced HCC
Intervention(s)	SIRT with QuiremSpheres™
Comparator(s)	None
Indicate if study supports application for marketing authorisation (yes/no)	No
Reported outcomes specified in the decision problem	The outcomes measured are Adverse effects of treatment Response rates Time to progression
All other reported outcomes	Rates of liver transplantation or surgical resection

Study	RECORD (Manuscript submitted for publication)
Study design	Real-world, multicenter, retrospective registry
Population	Unresectable very early, early, intermediate, and advanced HCC
Intervention(s)	SIRT with QuiremSpheres™
Comparator(s)	None

Study	RECORD (Manuscript submitted for publication)
Indicate if study supports application for marketing authorisation (yes/no)	No
Reported outcomes specified in the decision problem	The outcomes measured are Adverse effects of treatment Response rates Progression free survival Overall survival
All other reported outcomes	

Study	Jena Clinical Experience (18)
Study design	Prospective single center observational study
Population	Unresectable HCC
Intervention(s)	SIRT with QuiremSpheres™
Comparator(s)	None
Indicate if study supports application for marketing authorisation (yes/no)	No
Reported outcomes specified in the decision problem	The outcomes measured are Overall survival Progression free survival Response rates Adverse effects of treatment
All other reported outcomes	Rates of liver transplantation or surgical resection

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

Table 8. Summary of methodology of the clinical effectiveness.

Trial Number (acronym)	HEPAR Primary (17)	RETOUCH (Manuscript submitted)	RECORD (Manuscript submitted)	Jena clinical experience (18)
Location and settings where data were collected	Hepar Primary was carried out in 2 sites (UMC Utrecht and Erasmus MC) in the Netherlands	RETOUCH was carried out in Erasme ULB Brussels in Belgium	RECORD was carried out in 7 European centers located in the Netherlands, Belgium, Germany, Switzerland, Italy, Portugal and Spain	Jena clinical experience was carried out in Universitätskliniku m Jena in Germany
Trial design	Multicenter, interventional treatment, non-randomized, non-comparative, early Phase II	Open label, prospective, non-randomized, single-center pilot study	Real-world, multicenter, retrospective registry	Prospective single center observational study
Eligibility criteria for participants	The main inclusion and exclusion criteria were an age of at least 18 y with a life expectancy of at least 6 months, a diagnosis of HCC according to the criteria of the American Association for the Study of Liver Disease, a measurable lesion based on RECIST	Patients were referred from the multidisciplinary hepatobiliary tumor board and met the following inclusion criteria: adults ≥ 18 years-old with typical imaging- or biopsy-proven HCC according to EASL-EORTC guidelines19, unresectable BCLC B, or	All patients treated with QuiremSpheres^{TM} Holmium-166 Microspheres from 15 July 2019 to 15 July 2021 at the included hospitals	All patients who underwent SIRT with QuiremSpheres^{TM} at the Jena University Hospital in Germany. A Child-Pugh score of >8, a Karnofsky index of <70%, and a tumor load of >70% of the liver were considered

	(RECIST 1.1 and mRECIST), liver-dominant disease (a maximum of 5 lung nodules, all # 1.0 cm, and mesenteric or portal lymph nodes, all # 2.0 cm), no curative treatment options, a Child–Pugh score of B7 or less, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, no prior radioembolization, and no main-branch portal vein thrombosis.	contraindicated for ablation, resection or transplantation, BCLC A, or patients on the transplantation waiting list/in order to downstage the tumor to Milan criteria, or BCLC C patients with no extra-hepatic disease; at least one measurable lesion on multiphasic CT or MRI; preserved liver function with Child- Pugh score≤ B7; ECOG performance status ≤ 1; life expectancy ≥3 months.		exclusion criteria for TARE
Trial medical device (the interventions for each group with sufficient details to allow replication, including how	After a work-up session to validate eligibility. The intended average absorbed dose in the perfused volume was 60 Gy: A (MBq) = 3.781 x	After a work-up session the treatment activity was calculated to obtain a tumor dose ≥ 150 Gy and non-tumoral liver absorbed dose was ≤ 60 Gy and lung	The following data was recorded based on available examination / reports in the patient's medical file: **SIRT Work-up(s)**	After a work-up (either ^{99m}Tc- or ^{166}Ho-based) patients were treated with QuiremSpheres with an activity calculated to the target volume via the medical internal

and when they were administered) **Intervention(s) (n= [x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	W (g), where A is the prescribed activity in megabecquerels and W is the target liver mass in grams (1 mL = 1.04 g) Concomitant medication specified in the publication	absorbed dose was ≤ 30 Gy calculated using Q-Suite™ 2.0 software. The majority of the patients (13/15; 87%) received a single QuiremSpheres™ treatment Concomitant medication not specified	• Work up procedure • Occurrence of adverse event **SIRT procedure(s)** • Treatment with QuiremSpheres™ Holmium-166 Microspheres • Post-treatment evaluation • Occurrence of adverse event Concomitant medications were not recorded for this study	radiation dosimetry (MIRD)-based formula A [MBq] = liver dose [Gy] × liver weight [kg] × 63 [MBq/J] In patients with a bilobar approach, the liver lobe with the higher tumor load. The other liver lobe was treated after an interval of 6 weeks (median 42 days, range 33–49 days) Concomitant medication not specified
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the rate of unacceptable toxicity using CTCAE methodology, which was defined as grade 3 hyperbilirubinemia in combination with ascites and low albumin in the absence of disease	Feasibility of QuiremSpheres™ with this higher tumor dose in the HCC patient population, as well as the assessment of early (24-48h) and late (1 month) safety and toxicity profiles (CTCAE v5.0).	Safety primary endpoint analysis was performed for short term, median term, long term, and overall safety. OS, PFS, hPFS. Treatment response according to mRECIST or RECIST 1.1 is reported as a	Adverse events (early 48h) and late according to CTCAE. ORR at 3 months Overall survival Progression free survival

	progression (i.e., radioembolization -induced liver disease) or any serious adverse event or serious device defect possibly, probably, or causally related to treatment.		percentage of all patients with known outcome in the study.	
Pre-planned subgroups	NA	NA	NA	NA
Post-treatment verification of dose distribution	MRI was performed and the patients were discharged. Three to 5 d after treatment, the patients came back for posttreatment SPECT/CT. This scan was delayed to prevent detector dead time caused by the abundance of γ-photons	Timing not defined for SPECT/CT MRI not performed for dosimetry purposes	Post-procedural SPECT/CT where available	Post-procedural scintigraphy and SPECT/CT were performed on the following day MRI not performed

In accordance with Council Directive 2013/59/Euratom post-treatment verification of delivered radiotherapy is needed. In the selected studies it shows that post-treatment verification is performed either the day after treatment or 3-5 days after treatment. It is important to mention that in the setting that patients are only scanned 3-5 days after treatment patients aren't

hospitalized during this period but go home. They return for their scan in an ambulatory setting. We acknowledge that the SIRT practice is maintained within centers of excellence and travel distance could be long, but this SPECT imaging could be performed in peripheral hospitals as SPECT systems are widely available.

In Table 9 below, you can find a summary of the baseline characteristics of the patients included in the clinical effectiveness evaluation.

Table 9. Summary of baseline characteristics of patients included in the clinical effectiveness evaluation.

Trial Number (Acronym)	HEPAR Primary (17)	RETOUCH (Manuscript submitted)	RECORD (Manuscript submitted)	Jena Clinical Experience (18)
Age, in years				
Median (range)	73 (44-85)	72±11	66.2 ± 10.9 (total population)[$]	73 (58-82)
Sex, n (%)				
Male	28 (90%)	14 (93%)	99 (67.8%)	13 (93%)
Female	3 (10%)	1 (7%)	47 (32.2%) (total population) [$]	1 (7%)
Cirrhosis, n (%)				
Present	20 (65%)	9 (60%)	NR	12 (86%)
Absent	11 (35%)	6 (40%)		2 (14%)
Etiology of cirrhosis				
Alcohol abuse	20 (65%)	5/9 (56%)		0
Hepatitis B	1 (3%)	0/9		
Hepatitis C	4 (13%)	3/9 (33%)		1 (7%)
Nonalcoholic fatty liver disease	3 (10%)	0/9 (0%)		2 (14%
Hemochromatosis	2 (4%)	1/9 (11%)		1 (7%)
Unknown	6 (20%)			8 (57%)
Child–Pugh classification				
A5	19 (61%)	9/9 A5-6 (100%)	36/55 A5-6 (65.5%)	12 (86%)
A6	9 (29%)			1 (7%)
B7	3 (10%)		17/55 (30.9%)	1 (7%)
ECOG performance status, n (%)				
0	18 (58%)	13 (87%)	59 (40,9%)	NR
1	13 (42%)	2 (13%)	46 (31.5%)	

≥2	0 (0%)		8 (5.5%) (total population) [$]	
BCLC classification, n (%)				
0	0	0	2 (3.6%)	
A	0	11 (73%)	3 (5.5%)	2 (14%)
B	22 (71%)	1 (7%)	32 (58.2%)	9* (64%)
C	9 (29%)	3 (20%	11 (20%)	3* (21%)
Prior liver treatments				
Resection	4 (13%)	2 (13%)	NR	4 (29%)
Ablation	4 (13%)	0		0
TACE	1 (3%)	0		1 (7%)
Percutaneous radiation	0	0		1 (7%)
SIRT	0	0		2 (14%)
None	26 (84%)	13 (87%)		8 (57%)
Treatment approach				
Unilobar	20 (64%)	NR	84/167 (50.3%)	7 (50%)
Bilobar (excluding some segments	9 (29%)		24/167 (14.4%)	NR[#]
Whole liver	2 (6%)		16/167 (9.7%)	7[#] (50%)
Number of tumors				
1	4 (13%)	16/20 (80%)	NR	NR
2-3	4 (13%)	4/20 (20%)		
>3	23 (74%)			
Tumor burden (%) (range)	9.3 (0.5-46.8)		NR	6.5 (2-32)

[$] Retrospective data collected for the whole population, including 55 patients with HCC.

*Conservative assessment as 5 patients are characterized tumour Stage II that can also imply vascular invasion which would make patients BCLC C.

[#]Not specified if it was whole liver or bi-lobar with sparing some segments

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 10. Objectives, statistical analyses in studies, included in the evaluation.

Trial number (acronym)	Hypothesis objective	Statistical analysis, sample size, power calculation

HEPAR Primary (17)	Probability of unacceptable toxicity was 10% and that the alternative was a probability of unacceptable toxicity of 25%. Unacceptable toxicity of 10% of less was considered acceptable and 25% or more was not	Statistical power (85%) quantified the probability of stopping the study early if toxicity was unacceptably high (type II error, 15%), which was arguably equally as important as wrongly stopping the study in the absence of true high toxicity (type I error, 15%) Kaplan–Meier curves and log-rank tests were used to evaluate overall survival. Responders (complete or partial response) and nonresponders (progressive or stable disease) were compared using landmark analysis with first and second response assessment.
RETOUCH (Manuscript submitted)	Feasibility and safety study; data analysis was done on individual cases to assess safety and feasibility of the protocol.	A sample size of 20 patients was considered appropriate for the inclusion, taking into consideration that possible dropouts were to be expected due to unfavorable work-up Descriptive statistics are reported as mean and standard deviation (SD) for continuous variables. Categorical variables are presented as frequencies and percentages. Time-to-event variables, such as overall survival (OS), are analysed using the Kaplan–Meier method, presenting means ± standard errors (SE) and medians with 95% CIs of times to event and subjects remaining event-free at 3-monthly intervals including the 95%CI based on the Greenwood method. Given the small sample size of our study, a Swimmer plot was made to depict the time to progression or observation period (in case of no progression), and the mRECIST overall responses at each timepoint, and the possible time of death, separately by subject.
RECORD (Manuscript submitted)	Real world clinical evidence, retrospective	All eligible patients were part of the clinical investigation

	collection of hospital records	
Jena Clinical Experience (18)	Real world clinical evidence	Descriptive study, no statistics

In appendix D, provide details of the numbers of participants eligible to enter the studies.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

All four studies included in this appraisal are non-randomised, non-comparative single-arm studies, which poses limitations on data quality. Specific limitations for each study are presented in the Table 11 below.

Table 11. Quality assessment of relevant clinical effectiveness evidence.

Quality assessment criteria	**HEPAR Primary (17)**	**RETOUCH (Manuscript submitted)**	**RECORD (Manuscript submitted)**	**Jena Clinical Experience (18)**
Appropriateness of study design to the research objective	Appropriate: safety and toxicity study	Appropriate: feasibility and safety study	Appropriate: observational retrospective study	Appropriate: observational prospective study
Risk of bias	Moderate/high: non-randomized study	Moderate/high: non-randomized study	Moderate/high: non-randomized study	Moderate/high: non-randomized study
Choice of outcome measure	Appropriate: Primary endpoints of the study (safety and toxicity) reported as per CTCAE v.4.3	Appropriate: Primary endpoints of the study, feasibility of the procedure recorded, safety and toxicity	Not applicable: retrospective observational study was collecting available	Appropriate: OS, PFS, tumour response to evaluate clinical experience

		reported as per CTCAE v.5	endpoints from hospital records	
Statistical issues	Limited number of patients	Sample size was not justified properly, limited number of patients	Missing data, data quality (retrospective data)	Limited number of patients in the HCC subroup
Quality of reporting	High	Not applicable	Not applicable	High
Quality of the intervention	Medium: SIRT treatment planning was performed according to a standard approach, regardless of tumour and functional liver dosimetry	High: SIRT treatment planning to ensure high target tumour radiation dose	Medium/high: observational study, intervention as per hospital practice	Medium/high: observational study, intervention as per hospital practice
Generalisability	Medium: Relevant patient population, but limited number of patients	High: demonstrated feasibility and safety of high tumour dose with Ho-166 SIRT in HCC	High: Real-world experience	High: Real-world experience
Publication	(17)	Submitted for publication; presented at CIRSE 2023*	Submitted for publication*	(18)

*Unpublished studies results are provided for this evaluation in confidence.

In appendix D, provide the complete quality assessment for each trial.

B.3.6 Clinical effectiveness results of the relevant studies

Demonstration of efficacy of QuiremSpheres™ in HCC

Main results of each study are summarized in Table 12 and described in more detail in this section.

Table 12. Summary of the clinical outcomes reported in the studies with QuiremSpheres™ included in the evaluation.

Outcome	HEPAR Primary (17)	RETOUCH (Manuscript submitted)	RECORD (Manuscript submitted)	Jena Clinical Experience (18)
N of patients	31	15	55	14
BCLC stage	B: 22 (71%) C: 9 (29%)	A: 11 (73.3%) B: 1 (6.7%) C: 3 (20%)	0: 2 (3.6%) A: 3 (5.5%) B: 32 (58.2%) C: 11 (20.0%) Unknown: 7 (12.7%)	A: 2 (14%) B: 9* (64%) C: 3* (21%)
Tumour response at 3 m (mRECIST)	CR: 5 (19%) PR: 9 (35%) SD: 11 (42%)	CR: 12 (86%) PR: 2 (14%)	ORR: 26/37 (70.3%) DCR: 35/37 (94.6%)	CR: 1 (8%) PR: 7 (58%) SD: 2 (17%)
Overall survival (OS), months	mOS: 14.9	NA	mOS: 12.7 [8.8 ; 18]	Mean OS: 21.7±15.5
Progression-free survival (PFS) or time to progression (TTP), months	NA	mTTP: 18.8 [2.9 ; n.e]	mPFS: 5.3 [3.8 ; 7]	Mean PFS: 10.6±9.7

Safety (related SAEs*, Gr 3-5 AEs CTCAE)	Gr 3+: 19 (4 events in 3 patients related to treatment	SAE: not observed Only Gr 1-2 clinical and biological AEs	*In total population (n=146):* AESI: 5 Gr 3+: 9	Only liver function changes reported
QoL	No change in QoL	NA	NA ("Health improvements" reported)	NA

HEPAR Primary Study

Efficacy assessment was based on the modified RECIST (mRECIST) response evaluation criteria, which take into account the target lesions response, non-target lesions response and the occurrence of new lesions (17). In addition, the liver response in assessed. The response to the target liver lesions is shown in Figure 3.

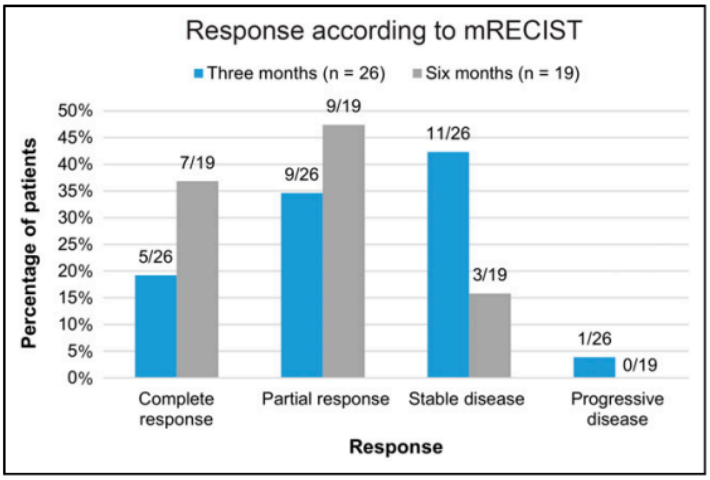

FIGURE 4. Response assessment of target liver lesions at 3 and 6 mo after treatment with ^{166}Ho-microsphere radioembolization according to mRECIST. Some patients did not undergo imaging at 3- or 6-mo follow-up because of death (n = 2 and 8, respectively) or withdrawn consent (n = 2 or 0, respectively). Some patients were not evaluable because of absence of arterial enhancement of tumor or low-quality imaging (e.g., artifacts or breathing motion) (n = 3 and 2, respectively).

Figure 3. Tumour response results in HEPAR Primary study.

Reproduced from (17).

Median overall survival was 14.9 months (95% CI, 10.4-24.9). The median post-landmark analysis of overall survival of patients who had a complete or partial response in the total body according to mRECIST at 3 months showed that it was 16.6 months (95% CI, 8.72-not reached) for responders and 13 months (95%, 8.95-not reached) for non-responders. The median overall survival of responders based on the target liver lesions response was not reached, and for non-responders it was 12.8 months (95% CI, 4.72-not reached).

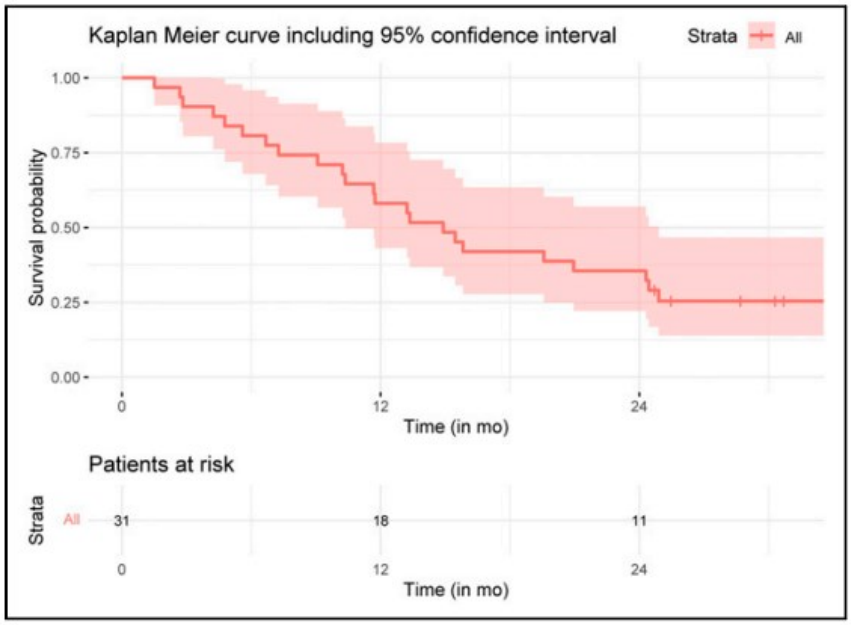

FIGURE 5. Overall survival of HEPAR Primary patients.

Figure 4. Overall survival results in HEPAR Primary study.

Reproduced from (17).

Quality of life was measured using measured using the EORTC QLQ-C30 global health scale and EORTC QLQ-HCC 18-question module. Therefore, questionnaires were provided at baseline and follow-up. No clinically relevant change in quality of life or pain was observed.

Supplemental Figure 2: Quality of life of HEPAR Primary patients based on self-reported scores. A) Global Health status B) Functioning scales C) Symptom scores.

IQR = Interquartile range, GHS = Global health score

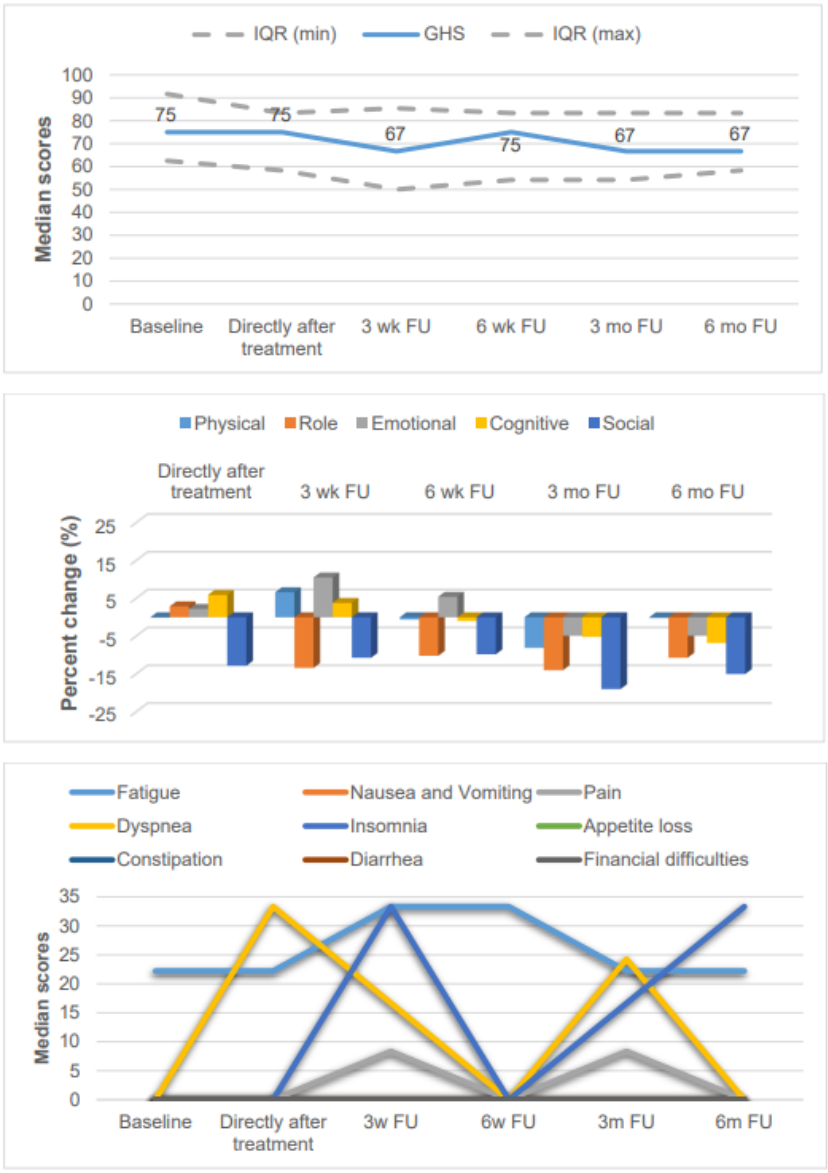

Figure 5. **Patient quality of life results in HEPAR Primary study.**

Reproduced from (17).

RETOUCH

A pilot study to evaluate feasibility, safety and efficacy of SIRT using high tumor dose of >150 Gy for the treatment of large hepatocellular carcinoma was conducted in Erasmus Hospital in Brussels. The study manuscript is submitted for publication to a peer-reviewed journal.

The target lesions in the fifteen patients evaluated at 1 month by mRECIST showed complete response (CR), partial response (PR) and stable disease (SD) in 46.67% (7 of 15), 46.67% (7 of 15) and 6.67% (1 of 15) according to mRECIST and 0% (0 of 15), 26.67% (4 of 15) and 73.33% (11 of 15) according to RECIST 1.1.

Fourteen patients underwent a morphological assessment at 3 months (Figure 3). Objective response in target lesions was observed in 100% of cases (CR in 78.57% [11 of 14] and PR in 21.43% [3 of 14] according to mRECIST. Partial response was observed in 57.14% [8 of 14] and SD in 42.86% [6 of 14]) of cases as by RECIST 1.1. Nevertheless, 4 patients had a progression outside the treated area (28.57%). The overall response by patient was of 71.43% (10 of 14, CR 57.14% and PR 14.29%) according to mRECIST and 50% (7 of 14, PR) according to RECIST 1.1.

Eight patients were assessed at 6 months. Complete response in the target lesions was still seen in 87.50% of patients (7 of 8) and PD in 12.50% (1 of 8) according to mRECIST and PR in 75% (6 of 8), SD 12.50% (1 of 8) and PD 12.50% (1 of 8) of patients according to RECIST 1.1.

Overall response at 6 months by patient was 62.5% (5 of 8) according to mRECIST and RECIST 1.1.

Median time to progression was 18.8 months (range 2.9; n.e.). Kaplan-Meier curves of time to progression is shown in Figure 6.

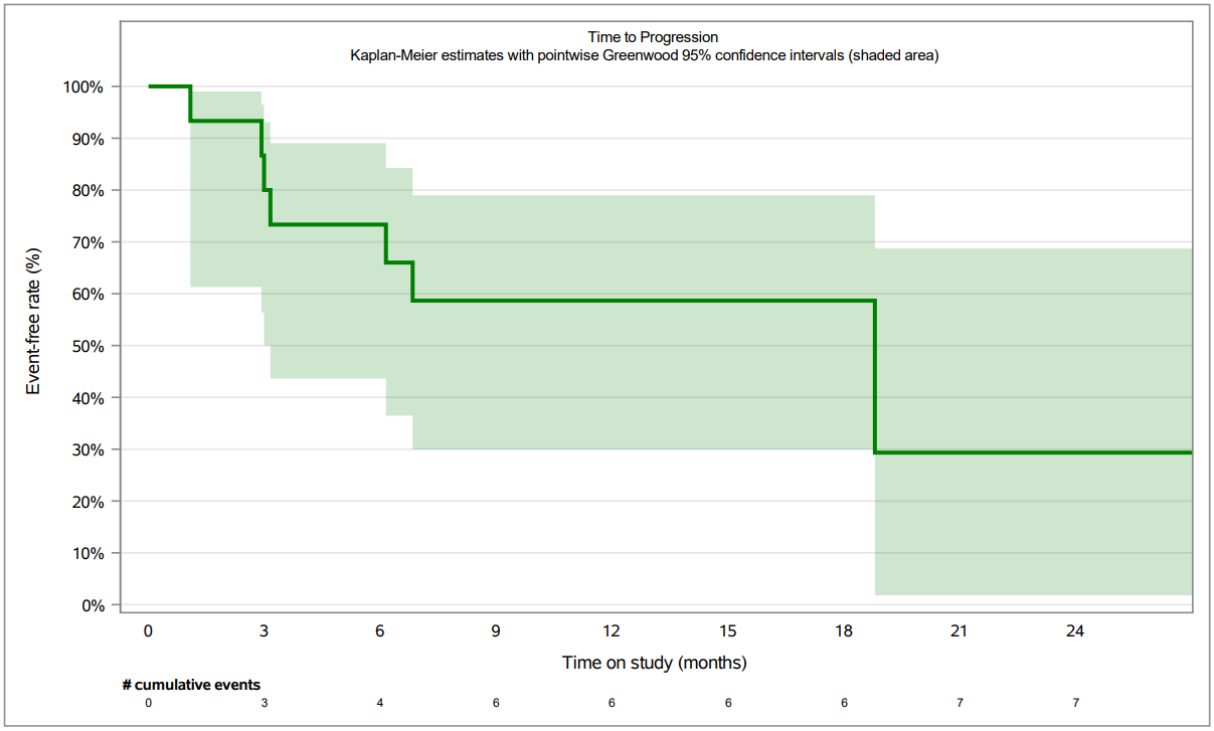

Figure 6. Kaplan-Meier curve for time to progression (TTP) in the RETOUCH study.

In this pilot study it was observed that during the follow-up period (6 months), 2 patients (13%) underwent surgery and 1 underwent liver transplantation (7%).

RECORD

For hepatocellular carcinoma, response rate beyond 3 months was 70.3% (26/37) of all HCC patients with data. Disease control rate beyond 3 months was 94.6% (35/37). The study manuscript is submitted for publication to a peer-reviewed journal.

Median progression free survival was 5.3 months [95% CI 3.8, 7] in the total evaluable population, 33.8% (49) of the total population was censored (145). Median PFS in HCC was 9.1 months [95% CI 7.1, 14].

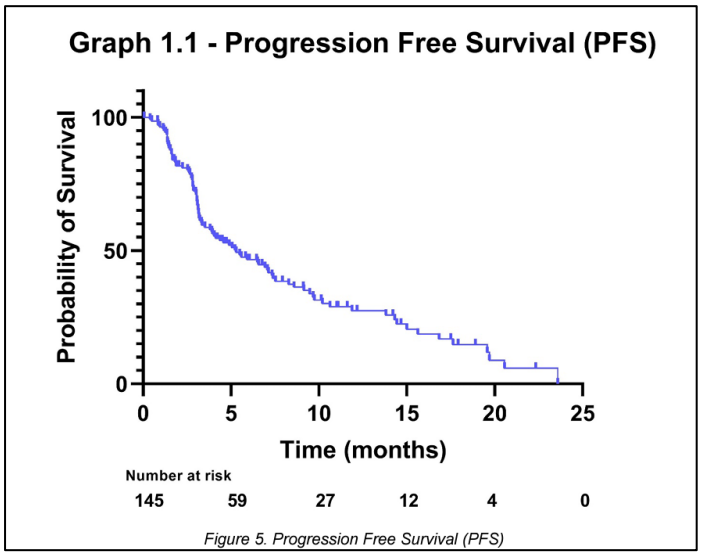

Figure 7. Progression-free survival results in the RECORD study.

Median hepatic progression free survival was 6.5 months [95% CI 4.1, 9] in the total evaluable population, 37.9% (55) of the total population (145) was censored. Median hPFS in HCC was 9.7 [95% CI 7.1, 14].

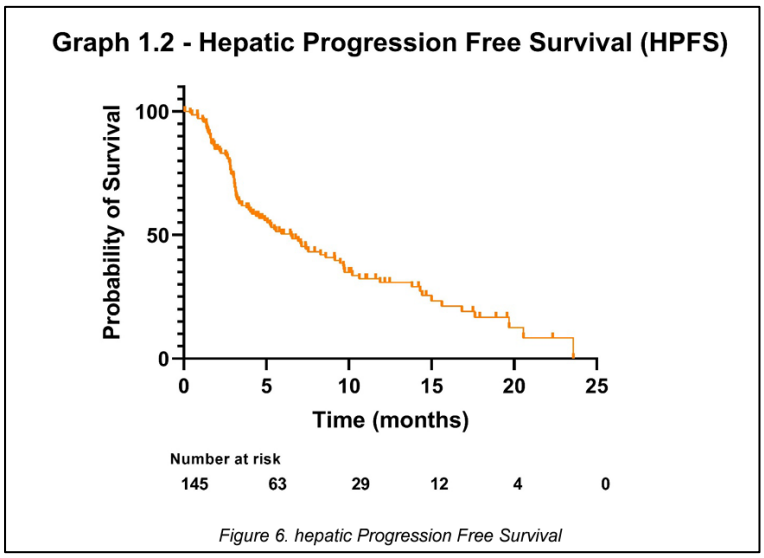

Figure 8. Hepatic progression-free survival results in the RECORD study.

Median overall survival was 12.7 months [95% CI 8.8,18] in the total evaluable population, 54.1% (79) of the total population was censored. Median OS in HCC was 14.7 months [95% CI 13.8, n.e.].

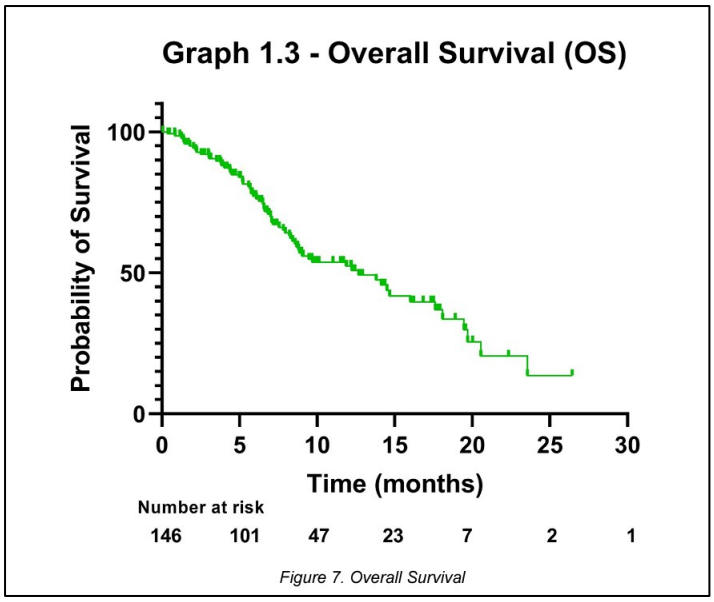

Figure 9. Overall survival results in the RECORD study.

Jena Clinical Experience

In this real-world experience, the mean progression free survival of the treated liver lobe(s) was 14.9 months (Figure 10) (18).

Table 2. Progression-free survival (PFS) in HCC and mCRC patients.

PFS after First ^{166}Ho-TARE (Months)	HCC (14 Patients)	mCRC (4 Patients)
hepatic, treated liver	* 14.9 ± 11.6 (10.3, 8.8–21.0)	* 5.3 ± 5.7 (2.6, 2.4–8.3)
hepatic, untreated liver	* 10.9 ± 8.3 (8.8, 6.6–15.2)	21.7 ± 28.6 (21.7, 6.8–36.7)
hepatic, whole liver	8.9 ± 7.2 (6.4, 5.1–12.6)	14.5 ± 18.9 (7.2, 4.6–24.4)
extrahepatic	19.9 ± 16.0 (17.9, 11.6–28.3)	15.4 ± 18.4 (8.5, 5.7–25.0)
whole body	10.6 ± 9.7 (7.3, 5.5–15.7)	12.3 ± 19.8 (2.9, 2.0–22.7)

Values are mean ± SD (median, 95% confidence interval), * patients with liver transplantation and surgery after downstaging not included.

Figure 10. Progression-free survival reported in Jena Clinical Experience study.

Reproduced as figure from (18).

The median overall survival after the first QuiremSpheres™ treatment was 22.1 months (CI: 13.6–29.8 months) and after the initial diagnosis, 27 months (CI:24.2-44.5 months).

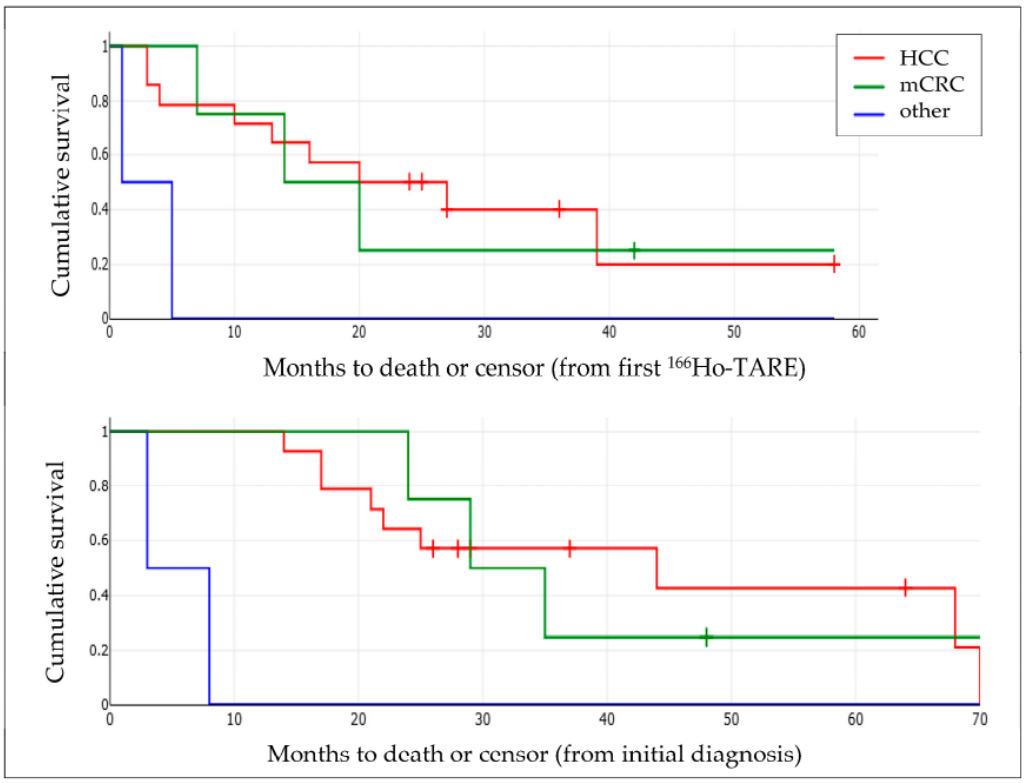

Figure 4. Overall survival of patients with HCC and mCRC after the first ^{166}Ho-TARE, and after initial diagnosis of the malignancy.

Figure 11. Overall survival of patients reported in Jena Clinical Experience study.

Reproduced from (18).

In the Swimmers plot it can also be observed that 2 patients underwent liver transplantation (14%).

B.3.7 Subgroup analysis

No subgroup analysis could be performed.

Provide a summary of the results for the subgroups in appendix E.

B.3.8 Meta-analysis

No meta-analysis could be conducted.

B.3.9 Indirect and mixed treatment comparisons

See appendix D for full details of the methodology for the indirect comparison or mixed treatment comparison.

In appendix D include full details of the methodology for the indirect comparison or mixed treatment comparison.

The review decision paper states that "*Given the committee's conclusion in TA688, it is unlikely that the evidence presented by the company, which is all observational, would add meaningful additional evidence to a mixed treatment comparison*. " We therefore performed a naïve visual comparison using forest plots of treatment estimates from clinical studies evaluating QuiremSpheres™ and Y-90 SIRT for HCC.

For QuiremSpheres™ studies, all relevant clinical studies in patients with HCC that were published or completed since the previous NICE appraisal were included. The Dutch Healthcare Agency, in its assessment of QuiremSpheres™ in HCC, used 3 RCTs to compare results with Y90: SARAH (19), SIRVENIB (20) and DOSISPHERE-01 (21). We have used the same studies and completed them with more recent, large single arm observational studies as they had a similar patient mix than QuiremSpheres™ studies and similar methodology: the prospective observational study with SIR-Spheres CIRT (22), the prospective real-world registry with SIR-Spheres RESiN (23), retrospective single-arm study with TheraSphere TARGET (24).

Published data from the listed studies were presented graphically to enable a visual comparison of estimates of overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) for QuiremSpheres™ versus Y90 SIRT, with consideration for differences in study design and patient populations (e.g. BCLC grade).

Exact 95% confidence intervals were derived for ORR estimates where published data were not available. ORR estimates were also pooled across studies based on available data and the following common elements - treatment (QuiremSpheres™ or Y90 SIRT), response

criteria (mRECIST or RECIST1.1), timepoint (3-month or best response) and study design (prospective or retrospective; single arm or randomised). Given potential differences in follow-up time and censoring approaches, estimates of OS and PFS were not pooled.

Given the published data for QuiremSpheres™ is based on single arm studies (both prospective and retrospective), meta-analysis to obtain estimated treatment differences in OS, PFS or ORR (QuiremSpheres™ versus Y90 SIRT) was not conducted.

Using this approach, we could demonstrate that survival outcomes mOS and mPFS reported in 3 QuiremSpheres™ studies were generally in line with previously reported outcomes in Y90 studies, taking into account differences in patient populations (Figure 12, 13). The comparison of tumour response was challenged by the lack of uniformity in response evaluation and reporting, however, by comparing either mRECIST or RECIST 1.1 reported outcomes in QuiremSpheres™ and Y90 studies, we could see that the outcomes for QuiremSpheres™ were in line with what has been published for Y90. Therefore, the results of this descriptive naïve comparison do not contradict the assumption that Ho-166 SIRT is a technical variant of SIRT with identical route of administration and mechanism of action, and with similar outcomes in terms of efficacy.

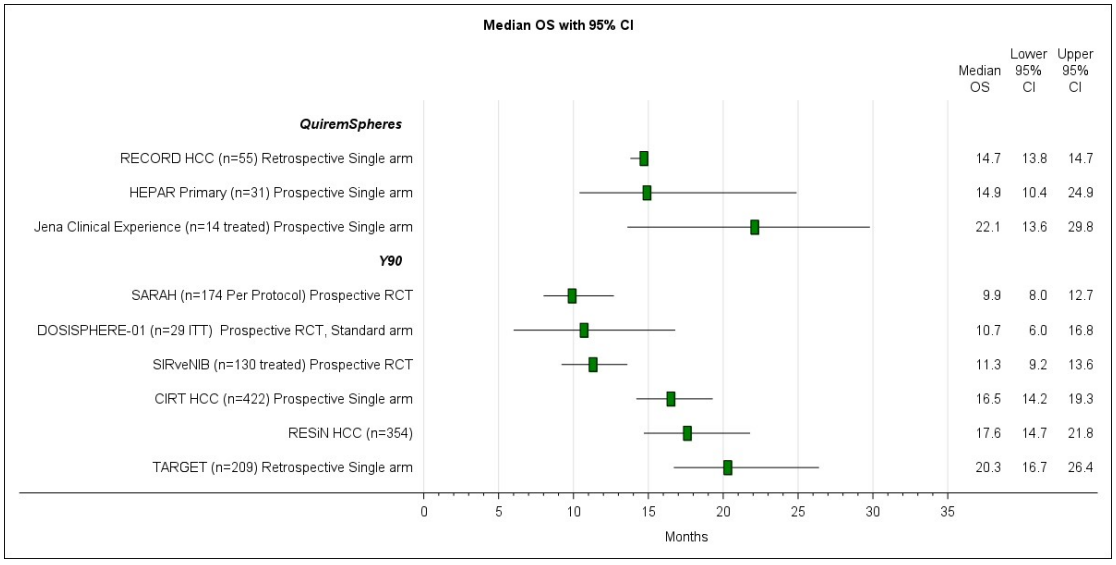

Figure 12. Naïve visual comparison of mOS in QuiremSpheres™ and Y90 studies.

NB: The results from the standard dosimetry arm from DOSISPHERE-01 study were used, since this treatment mode was consistent with the current IFU (as opposed to the personalized dosimetry approach in the experimental arm) and was also comparable with the other listed studies that did not use a personalized dosimetry approach.

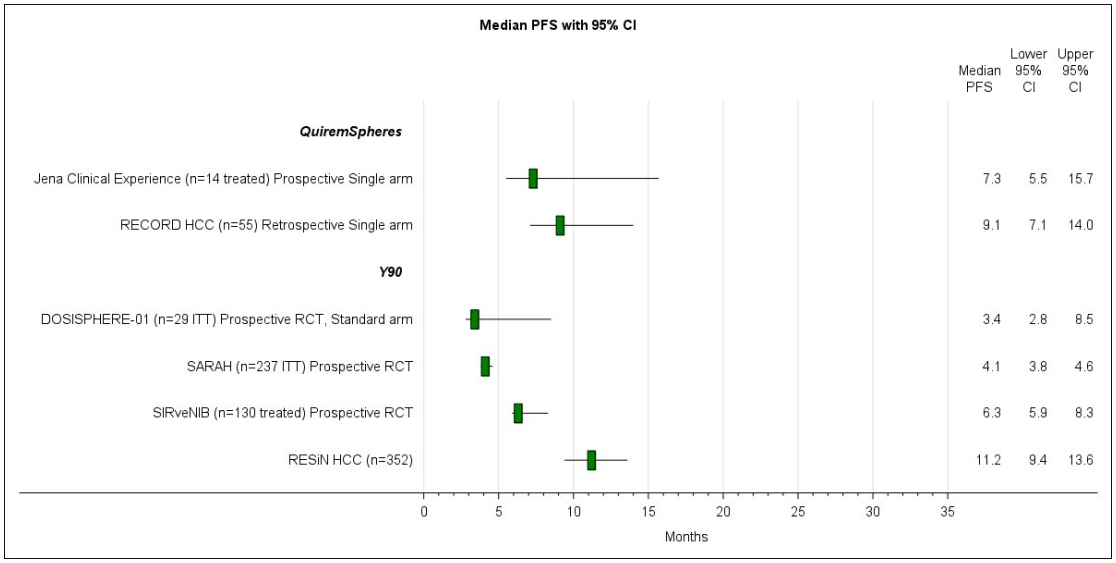

Figure 13. Naïve visual comparison of mPFS in QuiremSpheres™ and Y90 studies.

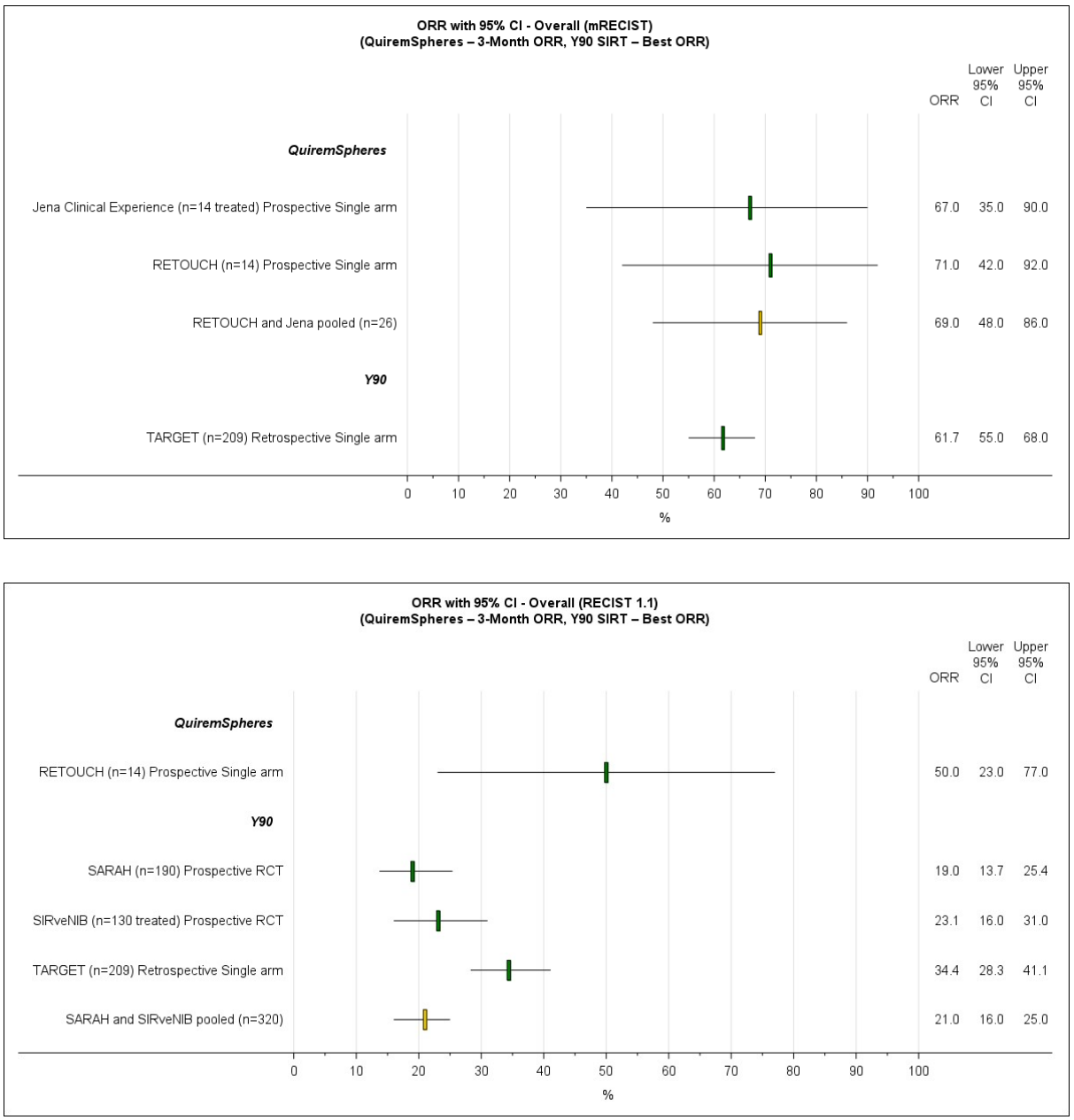

Figure 14. Naïve visual comparison of tumour response in QuiremSpheres™ and Y90 studies.

Response was reported according to mRECIST (above) and RECIST 1.1 (below).

Although the value of tumour response to locoregional treatment as surrogate for survival requires further validation (25), this endpoint is standardly used for assessment of treatment efficacy in clinical trials. Naïve comparison of the objective response rate (ORR) between studies was hindered by different response evaluation methods employed (mRECIST or

RECIST 1.1), however, it could show that the ORR achieved with Ho-166 SIRT was at least as good as that achieved in studies using Y-90 SIRT.

Clinical outcomes of studies used for the presented naïve comparison are presented in Table 13.

Table 13. Clinical outcomes of studies used for the naïve comparison.

Trial acronym	**ORR (CR/PR) %**	**Median PFS / TTP** **(95% CI) months**	**Median OS (95% CI)** **months**	**QoL at 3 months *(not used in the forest plots provided)***
QuiremSpheres™ studies				
HEPAR Primary (17)	54% (19/35%)	NR	14.9 (10.4-24.9)	Median 67% (IQR ~55-82%) EORTC QLQ C30 Global Health Status
RETOUCH (Manuscript submitted)	100% (79/21%)	NR	NR	NR
RECORD (Manuscript submitted)	70.3% (mixed tumour response evaluation reported in the study, not used for the comparison)	9.1 (7.1-14.0)	14.7 (13.8-n.e.)	NR
Jena Clinical Experience (18)	67% (8/58%)	7.3 (5.5-15.7)	22.1 (13.6-29.8)	NR
Y-90 SIRT studies				
SARAH (19)	RECIST 1.1 19% (3/16%)	IIT 4.1 (3.8-4.6)	Per protocol 9.9 (8.0-12.7)	Per Protocol Mean ~60% (SD 35-85%) EORTC QLQ C30 Global Health Status
SIRveNIB (20)	RECIST 1.1 23.1% (NR)	Treated 6.3 (5.9-8.3)	Treated 11.3 (9.2-13.6)	EQ 5D, mean ~75% (CI 70-83%)

DOSISPHERE-01 (21) Standard arm	RECIST 1.1 (according to EASL criteria; not used in the plots) 43% (21/21%)	3.4 (2.8-8.5)	10.7 (6.0-16.8)	NR
DOSISPHERE-01 (21) Personalized dosimetry arm	RECIST 1.1 according to EASL criteria; not used for the naïve comparison 79% (18/61%)	6.0 (3.5-11.6)	26.6 (11.7-NR)	NR
CIRT (22)	NR	NR	16.5 (14.2-19.3)	NR
TARGET (24)	mRECIST 61.7% RECIST 1.1 34.4%	NR	20.3 (16.7-26.4)	NR
RESiN HCC (23)	NR	Total cohort 11.2 (9.4-13.6) BCLC C 6.3 (4.8-30.2)	Total cohort 17.6 (14.7-21.8) BCLC C 13.6 (6.2-21.8)	NR

N.e.; not evaluable; NR, not reported.

Uncertainties in the indirect and mixed treatment comparisons

No sensitivity analysis was conducted to explore the uncertainties in this comparison.

B.3.10 Adverse reactions

- QuiremSpheres™ has an acceptable safety profile within the context of a SIRT procedure in HCC patients
- Adverse events observed with QuiremSpheres™ are comparable with the adverse events observed for the Y90-SIRT products

Safety of QuiremSpheres™ SIRT in patients with HCC was evaluated with two prospective clinical studies, HEPAR Primary and RETOUCH (Tables 14, 15). The two other studies included in this evaluation, RECORD and Jena Clinical Experience, were not used for safety evaluation. The RECORD study was a retrospective study of hospital records that was not

suited for proper safety assessment, and Jena Clinical Experience did not report the safety endpoints in a comparable manner.

Table 14. Summary of clinical adverse events during follow-up of HEPAR Primary and RETOUCH studies.

Adverse event	HEPAR Primary (17)	RETOUCH (Manuscript submitted)
Back pain		
Grade 1/2	17/31 (55%)	0
Fatigue		
Grade 1/2	17/31 (55%)	4/15 (27%)
Ascites		
Grade 1/2	9/31 (29%)	0
Grade 3	1/31 (3%)	0
Dyspnea		
Grade 1	7/31 (23%)	0
Nausea		
Grade 1/2	7/31 (23%)	1/15 (7%)
Abdominal pain		
Grade 1/2	6/31 (19%)	3/15 (20%)
Grade 3	1/31 (3%)	0
Dizziness		
Grade 1	4/31 (13%)	0
Edema limbs		
Grade 1	4/31 (13%)	0
Grade 2	1/31 (3%)	0
Fever		
Grade 1/2	4/31 (13%)	3/15 (20%)
Hepatic pain		
Grade 1	4/31 (13%)	0
Itch		
Grade 1	3/31 (10%)	0
Grade 2	1/31 (3%)	0
Abdominal infection		
Grade 3	1/31 (3%)	0
Allergic reaction		
Grade 3	1/31 (3%)	0
Arthritis		
Grade 3	1/31 (3%)	0
Bradycardia		
Grade 1/2	0	1/15 (7%)
Atrial fibrillation		

Grade 3	1/31 (3%)	0
Bile duct stenosis		
Grade 3	1/31 (3%)	0
Biliary fistula		
Grade 3	1/31 (3%)	0
Cholecystitis		
Grade 3	1/31 (3%)	0
Endocarditis infective		
Grade 4	1/31 (3%)	0
Esophageal varices hemorrhage		
Grade 3	2/31 (6%)	0
Gastric hemorrhage		
Grade 3	1/31 (3%)	0
Hepatic failure due to disease progression		
Grade 5	2/31 (6%)	0
Hip fracture		
Grade 3	1/31 (3%)	0
Intracranial hemorrhage		
Grade 5	1/31 (3%)	0
Ischemia cerebrovascular		
Grade 5	1/31 (3%)	0
Lung infection		
Grade 3	1/31 (3%)	0
Sepsis		
Grade 3	1/31 (3%)	0
Lipothemia		
Grade 1/2	0	1/15 (7%)

Table 15. Laboratory Adverse Events According to CTCAE during follow-up of HEPAR Primary and RETOUCH studies.

Adverse event	HEPARPrimary	RETOUCH
AST increase		
Grade 1/2	24/31 (77%)	5/15 (33%)
Grade 3	5/31 (16%)	0
Platelet count decreased		
Grade 1/2	23/31 (74%)	0
INR increased		
Grade 1/2	24/31 (77%)	0
AP increased		
Grade 1/2	24/31 (77%)	4/15 (27%)
Anemia		
Grade 1/2	21/31 (68%)	0

Grade 3	2/31 (6%)	0
ALT increased		
Grade 1/2	17/31 (54%)	5/15 (33%)
Hypoalbuminemia		
Grade 1/2	19/31 (61%)	0
Grade 3	1/31 (3%)	0
Prolonged APTT		
Grade 1/2	15/31 (48%)	0
Hyponatremia		
Grade 1/2	12/31 (39%)	0
Grade 3	3/31 (10%)	0
Hypokalemia		
Grade 1/2	9/31 (29%)	0
Hyperglycemia		
Grade 1/2	22/31 (71%)	0
Grade 3	6/31 (19%)	0
Creatinine increased		
Grade 1/2	8/31 (26%)	0
Bilirubin increased		
Grade 1/2	10/31 (32%)	5/15 (33%)
Grade 3	1/31 (3%)	
GGT increased		
Grade 1/2	14/31 (45%)	0
Grade 3	14/31 (45%)	0
Hypoglycemia		
Grade 1/2	3/31 (10%)	0
Lymphopenia		
Grade 1/2	14/31 (45%)	
Grade 3	9/31 (29%)	0

For HEPAR Primary, a total of 120 laboratory events with no grade 4-5 events and 168 clinical events were recorded ranging from grade 1-5. The vast majority of patients experienced a grade 1-2 increase in liver enzymes, with maximum grade 3 AST increase in 5/31 (16%) of the patients. However, the dynamic trajectory of these changes during six months follow-up did not show a clear peak or slope. Grade 2 or higher haematological toxicity rarely occurred, besides expected lymphopenia. Patients with diabetes mellitus type II (n=14) experienced a high number of hyperglycemic adverse events, probably due to medication after treatment (i.e.

steroids). Sixteen patients experienced grade 1 and one patient grade 2 back pain on the day of treatment as they had to hold supine position while undergoing a one-day procedure. Clinical serious adverse events occurred 19 times, of which 4 events in 3 patients were related (3 were possibly related to treatment, and 1 definitely). Two of these treatment-related events were from spontaneous bacterial peritonitis (both originated approximately 12 weeks after treatment). One patient deceased due to the infection after one day (treated with iv antibiotics) and the other patient recovered after five days (treated with iv and oral antibiotics). The third patient with BCLC stage B, multifocal HCC, ECOG 0, previously treated with resection and microwave ablation, suffered from radiation-induced cholecystitis and cholangitis one month after treatment, which developed into biliary fistula (grade 3 bilirubin increase), and finally stabilized after endoscopic intervention. His liver function and clinical performance gradually declined until his death one year after treatment. The three patients that experienced worsening of CP score with 3 or 4 points (besides the patient with biliary fistula) had proven progression of disease. These patients received unilobar treatments and showed no signs of radioembolization induced liver disease during the first three months after treatment. Two other patients died of progressive disease and hepatic failure within six months (considered unlikely related to treatment).

In RETOUCH, no adverse events were noted during or immediately after the procedure and no grade ≥3 clinical adverse events were recorded during follow-up. At 24-48 hours after treatment, patients presented with grade 1-2 abdominal pain (20%, 3/15), fever (20%, 3/15), fatigue (13.3%, 2/15), nausea (6.7%, 1/15), lipothymia (6.7%, 1/15) and bradycardia (6.7%, 1/15). One month after the treatment, patients presented with grade 1-2 abdominal pain (6.7%, 1/15), grade 1-2 fatigue (26.7%, 4/15) and grade 1-2 nausea (6.7%, 1/15), demonstrating that the adverse events are limited and for most patients transient in time with the exception of fatigue that increases at the 1-month follow-up. Furthermore, no liver decompensations or worsening of CP score was noted. Laboratory values equally showed only grade 1-2 changes in AST (33%, 5/15), ALT (33% 5/15), bilirubin (33%, 5/15) and ALP (27%, 4/15).

Table 16. Safety endpoints reported by Ho-166 and Y-90 SIRT studies.

Adverse event	HEPAR Primary (17)	RETOUCH (Manuscript submitted)	SARAH (SIRT arm) (19)	SIRveNIB (SIRT arm) (20)	DOSI-SPHERE 01 (Standard arm) (21)	DOSI-SPHERE 01 (Personalized arm) (21)
Constitutional symptoms						
Infection						
Grade 1/2	0/31 (0%)	0/15 (0%)	6/226 (3%)	0/130 (0%)	NR	NR
Grade ≥3	2/31 (6%)	0/15 (0%)	3/226 (1%)	0/130 (0%)	NR	NR
Fever						
Grade 1/2	4/31 (13%)	3/15 (20%)	13/226 (6%)	6/130 (5%)	2/21 (10%)	2/35 (6%)
Grade ≥3	0/31 (0%)	0/15 (0%)	0/226 (0%)	0/130 (0%)	0/21 (0%)	0/35 (0%)
Fatigue / Asthenia						
Grade 1/2	17/31 (54%)	4/15 (27%)	81/226 (36%)	5/130 (3.8%)	8/21 (38%)	12/35 (34%)
Grade ≥3	0/31 (0%)	0/15 (0%)	20/226 (9%)	0/130 (0%)	1/21 (5%)	1/35 (3%)
Gastrointestinal disorders						
Diarrhea						
Grade 1/2	0/31 (0%	0/15 (0%)	26/226 (12%)	2/130 (2%)	1/21 (5%)	5/35 (14%)
Grade ≥3	NR	NR	3/226 (1%)	0/130 (0%)	0/21 (0%)	0/34 (0%)
Nausea & Vomiting						
Grade 1/2	7/31 (23%)	1/15 (7%)	25/226 (11%)	10/130 (8%)	4/21 (19%)	9/35 (26%)
Grade ≥3	0/31 (0%)	0/15 (0%)	1/226 (<1%)	1/130 (<1%)	0/21 (0%)	0/35 (0%)
Abdominal pain						
Grade 1/2	6/31 (19%)	3/15 (20%)	43/226 (19%)	11/130 (9%)	2/21 (10%)	7/35 (20%)
Grade ≥3	1/31 (3%)	0/15 (0%)	6/226 (3%)	3/130 (2%)	0/21 (0%)	0/35 (0%)
Gastrointestinal ulceration						
Grade 1/2	0/31 (0%)	0/15 (0%)	2/226 (1%)	0/130 (0%)	0/21 (0%)	0/35 (0%)
Grade ≥3	0/31 (0%)	0/15 (0%)	3/226 (1%)	1/130 (1%)	0/21 (0%)	0/35 (0%)
Gastrointestinal bleeding						
Grade 1/2	0/31 (0%)	0/15 (0%)	1/226 (<1%)	1/130 (1%)	0/21 (0%)	0/35 (0%)
Grade ≥3	1/31 (3%)	0/15 (0%)	9/226 (4%)	1/130 (1%)	2/21 (10%)	0/35 (0%)
Liver disorders						
Ascites						
Grade 1/2	9/31 (29%)	0/15 (0%)	19/226 (8%)	5/130 (4%)	6/21 (29%)	3/35 (9%)
Grade ≥3	1/31 (3%)	0/15 (0%)	11/226 (5%)	5/130 (4%)	2/21 (10%)	1/35 (3%)
Liver dysfunction						
Grade 1/2	0/31 (0%	0/15 (0%)	28/226 (12%)	1/130 (1%)	0/21 (0%)	1/35 (3%)

Grade ≥3	2/31 (6%)	0/15 (0%)	25/226 (11%)	1/130 (1%)	0/21 (0%)	2/35 (6%)
Radiation hepatitis						
Grade 1/2	0/31 (0%)	0/15 (0%)	0/226 (0%)	0/130 (0%)	0/21 (0%)	0/35 (0%)
Grade ≥3	0/31 (0%)	0/15 (0%)	0/226 (0%)	2/130 (2%)	0/21 (0%)	1/35 (3%)
Radiation pneumonitis						
Grade 1/2	0/31 (0%)	0/15 (0%)	0/226 (0%)	0/130 (0%)	0/21 (0%)	0/35 (0%)
Grade ≥3	0/31 (0%)	0/15 (0%)	1/226 (<1%)	0/130 (0%)	0/21 (0%)	0/35 (0%)
Hypertension						
Grade 1/2	0/31 (0%)	0/15 (0%)	6/226 (3%)	0/130 (0%)	NR	NR
Grade ≥3	0/31 (0%)	0/15 (0%)	0/226 (0%)	0/130 (0%)	NR	NR
Laboratory abnormalities						
Hyperbilirubinaemia						
Grade 1/2	10/31 (32%)	5/15 (33%)	25/226 (11%)	NR	5/21 (24%)	5/35 (14%)
Grade ≥3	1/31 (3%)	0/15 (0%)	8/226 (4%)	NR	1/21 (5%)	1/35 (3%)

The adverse events observed in QuiremSpheres™ treated patients are well in line with the published adverse events of Y-90 SIRT treated patients.

The fact that the adverse events profile of QuiremSpheres™ is highly comparable to the other comparator treatments in this cost-comparison assessment further supports the rationale that the mechanism of action of SIRT is mediated via the β-particle and the microspheres delivered in the capillary bed of tumours and liver tissue.

In appendix F, provide details of any studies that report additional adverse reactions to those reported in the studies in section 3.2.

B.3.11 Conclusions about comparable health benefits and safety

- Health benefits are expected to be comparable for all SIRT devices (using either Y-90 or Ho-166), since the mechanism of action is similar: transarterial delivery of microspheres loaded with beta-emitting isotopes that elicit cell death in the tumour tissue.

- QuiremSpheres™ has demonstrated efficacy in treating HCC patients across BCLC stages. The outcomes observed for OS, PFS, and ORR are similar to the literature of Y-90-SIRT.

- The adverse events profile of QuiremSpheres™ in the HCC setting is very similar to the adverse events profile observed in the literature of Y-90-SIRT.

- In summary, the naïve comparison shows the following: mOS achieved with Ho166 SIRT (ranging from 14.7 to 22.1 months) was not different from that reported for Y-90 SIRT (ranging from 9.9 to 20.3 months) for HCC patients in comparable studies. Likewise, mPFS reported for Ho-166 SIRT (ranging from 7.3 to 9.1 months) was in line with that reported for Y-90 SIRT (ranging from 3.4 to 11.2 months). The comparison of tumour response rate between treatments was challenging because of varying methodologies of evaluation adopted by different studies but was generally aligned between the treatments. Grade 3-5 complications occured after Y-90 SIRT in 28-76% of patients compared with 23% of patients after Ho-166 SIRT. The higher rates of complications observed with Y-90 may be explained in part by the tumour stage of patients included in the studies.

- The results seem to indicate that Ho-166 is not different from Y-90 in terms of efficacy and safety for the treatment of HCC.

B.3.12 Ongoing studies

HolmBrave (NCT 05705791) is an open-label, single arm, multicenter clinical investigation, evaluating the added value of QuiremSpheres™ to Atezolizumab + Bevacizumab for patients with non resectable HCC. The study will evaluate Best Objective Response Rate at 6 months after QuiremSpheres™ SIRT according to mRECIST. Secondary objectives will be to evaluate safety (NCI-CTCAE v5.0), ORR, PFS, Liver PFS, and OS.

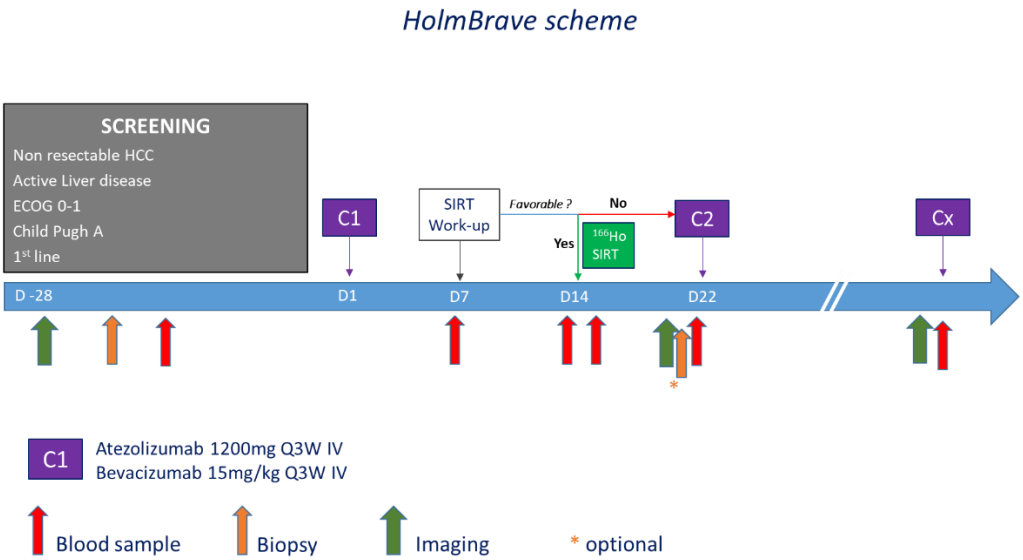

Figure 15. Design presentation of HolmBrave study.

HOMIE-166 (NCT05451862) is a prospective single-arm study to to evaluate ^{166}Ho-SIRT in unresectable early-stage HCC patients with well-preserved liver function and performance status, eligible for curative treatment (SIRT is used as bridge therapy), which will assess ORR as primary objective and duration of response, time to progression, PFS, and OS as secondary objectives.

IHEPAR (NCT05114148) is a Phase II study assessing safety and toxicity profile of a personalized dosimetry approach (healthy liver 45-60 Gy - tumour dose ≥150 Gy) for non-resectable HCC. The study will also assess efficacy, biodistribution/dosimetry, tumor markers response, quality of life, hepatic function, and liver (de)compensation.

RHEPaiR is UK based (Imperial College) Phase II study assessing safety and toxicity profile of a personalized dosimetry approach (healthy liver 45-60 Gy - tumour dose ≥150 Gy) for non-resectable HCC. The study will also assess efficacy, biodistribution/dosimetry, tumor markers response, quality of life, hepatic function, and liver (de)compensation.

Terumo does not anticipate that data from these studies will provide additional evidence for QuiremSpheres™ in the next 12 months for the condition being appraised.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

There are no differences between QuiremSpheres™ and its comparators in terms of location or setting of care.

SIRT is done in specialist centres. Suitability of SIRT is discussed by a multidisciplinary team experienced in interventional and vascular radiology and nuclear medicine.

The procedure is done in 2 stages. First, the work-up is done to assess blood supply to the tumour, assess lung shunt, exclude extrahepatic uptake and plan personalised dosimetry. The treatment occurs after assessment, usually within 2 weeks of a successful work-up phase. It takes 1 to 2 hours to complete. Both work-up and treatment are performed in the Interventional Radiology angiography suite. Post treatment a scan is performed in Nuclear Medicine to determine the distribution of the radioactive particles in the liver.

The complete work-up and SIRT procedure can be performed either in one day or in several days. In the early HEPAR I and HEPAR II studies, a same-day procedure was used (26, 27). However, the adoption of same-day procedure in the UK and other geographies is low due to scheduling challenges and patient preference, and it also incurs additional costs for hospital and/or patient as hotel rooms need to be booked for overnight stays prior to the case.

Post SIRT treatment many centres will keep the patient in overnight – this can be in a specific ward dependent on the radiation dose measurements taken and what the centres 'local' plans are relating to this.

There are no differences in resource use between the technology and the comparators. In NICE TA688 guidance, it is noted that there are identical procedure-related administration costs for all SIRTs. In the previous appraisal, the only cost difference between the technology and the comparators was the price of the technology. Terumo has submitted a new PAS proposal for QuiremSpheres™.

B.4.2 Cost-comparison analysis inputs and assumptions

Features of the cost-comparison analysis

Terumo is not submitting a cost-comparison analysis. In the original TA688, the time-horizon is lifetime (10 years). Although the comparator is different, the time-horizon should remain the same.

Intervention and comparators' acquisition costs

Table 17. Acquisition costs of the intervention and comparator technologies

	QuiremSpheres™	SIR-Spheres	TheraSphere	[Add more columns as needed]
Microspheres (medical device)				
(Anticipated) care setting	Inpatient, NHS hospitals	Inpatient, NHS hospitals	Inpatient, NHS hospitals	
Acquisition cost (excluding VAT) *	[redacted] (PAS under evaluation)	PAS price from TA688 to be used	PAS price from TA688 to be used	
Method of administration	SIRT procedure – Interventional Radiology angio suite	SIRT procedure – Interventional Radiology angio suite	SIRT procedure – Interventional Radiology angio suite	
Doses	MIRD model	BSA model	MIRD model	
Dosing frequency	One-off procedure	One-off procedure	One-off procedure	
Dose adjustments	Not applicable	Not applicable	Not applicable	
Average length of a course of treatment	One-off procedure	One-off procedure	One-off procedure	
Average cost of a course of treatment (acquisition costs only)	One-off procedure	One-off procedure	One-off procedure	
(Anticipated) average interval between courses of treatment	One-off procedure	One-off procedure	One-off procedure	
(Anticipated) number of repeat courses of treatment	1.28	1.28	1.28	

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme or other nationally available price reduction. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

Intervention and comparators' healthcare resource use and associated costs

In appendix G describe how relevant cost and healthcare resource data for England were identified.

Table 18. Resource costs of the intervention and comparator technologies.

	QuiremSpheres™	SIR-Spheres	TheraSphere	Source
Proportion of work-ups leading to SIRT	81.4%	81.4%	81.4%	TA688, Appraisal consultation document Committee papers, pg 139
Treatment of SIRT work-up failure patients	Sorafenib 61.9% BSC 38.1%	Sorafenib 61.9% BSC 38.1%	Sorafenib 61.9% BSC 38.1%	TA688, Appraisal consultation document Committee papers, pg 139
Mean number of work-ups (treated patients)	1.09	1.09	1.09	TA688, Appraisal consultation document Committee papers, pg 139
Mean number of SIRT procedures	1.28	1.28	1.28	TA688, Appraisal consultation document Committee papers, pg 139
Treatment cost inputs				
Work-up	£860.32	£860.32	£860.32	TA688, Appraisal consultation document Committee papers, pg 139. Cost was not inflated. TA688 guidance 3.40, pg 29 (*identical procedure-related administration costs for all SIRTs*)
Procedure costs	£2,790	£2,790	£2,790	TA688 refers to HRG YR57Z.

				TA688 guidance 3.40, pg 29 (*identical procedure-related administration costs for all SIRTs). Cost was not inflated*

Adverse reaction unit costs and resource use

	QuiremSpheres™	SIR-Spheres	TheraSphere	Source
Adverse events costs (total)	£477.69	£477.69	£477.69	TA688, Appraisal consultation document Committee papers, pg 14 Cost was not inflated

Miscellaneous unit costs and resource use

Clinical expert validation

Aspects for clinical validation	**Dr Matthew Seager** **Consultant Interventional Radiologist** **Kings College Hospital, London**	**Professor Marnix Lam** **Professor of Nuclear Medicine, UMC Utrecht, the Netherlands**	**Dr. J.K. Bell** **Consultant Interventional Radiologist & Clinical Director** **Christie Hospital, Manchester**
Numbers of patients with adults with unresectable	Approximately 150 per year at King's	In the UMC Utrecht in the Netherlands, on an annual basis, we see approximately	Approximately 50 patients a year at The Christie NHS Foundation Trust.

advanced hepatocellular carcinoma		50 new HCC patients in this scenario	
Current clinical pathway of care	Patients are discussed at MDT with all locoregional and systemic options considered.	Treatment options include both locoregional treatment (e.g., ablation, TACE, SIRT) and systemic options. Patients are always first evaluated for locoregional treatment options	Patients are referred to the regional liver/hepatobiliary MDT for consideration of different treatment options. The MDT broadly follows the BCLC strategy and all locoregional therapies are considered e.g., ablation, TACE and SIRT.
Treatment setting for Y-90-SIRT	BCLC A-C. Predominantly B/C. Local criteria for SIRT are: • Irresectable tumours > 5 cm • Irresectable tumours non-responsive to TACE • Tumours with portal vein invasion up to the lobar level • Downstaging with a view to surgery, but FLR insufficient	In all stages of disease, from BCLC (very) early stage disease to advanced stage disease.	This has been an established therapy at The Christie since 2005. There are ten commissioned treatment centres in England. The number of centres is increasing due to growing clinical evidence and increased demand. SIRT is delivered by expert teams to ensure that the treatment is delivered in accordance with international standards e.g., ARSAC licence, cone beam CT capability, medical physics and

			radiopharmacy support etc.
The similarity of clinical efficacy between QuiremSpheres™ and Y-90-SIRT	Direct head to head trials are lacking. The data produced thus far suggests a similar efficacy of QuiremSpheres™. There are differences in the products in terms of specific activity, material used, specific weight, but the method of action in terms of radiation is the same.	All products SIRT may be regarded as a 'technical variant' of SIRT with clinically equivalent results. The medical devices differ by used isotope, specific activity, material used and specific weight, but clinical accuracy is equivalent since the method of action (i.e., radiation) is the same for all.	No difference in safety and efficacy. Fewer microspheres are delivered with QuiremSpheres™, so it is less embolic than SIR-Spheres. There is less activity per sphere than TheraSphere so there is potentially less risk of radioembolisation induced liver disease (REILD). Holmium offers advantages as it can be imaged with MR and enables more advanced dosimetry.
The similarity of adverse events between QuiremSpheres™ and Y-90-SIRT	Adverse effects are also expected to be the same as QuieremSpheres™ is a variation of the same procedure and the evidence produced to date suggests a similar side effect profile.	The clinical accuracy, both efficacy and toxicity, is similar as all used medical devices may be regarded as technical variant of the same procedure.	Similar safety profile. No additional concerns regarding adverse events.
Position of QuiremSpheres™ in the clinical care pathway	It is an alternative to the Yttrium products.	Because of the above, the position of QuiremSpheres™ in the clinical care pathway is the same as for all medical devices used for SIRT.	QuiremSpheres™ can be used for the same clinical indication as Y90 microspheres, which were approved for use in HCC in February 2021 following a NICE MTA. SIRT is indicated

			in patients with Child Pugh A liver impairment and when conventional transarterial therapies are inappropriate. The evidence base for QuiremSpheres™ has increased and data demonstrates that it is equivalent.
Switching patients currently receiving Y-90 SIRT to QuiremSpheres ™	This is not anticipated to be a problem as it is a variant of the same technique and we are able to re-treat patients with SIRT if we remain within dose limits.	Most hospitals choose one of the used medical devices to treat all their patients. Changing between products would therefore be the same as changing between hospitals, which should not make a difference.	Either Yttrium or Holmium isotopes can be used, and device selection would be at the discretion of the clinical team. There are some potential advantages offered by QuiremSpheres™, which are described above.

Uncertainties in the inputs and assumptions

B.4.3 Base-case results

Terumo did not complete a full cost-comparison model, but rather we used assumptions from TA688 as well as updated acquisition costs to present the base-case results below.

Table 19. Base-case results.

Technologies	Acquisition costs (£)	Resource costs (£) (work-up + procedure) (TA688 values)	Adverse event costs (£) (TA688 values)	TOTAL CO
QuiremSpheres™	[redacted] PAS price	£3,650.32	£477.69	£4,128.01 + acquisition
SIR-Spheres	PAS price (unknown to Terumo)	£3,650.32	£477.69	£4,128.01 + acquisition
TheraSphere	PAS price (unknown to Terumo)	£3,650.32	£477.69	£4,128.01 + acquisition

B.4.4 Sensitivity and scenario analyses

No sensitivity analysis was performed.

B.4.5 Subgroup analysis

No subgroup analysis was performed.

B.4.6 Interpretation and conclusions of economic evidence

We argue that QuiremSpheres™ is cost-neutral compared to the comparators SIR-Spheres and TheraSphere. Indeed we have described that equivalent clinical results can be expected and that costs are similar.

The clinical equivalence and the ability to switch between QuiremSpheres™ and its comparators is validated by 3 clinical experts. Professor Lam is an internationally-renowned nuclear medicine professor and SIRT user and has the largest experience using QuiremSpheres™. Dr Seager, from Kings College, and Dr Bell, from the Christie Hospital are 2 of the most renowned and experienced SIRT users in England and the UK.

The HTA from the Netherlands states that “In summary, these results seem to indicate that holmium is about as effective as yttrium… As the treatment of holmium-166 SIRT does not have increment in cost, there will be no additional costs in general.” This supports our position of a neutral cost-comparison.

B.5 References

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B.6 Appendices

Appendix C: Instructions for Use (IFU)

C1.1 IFU QuiremSpheres

The instructions for use for QuiremSpheres can be found in the attached object.

We have submitted AIMDD and MDR IFUs

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

Search strategy

For this appraisal, we conducted a systematic literature research (SLR) based on the published SLR from Wade et al. (2020, https://doi.org/10.1186/s13643-020-01447-x). The protocol of the SLR in question is available on line: https://www.nice.org.uk/guidance/ta688/documents/final-protocol We reproduced the steps of this protocol (Appendix 12.1) only for the part concerning the SIRT treatments (not comparators, which were systemic treatments) for all studies with publication dates between January 25th 2019 (end date of the SLR of Wade et al.) and December 1st 2023. We applied the abovementioned search strategy to conduct a search in MEDLINE for articles, published in English and with available full texts.

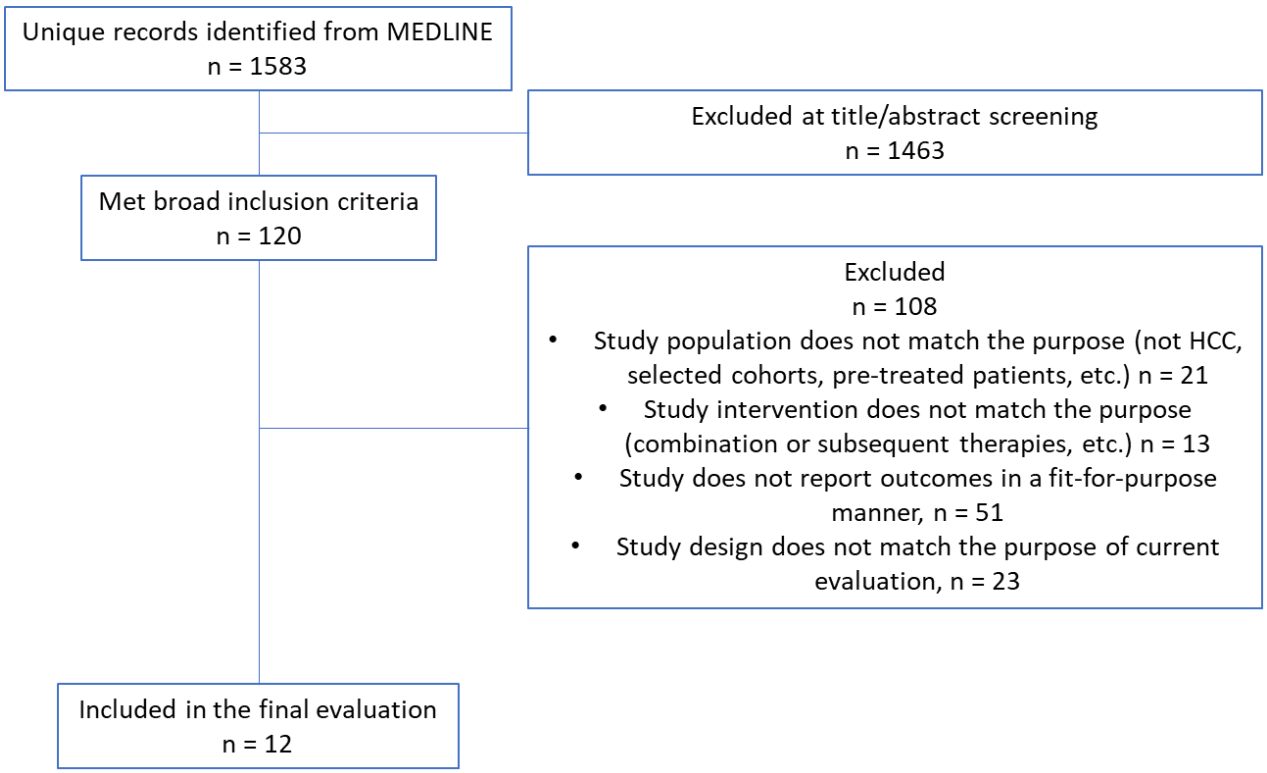
The search and study selection were performed by a single person experienced in conducting SLRs via a two-step process of title/abstract (selection 1) and full text (selection 2) screening. The search and study selection were then verified by a second independent reviewer on a random sample of 10% of the records. The final lists of excluded and included studies were verified and approved by the whole team, with dispute resolution in the process.

Study selection

A total of 1583 unique records published between January 25th 2019 and December 1st 2023 were delivered by the search (see PRISMA Flow Chart below). Study selection was performed based on pre-defined selection criteria:

- the study should include a cohort of HCC patients of a reasonable number;
- Patient population should fit for purpose of this evaluation: studies focussed on patients that have previously received another treatment, were treated with the intent of bridging to transplant, or studies, restricted to specific age cohort or tumour characteristics were not considered;

- Patients should be treated with SIRT as stand-alone therapy;
- The studies should report the outcomes of interest, namely: tumour response, PFS and OS;
- The studies should have appropriate design allowing for comparison with available data for QuiremSpheres™.



The list of studies included for the final evaluation (n = 12) is presented in the Table below. Out of these 12 studies that met the inclusion criteria, 6 were included in the final naïve comparison presented in this evaluation. Detailed reasons for exclusion of the other 6 studies are presented in the Table below.

1st author, year	doi	Title	Included in the naïve comparison?	Reason for exclusion from the naïve comparison
Makary M, 2023	10.1016/j.acra.2023.07.007	Long-term Clinical Outcomes of Yttrium-90 Transarterial Radioembolization for Hepatocellular Carcinoma: A 5-Year Institutional Experience	No	The study included a mixed cohort of patients, of which more than 77% could be downstaged to or maintained within the Milan criteria
Casáns-Tormo I, 2023	10.1016/j.remnie.2023.05.004	Evaluation of results after 112 radioembolizations with (90)Y-microspheres	No	The study included only a small cohort of patients with HCC treated with SIRT only
Hur M, 2023	10.3350/cmh.2023.0076	Transarterial radioembolization versus tyrosine kinase inhibitor in hepatocellular carcinoma with portal vein thrombosis	No	Long-term evaluation of OS in this study was not comparable with the other studies in this evaluation
Drescher R, 2023	10.3390/biomedicines11071831	Clinical Results of Transarterial Radioembolization (TARE) with Holmium-166 Microspheres in the Multidisciplinary Oncologic Treatment of	Yes	

		Patients with Primary and Secondary Liver Cancer		
Reinders M, 2022	10.2967/jnumed.122.263823	Safety and Efficacy of (166)Ho Radioembolization in Hepatocellular Carcinoma: The HEPAR Primary Study	Yes	
Dhondt E, 2022	10.1148/radiol.211806	(90)Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial	No	This study included patients that were also eligible to the conventional transarterial therapy (TACE)
Salem R, 2021	10.1002/hep.31819	Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study	No	This study included patients that were also eligible to the conventional transarterial therapy (TACE)
Lam M, 2022	10.1007/s00259-022-05774-0	A global evaluation of advanced dosimetry in transarterial radioembolization of hepatocellular carcinoma with Yttrium-90: the TARGET study	Yes	

Frantz S, 2021	10.1016/j.jvir.2021.03.535	Multicenter Evaluation of Survival and Toxicities of Hepatocellular Carcinoma following Radioembolization: Analysis of the RESiN Registry	Yes	
Van Thai N, 2021	10.1186/s12876-021-01805-6	Efficacy and safety of selective internal radiation therapy with yttrium-90 for the treatment of unresectable hepatocellular carcinoma	No	The overall patient population in this study was not reflecting the populations of the other selected studies well enough, and the results of this retrospective study were not presented with sufficient granularity to allow comparison
Garin E, 2021	10.1016/S2468-1253(20)30290-9	Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial	Yes	

Helmberger T, 2021	10.1007/s00270-020-02642-y	Clinical Application of Trans-Arterial Radioembolization in Hepatic Malignancies in Europe: First Results from the Prospective Multicentre Observational Study CIRSE Registry for SIR-Spheres Therapy (CIRT)	Yes	

Therefore, for QuiremSpheres™ studies, all relevant clinical studies in patients with HCC that were published or completed since the previous NICE appraisal were included. For studies with Y90 SIRT, apart from the recent studies delivered by the SLR, we have included the relevant studies that were part of the previous evaluation, namely, SARAH and SIRveNIB studies. The Dutch Healthcare Agency, in its assessment of QuiremSpheres™ in HCC, used 3 RCTs to compare results with Y90: SARAH (19), SIRVENIB (20) and DOSISPHERE-01 (21), and all 3 were included in the current evaluation, together with a prospective observational study with SIR-Spheres CIRT (22), a prospective real-world registry with SIR-Spheres RESiN (23), and a retrospective single-arm study with TheraSphere TARGET (24).

Complete reference list for included studies

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Complete reference list for excluded studies

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Summary of trials used for indirect or mixed treatment comparisons

No indirect or mixed treatment comparison performed.

Methods and outcomes of studies included in indirect or mixed treatment comparisons

No indirect or mixed treatment comparison performed.

Methods of analysis of studies included in the indirect or mixed treatment comparison

No indirect or mixed treatment comparison performed.

Programming language for the indirect or mixed treatment comparison

No indirect or mixed treatment comparison performed.

Risk of bias of studies included in indirect or mixed treatment comparisons

No indirect or mixed treatment comparison performed.

D1.2 Participant flow in the relevant randomised control trials

No randomised control trials available for QuiremSpheres

D1.3 Quality assessment for each study

Table 1. Summary of quality assessment – HEPAR Primary

Criterium	Assessment
1. Was the study question or objective clearly stated?	Yes, the aim of this early phase II study was to establish the safety and toxicity profile of QuiremSpheres in patients with HCC.
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes, there were clear prespecified inclusion and exclusion criteria
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?	Yes, these patients reflect the locally intermediate/advanced HCC populations for which SIRT is currently used

4. Were all eligible participants that met the prespecified entry criteria enrolled?	No, two patients discontinued the study because of significant lung shunt or because they chose an alternative treatment
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes, sample size of 30 patients was appropriate
6. Was the intervention clearly described and delivered consistently across the study population?	Yes, median treatment efficiency (prescribed vs net administered activity was 95% (range, 74-100%)
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes, primary endpoint was the rate of unacceptable toxicity using CTCAE methodology, which was defined as grade 3 hyperbilirubinemia in combination with ascites and low albumin in the absence of disease progression (i.e., radioembolization-induced liver disease) or any serious adverse event or serious device defect possibly, probably, or causally related to treatment. Laboratory values and ascites was assessed in all patients
8. Were the people assessing the outcomes blinded to the participants' interventions?	Yes, imaging findings were performed by two independent radiologist. In case of discordance a third radiologist was consulted. Laboratory analysis are performed in another department.
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes, only 2 patients were lost to follow-up (6%). Unclear if accounted for in the analysis but toxicity occurs normally within 2 months and no loss to follow-up was seen there.
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes, posttreatment follow-up at 3 and 6 wk and at 3 and 6 mo included blood and physical examinations, questionnaires, hepatobiliary scintigraphy (at 3 mo), and MRI (at 3 and 6 mo)

12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	

Table 2. Summary of quality assessment – RETOUCH

Criterium	Assessment
1. Was the study question or objective clearly stated?	Yes, the primary endpoint of the study was feasibility of QuiremSpheres with this higher tumor dose in our patient population, as well as the assessment of early (24-48h) and late (1 month) safety and toxicity profiles (CTCAE v5.0). Adverse events were subdivided in three categories: clinical, biological, radiological.
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes, there were clear prespecified inclusion and exclusion criteria
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?	Yes, the patients included in the study represent the place of SIRT in the recent BCLC algorithm
4. Were all eligible participants that met the prespecified entry criteria enrolled?	No, 5 patients were excluded because of poor tumor uptake, extra-hepatic deposition and angiographic lung shunt at day of treatment.
5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear
6. Was the intervention clearly described and delivered consistently across the study population?	Yes, as it was part of primary outcome a technical success was achieved for all attempted treatments (100%)
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed	Yes, feasibility and toxicity was assessed with all patients

consistently across all study participants?	
8. Were the people assessing the outcomes blinded to the participants' interventions?	Unclear, laboratory analysis are however performed in different department (for safety)
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes, 1 patient (6.7%) lost to follow-up but only after 3 months (beyond the primary end point)
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	No
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes individual-level data was provided by means of a Swimmersplot

Table 3. Summary of quality assessment – RECORD

Criterium	Assessment
1. Was the study question or objective clearly stated?	Unclear
2. Were eligibility/selection criteria for the study	No; real-world evidence study from retrospective hospital records

population prespecified and clearly described?	
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	No sample size calculations were made
6. Was the intervention clearly described and delivered consistently across the study population?	No: intervention performed according to each hospital's practice
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' interventions?	No
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Not applicable
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	No
11. Were outcome measures of interest taken multiple times before the intervention and multiple	No

times after the intervention (i.e., did they use an interrupted time-series design)?	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	No

Table 4. Summary of quality assessment – Jena Clinical Experience

Criterium	Assessment
1. Was the study question or objective clearly stated?	Yes, the objective of the study was to prospectively capture the performance of QuiremSpheres in a real-world setting by OS, PFS, treatment-free interval, response rate
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes, despite being an observational study inclusion and exclusion criteria were clearly mentioned
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?	Yes, real-world setting
4. Were all eligible participants that met the prespecified entry criteria enrolled?	No, the decision of which SIRT product to use was made at the discretion of the nuclear medicine specialists and radiologists performing the treatment.
5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear, descriptive observational study
6. Was the intervention clearly described and delivered consistently across the study population?	Yes, both the procedure and dosing strategy have been described.
7. Were the outcome measures prespecified, clearly defined, valid,	Yes

reliable, and assessed consistently across all study participants?	
8. Were the people assessing the outcomes blinded to the participants' interventions?	Unclear
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Unclear
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	No
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes, detailed description for majority of patients and overview of single patient data by Swimmersplot

Appendix E: Subgroup analysis

No subgroup analysis performed

Appendix F: Adverse reactions

In the Jena Clinical Experience study, which was a prospective single center observational study, the adverse events results were not structurally described in the paper with the accorded grading. Therefore, we have not included them in the table format.

But we would like to describe their findings here: In the 24-48h after the procedure, 21% (3/14) experienced abdominal pain. No other adverse events were described in the first 48 hours. The liver function, determined by Child-Pugh Score was in 13 out of 14 patients (93%) A5/A6, and in one patient (7%) B7. In 8 out of 14 patients (57%), the CPS remained unchanged at the 3-month follow-up. In 4 out of 14 patients (29%), CPS changed from A5 to A6, in three cases due to new ascites. In 2 out of 14 patients (14%) the liver function significantly deteriorated, from CPS A5/B7 to C10, respectively.

Appendix G: Cost and healthcare resource identification, measurement and valuation

[Describe how relevant cost and healthcare resource data for England were identified.] [Explain any assumptions made and the rationale for these.] [It may be appropriate to use a systematic approach to identify resource use and cost data, for example if service provision or disease management has changed since the technology appraisal of the comparator(s), or if there are differences in resource use between the technology and the comparators which warrant the identification of new data sources.]

[Search strategies and inclusion criteria should be provided in the appendix. Published and unpublished studies may be considered.] [If there are limited data for England, the search strategy may be extended to capture data from other countries. Please give the following details of included studies:]

- [country of study]
- [date of study]
- [applicability to clinical practice in England]
- [cost valuations used in the study]
- [costs for use in the economic analysis]
- [technology costs.]

[When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment-by-results (PbR) tariffs are appropriate for costing the intervention being appraised.] [Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the PbR tariff.] [Provide the relevant Healthcare Resource Groups and PbR codes and justify their selection.]

Appendix H: Price details of treatments included in the submission

H1.1 Price of intervention

Table 1 Details of intervention costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	PAS price
QuiremSpheres	Nuclear medicine / Interventional Radiology	Not relevant	Not relevant	£12,000		[redacted]
Abbreviations: PAS, Patient access scheme						

H1.2 Price of comparators and subsequent treatments

Table 2 Details of comparators and subsequent treatment costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source
SIR-Spheres	Nuclear medicine/Interventional Radiology	Not relevant	Not relevant	£8,000 PAS price not available to Terumo	NICE TA688
Therasphere	Nuclear medicine/Interventional Radiology	Not relevant	Not relevant	£8,000 PAS price not available to Terumo	NICE TA688
Abbreviations: PAS, Patient access scheme					

Appendix I: Checklist of confidential information

Provided in separate document: Appendix D_ID6376_Confidential information checklist

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

QuiremSpheres™ for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

Summary of Information for Patients (SIP)

January 2024

File name	Version	Contains confidential information	Date
ID6376_Summary_Info_Patients_QuiremSpheres_no CON_22Jan2024	V1	Yes	22/01/2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

Note to reviewers: we have chosen to reference documents and sources in each section, favouring weblinks that can be easily accessible rather than traditional referencing styles and favouring patient-directed sources (such as cancer charities websites) rather than scientific articles. We hope our document is useful and that we have succeeded in writing in plain language.

1a) Name of the medicine (generic and brand name):

Response: Holmium-166 Microspheres / QuiremSpheres™

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response: Adults with unresectable advanced hepatocellular carcinoma with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: QuiremSpheres™ is indicated for the treatment of unresectable liver tumours. CE Mark was first obtained in April 2015 under the Active Implantable Medical Device Directive (AIMDD). CE Mark under the Medical Device Regulation (MDR) has been

obtained in April 2023 and will start being valid as of March 2024. QuiremSpheres™ is also registered with the MHRA.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:
There are no existing collaboration with any patient group based in the UK. Terumo has had interactions and collaboration in 2021/22 with 2 European associations: Digestive Cancers Europe (DiCE) and the European Liver Patients' Association (ELPA).

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

- Primary liver cancer is rare in the UK, but the number of people developing the disease is increasing (1)
- Hepatocellular carcinoma (HCC) is the most common form of liver cancer in England. It is sometimes called hepatoma. About 85% of people diagnosed with primary liver cancer will have Hepatocellular Carcinoma (HCC) (2)
- In the UK, between 2016 and 2018, on average 6,214 people were diagnosed with liver cancer every year. (3)

Compared with other cancers, there is a very poor survival rate - on average only 12% of those diagnosed will live for five years. There are often no symptoms in the early stages and patients are usually diagnosed very late. People diagnosed frequently also have advanced liver disease (as well as cancer) which means treatment is more complicated than for many other types of cancers. Diagnosis of cancer often comes at the same time as the diagnosis of underlying liver disease.
Symptoms at an advanced stage may include unexplained weight loss, jaundice, itchy skin, a very swollen abdomen (ascites), nausea and vomiting. (2)

Patient experts explained that HCC can have a substantial impact on quality of life. (British People with HCC and their carers live with uncertainty and hopelessness. Often people with HCC also live with stigma and isolation because of underlying causes of disease, such as alcohol. (4)

If HCC is detected early, potentially curative treatment options are available such as transplant or surgical removal but for advanced HCC there are no specific symptoms, and so less than 30% of patients are diagnosed in the early stages of the disease where potentially curative treatment is available. (2)

Patients with advanced HCC have a very poor prognosis and there are very few treatment options. Patients are often relatively young and are completely shell shocked and devastated on hearing about the poor prognosis on diagnosis. Patients also report feeling extremely unwell, very tired and weak. (2)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

To start with, most people see their GP, who may do some blood tests. If these are abnormal, your GP will refer you to a specialist. At the hospital, you may have:

- more blood tests
- an ultrasound, CT and MRI scan.
- If you have a long term liver condition, you may already be having regular blood tests and ultrasounds. This 'surveillance' is to pick up any cancer as early as possible.

Your specialist can often diagnose HCC from a scan. But sometimes they need a tissue sample (biopsy). To get this, they may put a needle through the skin and into the liver. The biopsy will be examined for signs of cancer, this can take a week or so.

After your tests, a group of specialists called a multi-disciplinary team (MDT) will meet to look at the results of your tests and decide on the best course of treatment for you. (5)

When Selective Internal Radiation Therapy (SIRT) is recommended by the MDT, there would be no additional tests required when QuiremSpheres™ is used compared to other SIRT technologies approved by NICE (TA688, SIR-Spheres and TheraSphere).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:
Your treatment depends on the size, number and position of tumours in your liver and whether the cancer has spread. Your doctor will also consider any other medical

conditions you have and how well your liver is working. Your doctor will talk through the options with you and your family, so you can decide together what's best for you.

You will be given a clinical nurse specialist who will be your main point of contact during your treatment. They are a good person to talk to about your treatment options and you can call them with any questions or concerns. (5)

Treatment options include surgery or ablation in early-stage disease, transarterial therapies in intermediate-stage disease, and chemotherapy or systemic therapy in advanced-stage disease, as well as best supportive care. (NICE appraisal TA688)

NICE recommends selective internal radiation therapy (SIRT), a locoregional transarterial therapy: SIR-Spheres or TheraSphere as an option for treating unresectable advanced HCC only for adults with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate.

What does unresectable mean?
Unresectable liver cancer is the one that is at the current moment cannot be safely treated with surgery because of its size or location.

What does advanced mean?
Advanced liver cancer means that the disease have spread beyond the liver or invaded the blood vessels (such as portal vein), however, the liver still functions properly.

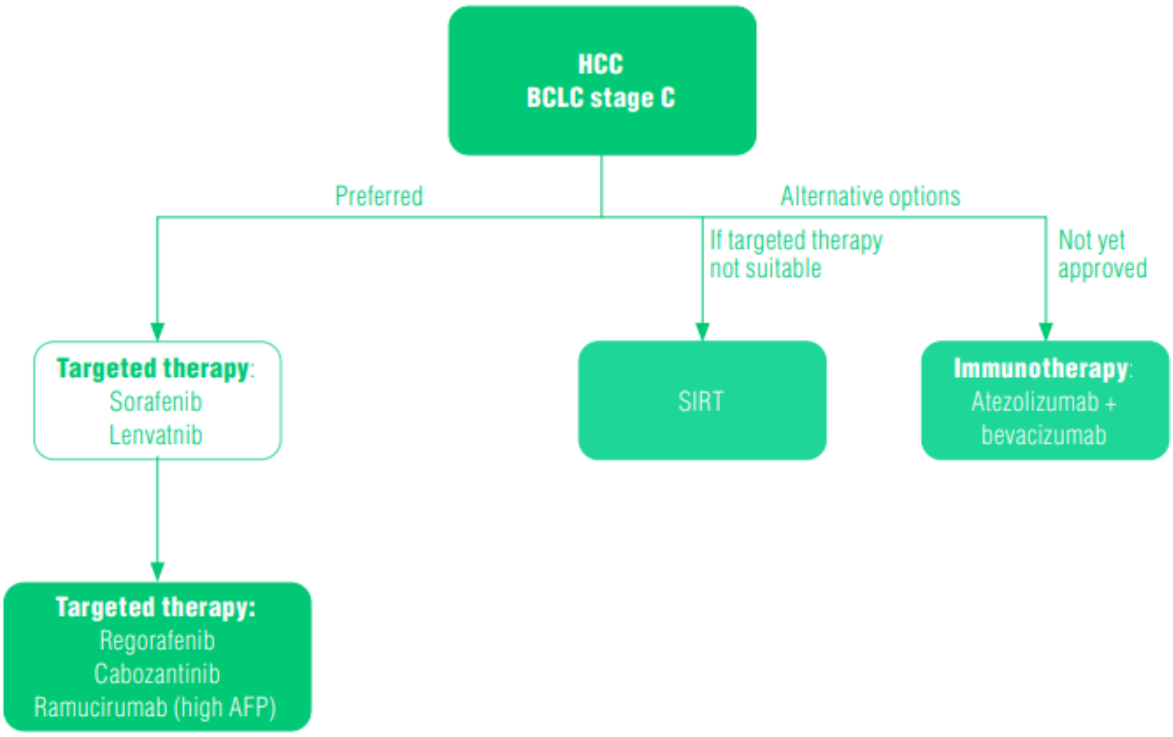
What does Child-Pugh grade A mean?
If you have liver cancer, doctors assess how well your liver is working using the Child-Pugh classification system. Child-Pugh looks at:

- the level of a waste product (called bilirubin) in the blood
- the level of a protein (called albumin) in the blood
- how quickly your blood clots
- whether there is any build-up of fluid in the tummy area (abdomen), called ascites
- whether liver damage is affecting how the brain is working (encephalopathy).
- The results help doctors decide which treatments are best for your situation. Having certain treatments will depend on how well the liver is able to cope. They will also look at the stage of the cancer when planning your treatment.

Based on this, people fall into 1 of 3 groups:

Child-Pugh A – the liver has some damage, but is working normally.
Child-Pugh B – there is some damage to the liver, affecting how well it works.
Child-Pugh C – the liver is very damaged and is not working well. It may not be able to cope with treatment for the cancer.

Therapy options recommended by the European Society for Medical Oncology (ESMO) for the advanced HCC are presented on the Figure below (6).



In the UK, NICE recommends the following systemic treatments for advanced disease:
• Cabozantinib as an option for treating advanced HCC only for adults who have had sorafenib, have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 (TA849).
• Atezolizumab plus bevacizumab as an option for treating advanced or unresectable HCC only for adults who have not had previous systemic treatment and have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 (TA666).
• Regorafenib as an option for treating advanced unresectable hepatocellular carcinoma only for adults who have had sorafenib, have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 (TA555).
• Lenvatinib as an option for untreated, advanced, unresectable HCC only for adults with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 (TA551).
• Sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment (TA474).

NICE currently also recommends SIRT treatment as alternative option to systemic treatments for advanced HCC with SIR-Spheres and TheraSphere. (4) QuiremSpheres™ is an alternative to SIR-Spheres and TheraSphere, which has the same position in the treatment pathway.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include

the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:
HCC, as well as side effects of therapies necessary for treatment of HCC, can have significant negative effect on the patient's quality of life (QoL). Patient experience in HCC is the subject of several studies evaluating patient-reported outcomes (PROs). In the UK, a recent large (256 respondents) patient survey conducted in collaboration with London School of Economics & Political Science reported insights on patients' experience, quality of life, and the effect of therapies. (7)

The survey has demonstrated that side effects of late-stage treatments of HCC (including systemic treatments such as sorafenib) reduced the patients' QoL. Fatigue and pain were reported as the greatest burden on QoL. In patients receiving noncurative treatment, those using oral anticancer therapy were more likely to rate their QoL as poor compared with those taking selective internal radiation therapy or TACE. (8)

The importance of collecting PROs in clinical studies of treatments for HCC was investigated in a recent study, in which patients living with HCC (25 respondents) were invited to participate in qualitative interviews and rate the disturbance of their experiences (8). The most prevalent and disturbing experiences across the disease stages were fatigue/lack of energy and emotional impacts such as frustration, fear, and depression. Abdominal pain and skin-related issues were particularly common and disturbing in individuals with HCC stage C. (8)

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Selective internal radiation therapy or SIRT is a treatment that delivers targeted internal radiation directly to the tumour. It is a treatment for liver tumours that cannot be removed by surgery. SIRT can also be known as Transarterial Radioembolization (TARE) or simply radioembolization.

A therapeutic dose of radioactive microspheres is delivered to the liver tumors. Very small radioactive spheres (microspheres) are inserted directly into the liver lesions. (9) These spheres are 30 times smaller than a millimetre. This is comparable to the thickness of a hair. These spheres contain the radioactive substance holmium-166 (for QuiremSpheres™) or yttrium-90 (for SIR-Spheres and TheraSphere). These get stuck in the smallest blood vessels feeding the tumour. In this way, liver lesions are irradiated from within, with the intention of killing the tumour. The therapeutic radiation from these

radioactive micropsheres reaches a maximum of 1cm. The surrounding healthy liver tissue receives virtually no radiation as a result.

QuiremSpheres ™ are microspheres that contain the radioactive element Holmium-166, the therapeutic effect of these microspheres is due to the radiation emitted by Holmium-166. They deliver more than 90% of their radiation dose within the first 4 days with nearly 100% delivered within 8 days after the treatment procedure.

After implantation the microspheres can be viewed in the body via SPECT and MRI medical imaging modalities.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:
Not applicable

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

A typical SIRT therapy consists of two procedures. First comes the SIRT Work-up procedure, followed by the SIRT Treatment procedure. procedure, usually 1 - 3 weeks apart. Both of these stages are performed in the angiography suite of Interventional Radiology. The first stage involves an angiogram and possible embolisation to ensure that any blood vessels that are not directly feeding the tumour are blocked off to protect other organs from damage by the therapy. Following this a small dose of radioactive tracer material is injected into the liver arteries to ensure that the treatment can be performed safely. This will help to plan and maximise the effects of the treatment thereby minimising any unwanted side effects.

During the second stage, the therapy stage, the treatment is delivered using microspheres that have been pre-loaded with Holmium-166. These are carried by the bloodstream directly to the tumours in the liver. SIRT is a localised treatment, and the effect of the treatment is concentrated in the liver. At both stages the therapy is delivered via a microcatheter directly into the liver where they tend to lodge in the small vessels feeding the tumour, delivering their dose of radiation for a period of approximately 10 days.

Dosage is carefully calculated following the work-up procedure and takes into account disease burden, distribution of work-up tracer along with other disease markers and is therefore individually tailored.

This is a painless procedure that does not require general anaesthesia. You remain conscious throughout the procedure

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Completed clinical studies:

1) HEPAR Primary – UMC Utrecht, The Netherlands: 31 patients with unresectable HCC, published in 2022 (10)
2) RETOUCH – Erasmus ULB Bruxelles, Belgium : 15 patients with unresectable HCC, manuscript submitted for publication
3) RECORD – Multicenter study performed in 7 European centers located in Netherlands, Belgium, Germany, Switzerland, Italy, Portugal and Spain: 157 patients of which 55 patients with unresectable HCC. All patients treated with QuiremSpheres™ from 15 July 2019 to 15 July 2021 were included. Manuscript submitted for publication
4) Jena Clinical Experience – University Hospital Jena, Germany: 20 patients of which 14 were unresectable HCC. All patients treated with QuiremSpheres were included. Published in 2023 (11)

Ongoing clinical studies:

1) HOMIE-166 (NCT05451862) is a study in Germany investigating tumor response in 73 unresectable early-stage HCC patients
2) iHEPAR (NCT05114148) is a study in the Netherlands and Italy assessing the safety and toxicity profile of personalized dosimetry approach in 30 non-resectable HCC patients
3) RHEPAIR is a UK based (Imperial College London) study assessing the safety and toxicity profile of personalized dosimetry approach in 15 non-resectable HCC patients
4) HolmBrave (NCT 05705791) is a study in France investigating the added value of QuiremSpheres to systemic treatment in maximum 33 unresectable advanced HCC patients

3e) Efficacy

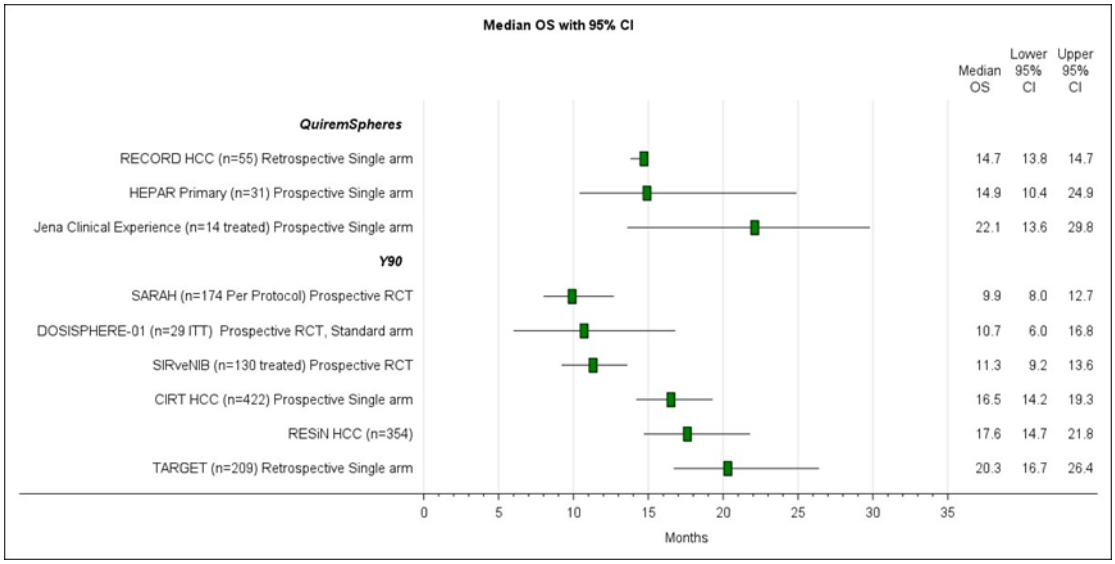
Efficacy is the measure of how well a treatment works in treating a specific condition.

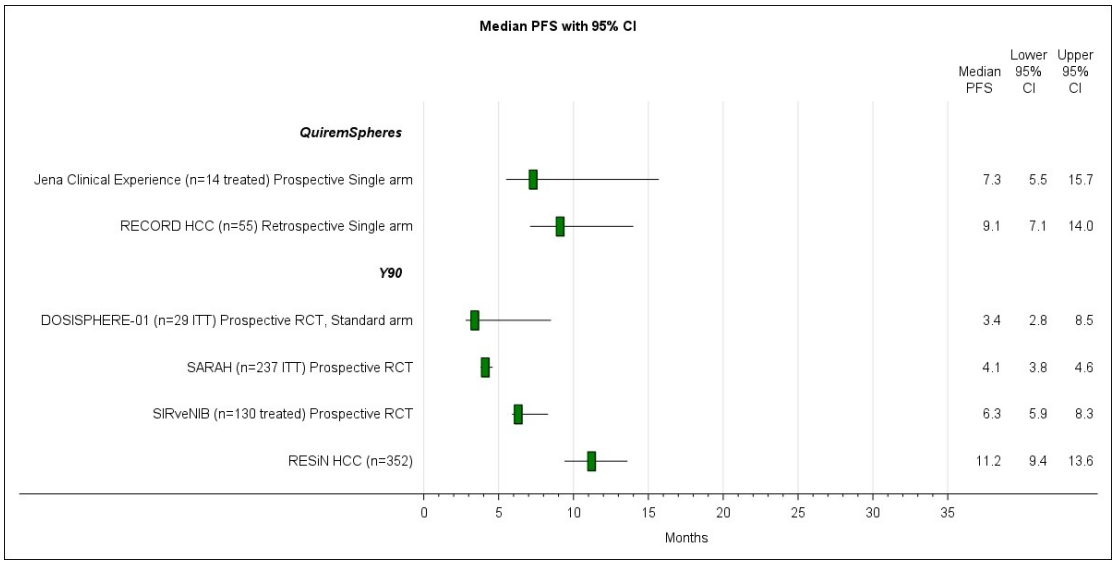
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

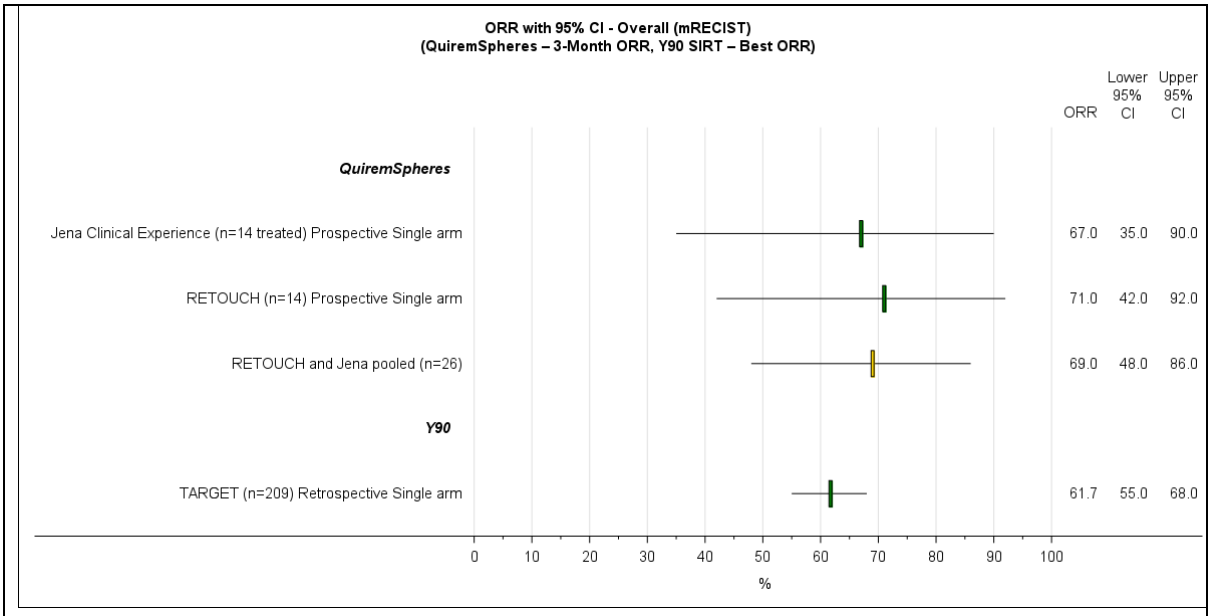
As there is no direct comparative evidence for QuiremSpheres™ to the other SIRT products, a naïve visual comparison was made for treatment estimates from clinical studies evaluating QuiremSpheres™ and Y-90 SIRT in HCC. Using this approach, we could demonstrate that survival outcomes (median overall survival and median

progression free survival) were generally in line with previously reported outcomes in Y90 studies.





Naïve comparison of the tumor objective response rate (ORR) between studies was hindered by different response evaluation methods employed, however, it could show that the ORR achieved with Ho-166 SIRT was at least as good as that achieved in studies using Y-90 SIRT.



3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

For QuiremSpheres™ quality of life (QoL) was only measured in HEPAR Primary and reported no clinically relevant change in quality of life or pain for patients meaning that the treatment was well tolerated. (10)

However, for Y-90 SIRT, a positive effect on patients' QoL as compared to sorafenib has been reported in the SARAH trial. In the QoL analysis of this study, the global health status subscore was significantly better in the SIRT group than in the sorafenib group. In the SARAH trial, QoL was evaluated by means of standard questionnaires European Organisation for Research and Treatment of Cancer (EORTC) (QLQ-C30) and the specific hepatocellular carcinoma module QLQ-HCC18 filled by patients before the treatment, 1 month, and every 3 months after the treatment for at least 1 year. (12)

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main

side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

All treatments used for advanced stage HCC are associated with side effects of varying severity. As explained in the ESMO Patient Guide series for Hepatocellular carcinoma, SIRT is associated with a number of mild side effects including fever, chills, nausea, diarrhoea, stomach ache and a feeling of pressure in the abdomen. Rarely, some of the radioactive microspheres can travel to the gastrointestinal system, which can cause pain in the abdomen, vomiting, bleeding and stomach ulcers. To prevent irritation, you may be given anti-ulcer medication. (6)

The use of systemic drugs, such as sorafenib, is associated with several commonly occurring side effects, including alopecia, diarrhoea, fatigue, hand-foot syndrome, infection, and rash. (6) In the SARAH trial, the frequency and severity of side effects provoked by sorafenib were compared to those associated with Y-90 SIRT. A total of 77% of patients in this trial experienced a treatment-associated side effect in the SIRT group, as compared to 94% in the sorafenib group. The most frequent treatment-related adverse events that were graded as 3 or worse on a 5-grade severity scale were fatigue (9% in the SIRT group vs 19% in the sorafenib group), liver dysfunction (11% vs 13%), increased laboratory liver values (9% vs 7%), haematological abnormalities (10% vs 14%), diarrhoea (1% vs 14%), abdominal pain (3% vs 6%), increased creatinine (2% vs 6%), and hand-foot skin reaction (<1% vs 6%). (12)

Safety of QuiremSpheres™ was evaluated in several clinical studies that did not compare it to systemic or other SIRT treatments but monitored the occurrence and severity of treatment-associated side effects. The obtained results showed that tolerability of QuiremSpheres™ was generally in line with that observed with Y-90 SIRT. (10, 11)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

QuiremSpheres™ and SIRT in general is a well-tolerated treatment with good local tumor response. QuiremSpheres™ provides improved imaging possibilities for determining the dose given to the tumors and healthy liver after the treatment.

Holmium-166 has a half-life of 26.8 hours in contrast to 64.1 hours for Yttrium-90. Therefore, in the unfortunate event of death or a medical intervention shortly after therapy, patients treated with QuiremSpheres™ can be treated as non-radioactive within 15-20 days after treatment. For Y-90-treated patients this is 35-45 days calculated based on a tool of the Belgian radioprotection authority (13).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

No disadvantages compared to the established Y90 SIRT products.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

This appraisal is not a traditional single technology appraisal providing incremental cost-effectiveness ratios (ICERs) in the form of £/QALY, but a cost-comparison analysis looking at partly updating TA688 guidance for SIRT in HCC.

Therefore the submission is looking at whether we can expect any difference in clinical effectiveness and in costs between QuiremSpheres and its comparators.

Regarding clinical effectiveness, see 3e), 3f), 3g).

Regarding costs, we have used an assumption presented in the previous NICE guidance that procedure-related administration costs for all SIRTs are identical. We updated the acquisition costs (price) through a Patient Access Scheme proposal.

We therefore argue that QuiremSpheres™ is cost-neutral compared to its comparators

SIR-Spheres and TheraSphere.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Response: Although there are differences between QuiremSpheres™ and its comparators, we do not expect it would lead to a step-change in treatment effectiveness.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Response: We do not expect any equality issue

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: We have tried to refer to sources that are easily accessible and directed to patients as much as possible. Please refer to the References. Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

(1) MacMillan Understanding Primary Liver Cancer https://www.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/3243-source/mac11917-e05-primaryliver.pdf
(2) British Liver Trust NICE submission to NICE TA688 https://www.nice.org.uk/guidance/ta688/documents/committee-papers
(3) Cancer Research UK (2021) Liver cancer incidence statistics https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer#:~:text=1%20in%20130%20UK%20females,UK%20are%20caused%20by%20infections Accessed January 2024
(4) NICE Guidance Selective internal radiation therapies for treating hepatocellular carcinoma TA688, March 2021. https://www.nice.org.uk/guidance/ta688 (accessed January 2024)
(5) Liver Cancer UK, HCC Liver cancer patient information. https://livercanceruk.org/liver-cancer-information/types-of-liver-cancer/hcc/ accessed January 2024
(6) ESMO Patient Guide series. Hepatocellular carcinoma. https://www.esmo.org/content/download/304418/6053252/1/EN-Hepatocellular-Carcinoma-Guide-for-Patients.pdf
(7) Gill J. et al. Insights into the hepatocellular carcinoma patient journey: results of the first global quality of life survey. Future OncologyVolume 14, Issue 17, July 2018, Pages 1701-1710 https://www.futuremedicine.com/doi/epub/10.2217/fon-2017-0715
(8) Patel N. et al. Understanding the patient experience in hepatocellular carcinoma: a qualitative patient interview study. Qual Life Res. 2022 Feb;31(2):473-485. https://pubmed.ncbi.nlm.nih.gov/34115280/
(9) AZDelta patient information leaflet on Selective Internal Radiation Therapy (in Dutch, translated) Selectieve interne radiotherapie (SIRT) (azdelta.be)
(10) Reinders MTM, van Erpecum KJ, Smits MLJ, Braat A, Bruijne J, Bruijnen R, et al. Safety and Efficacy of (166)Ho Radioembolization in Hepatocellular Carcinoma: The HEPAR Primary Study. J Nucl Med. 2022;63(12):1891-8.
(11) Drescher R, Kohler A, Seifert P, Aschenbach R, Ernst T, Rauchfuss F, et al. Clinical Results of Transarterial Radioembolization (TARE) with Holmium-166 Microspheres in the Multidisciplinary Oncologic Treatment of Patients with Primary and Secondary Liver Cancer. Biomedicines. 2023;11(7).
(12) Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18(12):1624-36.
(13) Controle FAvN. Radioactieve Stoffelijke Overschotten. 2021. https://5162.f2w.fedict.be/nl/professionelen/medische-professionelen/nucleaire-geneeskunde/fanc-initiatieven/radioactieve

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

Clarification questions

January 2024

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Clinical pathway

A1. Priority question: Please indicate on Figure 1 (Company submission [CS], p13) and Figure 2 (CS, p15) where you anticipate QuiremSpheres™ to be positioned.

This assessment is a cost-comparison against Y90 SIRT and the same treatment position as Y90 SIRT described in TA688 will be taken. Meaning QuiremSpheres will be positioned according to the scope, namely adults with unresectable advanced hepatocellular carcinoma with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate.

When looking at Figure 1 (CS, p13) this falls under the paragraph clinical decision making at intermediate stage B when TACE is not feasible/appropriate, or when diffuse, infiltrative, extensive bilobar disease is present or in the advanced stage (BCLC C). For the latter two, according to the BCLC group systemic treatment is recommended. Of note, the SIRT products within the scope of this cost-comparison assessment are not present in this algorithm in the foreseen patient population.

In Figure 2 (CS, p15) the patient flow according to Newcastle upon Tyne NHS Foundation Trust, the position of QuiremSpheres is BCLC-B when TACE is inappropriate or BCLC C as alternative to medical therapy.

Literature review

A2. Priority question: Appendix D of the CS is missing a description of search methods, sources, and search strategies used for identifying studies of QuiremSpheres™, TheraSphere, and SIR-Spheres for treating unresectable advanced hepatocellular carcinoma (HCC). Therefore, the EAG is uncertain whether a systematic review of the literature has been conducted to identify evidence on the clinical effectiveness of QuiremSpheres™, TheraSphere and SIR-Spheres. Please conduct a systematic review and provide all search methods, databases / resources searched, and search strategies.

Search strategy

For this appraisal, we conducted a systematic literature research (SLR) based on the previously published SLR from Wade et al. (2020, https://doi.org/10.1186/s13643-020-01447-x). The protocol of the SLR in question is available online: https://www.nice.org.uk/guidance/ta688/documents/final-protocol.

We reproduced the steps of this protocol (Appendix 12.1) only for the part concerning the SIRT treatments (not comparators, which were systemic treatments) for all studies with publication dates between January 25th 2019 (end date of the SLR of Wade et al.) and December 1st 2023. We applied the abovementioned search strategy to conduct a search in MEDLINE for articles, published in English and with available full texts.

A total of 1583 unique records published between January 25th 2019 and December 1st 2023 were delivered by the search (see PRISMA Flow Chart below). Study selection was performed based on pre-defined selection criteria:

- The study should include a cohort of HCC patients of a reasonable size;

- Patient population should fit for purpose of this evaluation: studies specifically evaluating patients that have previously received another treatment, were treated with the intent of bridging to transplant, or studies, restricted to a specific age cohort or tumour characteristics were not considered;
- Patients should be treated with SIRT as stand-alone therapy;
- The studies should report the outcomes of interest, namely: tumour response, PFS and OS;
- The studies should have appropriate design allowing for comparison with available data for QuiremSpheres^{TM}.

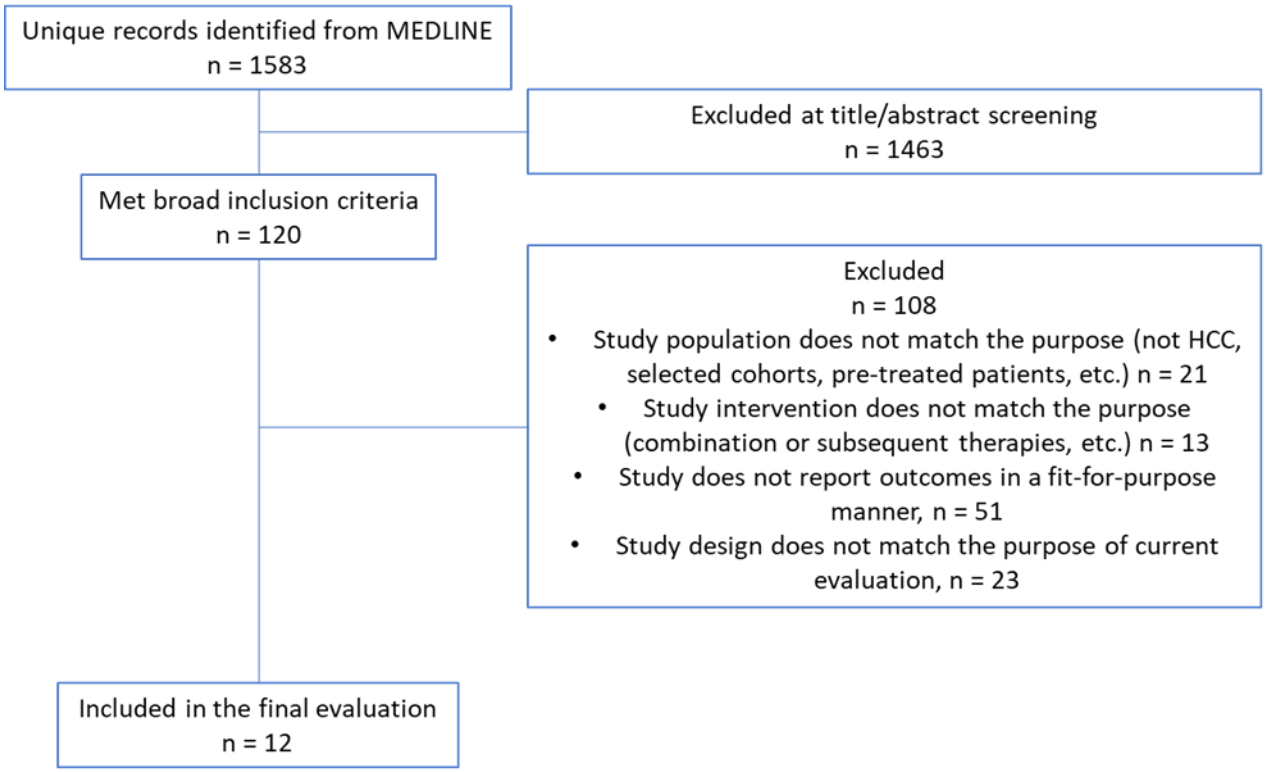
A final selection of 12 studies was further evaluated in terms of patient and tumour characteristics, and 6 studies that had comparable characteristics and treatments were selected for the naïve visual comparison. The reasons for exclusion of the other 6 studies are presented in the table below.

A3. Priority question: Please provide the following details for the clinical effectiveness review (CS, Appendix D1.1):

a. **General review methods (e.g. how many people performed screening, data extraction, and quality assessment, and whether these stages of the review performed by multiple reviewers independently).**

The search and study selection were performed by a single person experienced in conducting SLRs via a two-step process of title/abstract (selection 1) and full text (selection 2) screening. The search and study selection were then verified by a second independent reviewer on a random sample of 10% of the records. The final lists of excluded and included studies were verified and approved by the whole team, with dispute resolution in the process.

b. PRISMA flowchart for the study selection process.



c. A list of excluded studies (at full-text screening), with reasons for exclusion.

1st author, year	**doi**	**Title**	**Included in the naïve comparison?**	**Reason for exclusion from the naïve comparison**
Makary M, 2023	10.1016/j.acra.2023.07.007	Long-term Clinical Outcomes of Yttrium-90 Transarterial Radioembolization for Hepatocellular Carcinoma: A 5-Year Institutional Experience	No	The study included a mixed cohort of patients, of which more than 77% could be downstaged to or maintained within the Milan criteria

Casáns-Tormo I, 2023	10.1016/j.remnie.2023.05.004	Evaluation of results after 112 radioembolizations with (90)Y-microspheres	No	The study included only a small cohort of patients with HCC treated with SIRT only
Hur M, 2023	10.3350/cmh.2023.0076	Transarterial radioembolization versus tyrosine kinase inhibitor in hepatocellular carcinoma with portal vein thrombosis	No	Long-term evaluation of OS in this study was not comparable with the other studies in this evaluation
Drescher R, 2023	10.3390/biomedicines11071831	Clinical Results of Transarterial Radioembolization (TARE) with Holmium-166 Microspheres in the Multidisciplinary Oncologic Treatment of Patients with Primary and Secondary Liver Cancer	Yes	
Reinders M, 2022	10.2967/jnumed.122.263823	Safety and Efficacy of (166)Ho Radioembolization in Hepatocellular Carcinoma: The HEPAR Primary Study	Yes	
Dhondt E, 2022	10.1148/radiol.211806	(90)Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II	No	This study included patients that were also eligible to the conventional

		Randomized Controlled Trial		transarterial therapy (TACE)
Salem R, 2021	10.1002/hep.31819	Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study	No	This study included patients that were also eligible to the conventional transarterial therapy (TACE)
Lam M, 2022	10.1007/s00259-022-05774-0	A global evaluation of advanced dosimetry in transarterial radioembolization of hepatocellular carcinoma with Yttrium-90: the TARGET study	Yes	
Frantz S, 2021	10.1016/j.jvir.2021.03.535	Multicenter Evaluation of Survival and Toxicities of Hepatocellular Carcinoma following Radioembolization: Analysis of the RESiN Registry	Yes	
Van Thai N, 2021	10.1186/s12876-021-01805-6	Efficacy and safety of selective internal radiation therapy with yttrium-90 for the treatment of unresectable hepatocellular carcinoma	No	The overall patient population in this study was not reflecting the populations of the other selected studies well enough, and the results of this retrospective study were not

				presented with sufficient granularity to allow comparison
Garin E, 2021	10.1016/S2468-1253(20)30290-9	Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial	Yes	
Helmberger T, 2021	10.1007/s00270-020-02642-y	Clinical Application of Trans-Arterial Radioembolization in Hepatic Malignancies in Europe: First Results from the Prospective Multicentre Observational Study CIRSE Registry for SIR-Spheres Therapy (CIRT)	Yes	

Therefore, for the naïve visual comparison, for QuiremSpheres™ studies, all relevant clinical studies in patients with HCC that were published or completed since the previous NICE appraisal were included. For studies with Y90 SIRT, apart from the recent studies delivered by the SLR, we have included the relevant studies that were part of the previous evaluation, namely, SARAH and SIRveNIB studies. The Dutch Healthcare Agency, in its assessment of QuiremSpheres™ in HCC, used 3 RCTs to compare results with Y90: SARAH (19), SIRVENIB (20) and DOSISPHERE-01 (21), and all 3 were included in the current evaluation, together with a prospective observational study with SIR-Spheres CIRT (22), a prospective real-world registry with SIR-Spheres RESiN (23), and a retrospective single-arm study with TheraSphere TARGET (24).

A4. Priority question: For the Indirect and mixed treatment comparisons (CS, Section B.3.9)

a. **Please outline any additional selection criteria applied to select Y-90 SIRT studies with a "similar patient mix" and "similar methodology" to QuiremSpheres™ studies and similar methodology" (CS, p45)**

b. **Please also provide evidence to support this similarity; for example, a table comparing patient baseline characteristics and methodology of included studies of QuiremSpheres™ and Y-90 SIRT.**

c. **Please also provide details of patient flow through each of the included QuiremSpheres™ and Y-90 SIRT studies**

No indirect or mixed treatment comparison was performed in this evaluation. We performed a naïve visual comparison of the main outcomes of interest (namely, PFS, OS and tumour response). In order to select Y-90 studies for this comparison, we checked the following:

- Studies should have similar methodology, i.e. assessing the effect of SIRT used as a stand-alone therapy;

- Studies should include a fit-for-purpose patient population, i.e. predominantly patients with intermediate/advanced HCC that were not candidates for conventional transarterial therapies, as per the criteria outlined in the previous NICE evaluation.

Y-90 Study	Methodology	Patient group	Comments
SARAH	Phase III study evaluating Y-90 SIRT vs sorafenib	Patients with locally advanced HCC, not eligible for surgical treatments, or thermal ablation after a previously cured	Study included in the previous NICE evaluation

		hepatocellular carcinoma (cured by surgery or thermoablative therapy), or hepatocellular carcinoma with two unsuccessful rounds of transarterial chemo embolization. Patients were required to have at least one untreated target lesion.	
SIRveNIB	Phase III study, compared Y-90 SIRT with sorafenib	Patients with locally advanced HCC not amenable to curative treatments. Patients were excluded if they had received more than two previous administrations of hepaticartery–directed therapy, hepatic artery–directed treatment within 4 weeks	Study included in the previous NICE evaluation
DOSISPHERE-01	A Phase II study evaluating Y-90 SIRT applied with standard or personalized dosimetry approach	Patients with HCC not amenable to surgery or local ablative treatment; the study enrolled patients with BCLC B or C stage	Study included in the evaluation of The Dutch Healthcare Agency

CIRT	Prospective observational study of patients treated with Y-90 SIRT as standard of care	60.0% of patients with primary liver cancer received TARE with palliative intentions	A large observational study providing for the real-world evidence
RESiN	A multicenter real-world registry evaluating SIRT with resin Y-90 microspheres	The majority (59%) of patients were BCLC B, and only 66 (19%) were BCLC A.	A reasonably large observational study providing for the real-world evidence
TARGET	A retrospective single-arm study of patients with HCC that were treated with glass Y-90 SIRT	Patients that met standard inclusion criteria for SIRT; most of the patients BCLC B (32.5%) or C (54.5%).	

Critical appraisal

A5. Please provide details of the tools that were used to conduct the quality assessments of QuiremSpheres™ studies presented in the CS (Table 11, p34 and Appendix D1.3, Table 1, p74)?

For consistency with our TA688 submission (Terumo Europe, 2019) we used the same Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies provided by the National Heart; Lung and Blood Institute[1].

Table 11 (p34) also includes an assessment of risk of bias of the QuiremSpheres™ included studies. Please provide full details of the tool used and the results of the assessment per risk of bias domain.

We haven't used a specific risk of bias tool to assess the risk of bias of QuiremSpheres™ studies.

A6. Please perform a critical appraisal of the Y-90 SIRT studies included in the naïve comparison (DOSISPHERE, SARAH, SIRveNIB, RESiN HCC, CIRT, TARGET) using an appropriate quality assessment tool.

We will provide the critical appraisal for the 4 studies introduced in this evaluation, as we consider that SARAH and SIRveNIB have been critically appraised in TA688. We use the same tool as for QuiremSpheres™ studies.

Summary of quality assessment –DOSISPHERE

Criterium	Assessment
1. Was the study question or objective clearly stated?	Yes, the aim of this study was to compare the efficacy of a personalised versus standard dosimetry approach of selective internal radiation therapy with yttrium-90-loaded glass microspheres in patients with hepatocellular carcinoma
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes, there were clear prespecified inclusion and exclusion criteria
3. Were the participants in the study representative of those who would be eligible for the intervention in the	Yes

[1] https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

general or clinical population of interest?	
4. Were all eligible participants that met the prespecified entry criteria enrolled?	There were 60 patients randomised, 31 to the personalised dosimetry and 29 to standard dosimetry (intention to treat). Out of the 60 patients, 56 patients (28 in each group) were treated (modified intention-to-treat population).
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes
6. Was the intervention clearly described and delivered consistently across the study population?	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' interventions?	Imaging findings were performed both by unmasked (1) and masked (2) investigators to confirm findings.
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Unclear
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the	n/a

statistical analysis take into account the use of individual-level data to determine effects at the group level?	

Summary of quality assessment – RESIN

Criterium	Assessment
1. Was the study question or objective clearly stated?	Yes, the aim of the study was to determine overall survival (OS), progression-free survival (PFS), and toxicity in patients with hepatocellular carcinoma (HCC) in a multicenter, real-world data registry using transarterial radioembolization (TARE) with resin microspheres
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No. Inclusion criteria were based on local decision making and operator determination that SIRT was an appropriate therapy
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	No sample size calculations were made
6. Was the intervention clearly described and delivered consistently across the study population?	No, intervention performed according to each institution's protocol
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' interventions?	No

9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes. 4,2% were lost to follow-up and were accounted for in the analysis
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	n/a

Summary of quality assessment – TARGET

Criterium	**Assessment**
1. Was the study question or objective clearly stated?	Yes, the aim of the study was to investigate the relationships between tumour absorbed dose (TAD) or normal tissue absorbed dose (NTAD) and clinical outcomes in hepatocellular carcinoma (HCC) treated with yttrium-90 glass microspheres.
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes, there were clear defined inclusion and exclusion criteria in addition to the standard inclusion criteria for patients undergoing TARE
3. Were the participants in the study representative of those who would be eligible	Yes

for the intervention in the general or clinical population of interest?	
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes
6. Was the intervention clearly described and delivered consistently across the study population?	As it is a retrospective analysis, interventions were performed according to each institution's protocol
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' interventions?	No
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Not applicable (retrospective analysis)
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the	n/a

statistical analysis take into account the use of individual-level data to determine effects at the group level?	

Summary of quality assessment – CIRT

Criterium	Assessment
1. Was the study question or objective clearly stated?	Yes, the aim of the study was to investigate the relationships between tumour absorbed dose (TAD) or normal tissue absorbed dose (NTAD) and clinical outcomes in hepatocellular carcinoma (HCC) treated with yttrium-90 glass microspheres.
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	No, all consecutive patients included
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	No sample size calculation is provided
6. Was the intervention clearly described and delivered consistently across the study population?	Interventions were performed according to each institution's protocol
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes	No

blinded to the participants' interventions?	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No, 33,9% patients were lost to follow-up All patients lost to follow-up were accounted for (censored)
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	n/a

Clinical evidence

A7. Priority question: Please provide the following information for the population defined in the NICE scope (adult patients with unresectable advanced HCC with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate):

a. **baseline characteristics in the QuiremSpheres™ studies for the population of patients defined in the NICE scope.**

Following Terumo's question, and as per email communication forwarded by the NICE Project Manager on 08/02/2024: *"the EAG said that the relevant population for the topic should be determined by ineligibility for surgical resection or CTT, rather than by BCLC stage alone. The EAG would like Terumo to provide evidence on adult patients who are not eligible for CTT or surgical resection and have BCLC B or BCLC C HCC with Child-Pugh grade A liver impairment."*

The NICE scope mentions adults with unresectable advanced hepatocellular carcinoma with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate. Therefore, this includes patients with unresectable advanced hepatocellular carcinoma according to the BCLC algorithm stage C and HCC patients where conventional transarterial therapies are inappropriate. This is also reflected in the SARAH and SIRveNIB studies used in TA688 to recommend SIRT in this specific indication. In the SARAH study 4%, 28% and 68% of the SIRT arm were BCLC A, B and C respectively, while in the SIRveNIB study 51% and 48% of patients in the SIRT arm were BCLC B and C respectively.

This demonstrated that patients defined in the scope consist of intermediate and advanced HCC according to the BCLC algorithm and even in the rare case early stage. In the article by Newcastle upon Tyne Hospital, four groups of patients have been identified by the hepato-pancreatobiliary (HPB) multidisciplinary team according to the provided NICE criteria, namely group 1 BCLC B too large for TACE alone, group 2 BCLC B progression post TACE, group 3 BCLC C sorafenib eligible, group 4 BCLC C sorafenib unsuitable.

The definition of TACE unsuitable patients has been best described in the Asia-Pacific Primary Liver Cancer Expert Consensus Statements[2]:

> *Intermediate-stage HCC is an extremely heterogeneous disease in terms of (i) liver function, (ii) tumor size, and (iii) tumor number [13]. More precisely, liver function varies widely according to Child-Pugh class, from A5 to B9; tumor size varies from ≥ a few mm to huge (>10 cm); and the number of nodules varies from*

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7325125/#:~:text=A%20new%20paradigm%20for%20treatment,TACE%2C%20transarterial%20chemoembolization

2 to >100. Despite such extreme heterogeneity, TACE is the only standard of care recommended by guidelines worldwide.

The TACE suitable/unsuitable patients have been illustrated nicely in this expert consensus paper:

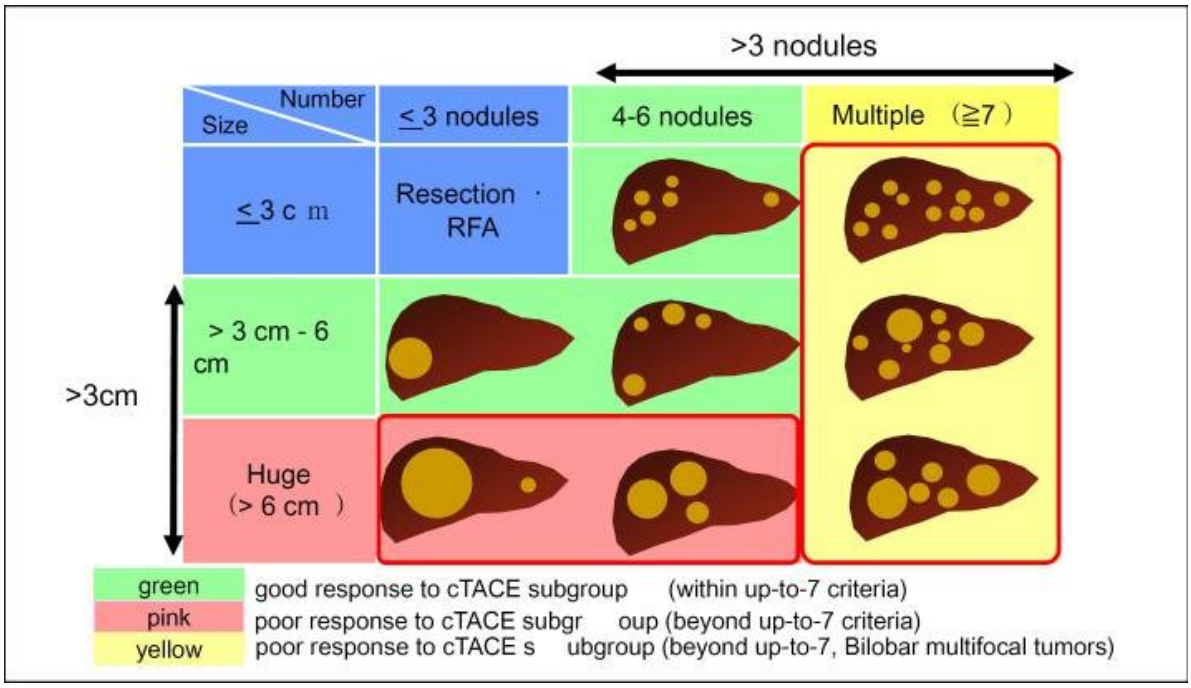


Figure 1: TACE suitable/unsuitable patients according to the Asia-Pacific Primary Liver Cancer Expert Consensus Statements

And reflect the statement from the Newcastle upon Tyne Hospital regarding group 1 BCLC B too large for TACE alone. In the Newcastle upon Tyne paper it is also shown that this group consist of a significant number of patients (21/51 (41%)), while the group 2 BCLC-B progression post TACE consists of only 7 patients (14%). This contrasts with the SARAH and SIRveNIB studies were 45% and 42% of patients respectively received previous TACE. This is probably the consequence of the improved understanding of TACE suitable and unsuitable patients in the intermediate stage and reflects why in our provided evidence intermediate stage without previous TACE was more prominent.

HEPAR Primary, RETOUCH and Jena Clinical Experience were independent investigator-initiated studies. We are therefore not the Sponsor of the study and have no access to the individual patient information. Prof. Lam of UMC Utrecht is a

nominated expert and would be able to address this question for HEPAR Primary. However, for HEPAR Primary we consider all patients matching the population of patients defined in the NICE scope based on the rationale provided above.

In Jena Clinical Experience individual patient information is provided in the manuscript. The center uses the tumour staging system instead of the BCLC algorithm and after conversion it is shown that at least 12 out of 14 patients match the patient population defined in the scope. The two others are BCLC A, of which one has a tumour of 323 ml (~8.5 cm in diameter) and one with only a tumour volume of 19 ml. As mentioned before, large HCC are TACE unsuitable. The patient with small solitary lesion should be excluded, however looking at all the outcomes of this patient and the rapid deterioration (pt 20: OS of 3.4 months) this does not cause a positive bias in our results, ratherthe opposite. Therefore, we believe all patients of the Jena study should be considered.

Patient and Disease Characteristics				
Patient no	Age	Gender	Underlying liver disease	Tumour stage
2	75	m	NAFLD	IVB
6	81	m	Cirrhosis	IVB
14	74	m	cirrhosis	IIIB

RECORD was an observational retrospective study capturing the real-world use of QuiremSpheres in 7 European centers. Looking at the baseline characteristics, the majority of patients are in the advanced stage C and only 5 are in an earlier BCLC stage. However, as this was a retrospective observational study it must have been decided in the MDT that these patients were inappropriate to conventional transarterial therapies and fall within scope of the assessment.

b. comparability of the trial patients in the QuiremSpheres™ studies to the patients defined in the NICE scope treated in UK practice.

All patients included in HEPAR Primary are comparable to the patients defined in the NICE scope treated in UK practice. As they consist of BCLC B (71%) and C (29%). We do acknowledge that the population is more dominated by BCLC B in contrast to SARAH and SIRveNIB. However, when looking at the number of tumours (>3 in 74% of patients) and largest tumour diameter is 56 mm (range 15[+]-195 mm) it demonstrates significant tumour burden with the majority of patients falling outside the TACE suitable candidates. Of note, 3 (10%) of patients had Child-Pugh classification B7, hence a worse liver status compared to the NICE scope. [+]*Patient had more than 15 small lesions*

The study of Jena consists of a real-world evidence study and as explained above all patients except potentially one are within scope of the NICE evaluation. Dr. Drescher informed us that in his university center SIRT is preferred over TACE for cases with multiple lesions, or lesions >5 cm as they consider them inappropriate to TACE, in line with the Newcastle upon Tyne manuscript.

For RETOUCH, only 1 (7%) and 3 (20%) of patients were BCLC B and C. This study was dominated by BCLC A patients (73%) with mainly solitary tumours (80%). This was part of the design of the study as patients considered for curative treatments such as resection or liver transplantation, received QuiremSpheres™ as downstaging or bridging-therapy, while other patients received it as palliative treatment. It must be noted that the mean tumour size was 55.67±28.42 mm and above the TACE suitable candidates. Unfortunately, we are not the sponsor of the study and don't have access to individual patient data.

In RECORD, as explained above all patients are within the scope of the assessment as it consists of a retrospective real world practice study. The cohort consists of advanced patients for which SIRT was selected during the MDT.

c. clinical effectiveness outcome data from the four QuiremSpheres™ studies for the population defined in the NICE scope.

For HEPAR Primary, Jena Clinical Experience and RECORD all clinical effectiveness outcome data in the original CS should be considered. For RETOUCH we are not the sponsor of the study and cannot provide individual patient information.

d. adverse events data from the four QuiremSpheres™ studies for the population defined in the NICE scope.

For HEPAR Primary, Jena Clincal Experience and RECORD all adverse events data in the original CS should be considered.

For the RETOUCH study, we don't have access to individual patient data and are therefore unable to specify adverse event data specific to the population defined in the NICE scope. However, in all patients in RETOUCH no clinical and biological adverse events above grade 2 were reported, including the palliative patients.

A8. Priority question: Patients treated in the QuiremSpheres™ studies received QuiremSpheres™ following a work-up procedure using either ^{99m}Tc-MAA or with QuiremScout

a. Please provide patient baseline characteristics, clinical effectiveness outcome data, and adverse events data for patients who received QuiremSpheres™ following ^{99m}Tc-MAA work-up.

The Jena Clinical experience reported the usage of both QuiremScout™ and ^{99m}Tc-MAA work-up product. However, they didn't describe the proportion nor the type of work-up received by individual patients.

In the RECORD total population, QuiremScout™ was used in 63.7% of patients and ^{99m}Tc-MAA in 36.3% of patients.

As the study was real world practice the decision to use QuiremScout™ and ^{99m}Tc-MAA was probably based on hospital preference and access to the products.

This statement supports that there were no significant differences between work-up products used for therapy decision: "*The visually graded targeting of QuiremScout™ Holmium-166 Microspheres was 'Good' in 79.8% (87), Moderate in 14.7% (16), Poor in 2.8% (3) and unknown in 2.8% (3). With ^{99m}Tc-MAA as work-up product, the targeting was graded as Good 77.4% (48), Moderate 16.1% (10), Poor 0.0% (0), and Unknown 6.5% (4)*".

b. Please provide evidence of similarity in clinical effectiveness outcomes and adverse events for patients treated with QuiremSpheres™ following work-up with QuiremScout compared to work-up with ^{99m}Tc-MAA.

In HEPAR Primary, RECORD and Jena Clinical Experience, the injected activity and hence delivered dose and therapeutic effect was based on the perfused volume. This perfused volume is calculated from anatomical imaging in isolation from the work-up product. The work-up product only serves as an exclusion factor based on extra-hepatic deposition or lung shunt.

To conclude, as the dosing is not dependent on work-up distribution all clinical effectiveness outcomes and adverse events presented are valid irrespective of work-up product used.

A9. The NICE scope (CS, Table 1, p7) lists progression-free survival (PFS) and time-to-progression (TTP) as two distinct outcomes. Please indicate which results are median PFS or median TTP within in Table 13 (CS, p49).

An error had occurred and TTP should have been removed from the heading of the table. All data in the table is median PFS. For RETOUCH TTP is provided in the manuscript, namely median TTP was 18.8 (range 2.9; n.e.) months but was excluded from the table as it did not allow naïve comparison to the other studies as it is a distinct different outcome.

A10. The RECORD unpublished manuscript states that 11/157 patients did not receive treatment and were excluded from analyses (Figure 1). How many of these patients had HCC?

Only 1 patient out of these 11 patients had HCC, more specifically BCLC B.

A11. Please clarify the statistical methods used to analyse OS within the Jena Clinical Experience study (CS, Figure 11, p44).

The survival curves and survival time estimates presented in the Jena Clinical Experience study are based on Kaplan-Meier methodology.

A12. Quality of life results from the HEPAR Primary study are presented in Figure 5 (CS, p39):

a. **Please provide data in tables on median scores, percentage change, and number of patients who completed the quality-of-life instruments by domain and by timepoint.**

We are not the sponsor of the HEPAR Primary study and don't have access to the data. However, we have transferred the results listed in the publication towards a table as requested. Prof. Lam of UMC Utrecht is a nominated expert and he is available to be contacted for more detailed information.

Time point	Median scores	Percentage change from baseline	Number of patients completed questionnaire
Baseline	75		Not reported (NR)
Directly after treatment	75	0	NR
3 week FU	67	-11%	NR

6 week FU	75	0	NR
3 month FU	67	-11%	NR
6 month FU	67	-11%	NR

b. Please provide a reference for a clinically relevant change in quality of life and of pain according to the EORTC QLQ-C30 global health scale and EORTC QLQ-HCC 18-question module.

A recent review has been published that provide guidance for interpreting minimally important differences in EORTC QLQ-C30 for different tumours, unfortunately not including HCC.

> *Musoro JZ., et al., Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: A synthesis across 21 clinical trials involving nine different cancer types. Eur J Cancer. 2023 Jul:188:171-182. doi: 10.1016/j.ejca.2023.04.027.*

Another recent article demonstrated psychometric validation of the EORTC QLQ-HCC18 in patients with previously treated unresectable hepatocellular carcinoma while also taking into consideration EORTC QLQ-C30.

> *Serrano, D., Podger, L., Barnes, G. et al. Psychometric validation of the EORTC QLQ-HCC18 in patients with previously treated unresectable hepatocellular carcinoma. Qual Life Res 31, 937–950 (2022). https://doi.org/10.1007/s11136-021-02992-1*

Section B: Clarification on cost-effectiveness data

Cost-effectiveness evidence

B1. Priority question: Please clarify whether a systematic review of cost-effectiveness evidence for SIRT was undertaken. If not, please provide

evidence that there are no economic analyses relevant to the decision problem published since TA688.

We haven't conducted a systematic review of cost-effectiveness evidence. Indeed, the review method for this appraisal is a cost-comparison of QuiremSpheres™ vs SIR-Spheres and Therasphere, not a cost-effectiveness study. There have been numerous publications on SIRT cost-effectiveness in HCC, especially following the NICE TA688 appraisal. However, to our knowledge, there have been no economic study published comparing QuiremSpheres and Y90 SIRT, whether through a cost-comparison or a cost-effectiveness analysis.

B2. Priority question: It is assumed that QuiremSpheres™ is equivalent to SIR-Spheres and TheraSphere with regards to several key aspects of resource use (CS, Table 18, p61). Please provide the following figures from the included QuiremSpheres™ studies in support of these assumptions:

a. **Proportion of work-ups leading to SIRT**

In HEPAR Primary 32 HCC patients received QuiremScout™ and 31 HCC patients were treated. Only 1 patient was excluded because of significant lung shunt and suboptimal targeting. Therefore, 96.9% of work-ups leading to SIRT.

In Jena Clinical Experience, this information was not provided.

In RETOUCH, 5 of the 20 patients were excluded after work-up. Therefore, 75% of work-ups leading to SIRT.

In RECORD for the entire population: 167 QuiremSpheres™ therapies were performed for 171 work-up procedures. Therefore, 97.7% of work-ups leading to SIRT.

b. **Mean number of work-ups per patient**

In HEPAR Primary, this information was not provided.

In Jena Clinical Experience, this information was not provided.

In RETOUCH, 2 out of 15 patients received 2 work-ups as two treatment sessions on the same lesion were provided. The mean number of work-up per patient was: 1.13.

In RECORD for the entire population, 171 work-ups were performed for 146 patients. The mean number of work-ups per patient was: 1.17.

In RECORD for the HCC population:

- 41/55 (75%) HCC patients had 1 work up (34 QuiremScout™, 6 ^{99m}Tc-MAA, 1 unknown) leading to 1 treatment session
- 12/55 (22%) HCC patients had 2 work ups (5 QuiremScout™/QuiremScout™, 2 ^{99m}Tc-MAA/QuiremScout™, 1 QuiremScout™/^{99m}Tc-MAA, 4 ^{99m}Tc-MAA/^{9m}Tc-MAA) leading to 2 treatment sessions
- 2/55 (4%) HCC patients had 2 works up on the same day (2 QuiremScout™/^{99m}Tc-MAA) leading to 1 treatment session

So overall, an average of 1.25 workups per patient for the HCC population within RECORD.

c. Mean number of SIRT procedures per patient

In HEPAR Primary, this information was not provided.

In Jena Clinical Experience, there were 21 SIRT procedures performed for 14 patients which results in a mean number of SIRT procedures per patient of 1.5. It must be noted that in the clinical practice of Jena patients with a billobar approach, the liver lobe with the higher tumour load (the right lobe in eight patients) was treated first. The other liver lobe was treated after an interval of 6 weeks (median 42 days, range 33–49 days).

In RETOUCH, there were 17 SIRT procedures performed for 15 patients which results in a mean number of SIRT procedures per patient of 1.13.

In RECORD for the entire population, 85.6% (125) received a single SIRT procedure, and 14.4% (21) received two treatment sessions. This means that 167

treatment procedures were performed for 146 patients of the entire cohort, which results in a mean number of SIRT procedures per patient of 1.14.

In RECORD for the HCC population, 1.22 SIRT treatments were performed per patient.

Please distinguish between patients who had QuiremScout work-up vs those in whom ^{99m}Tc-MAA was used.

This information is not available for the investigator-initiated studies. For RECORD, it is very difficult to retrieve this information, especially as we noted above, 14/55 patients had more than 1 work-up, sometimes with 2 different products.

B3. Priority question: The HEPAR Primary trial paper (Reinders et al. 2022 [CS, reference 17], p1897) states that dosimetry-based, patient-specific dosing and the SIRT procedure itself cannot be performed in a single day.

a. **Please clarify whether you anticipate ^{99m}Tc-MAA work-up and the QuiremSpheres™ procedure to be performed on the same day in NHS practice.**

We do not anticipate the procedure to be performed on the same day in NHS practice as it is currently not standard practice within the NHS.

Nevertheless, it would be feasible for hospitals willing to perform a single-day treatment to do it with QuiremSpheres. Indeed, in the HEPAR Primary trial, 28 out of 31 (90%) patients received a single day treatment. The limitation stated in the HEPAR Primary trial is linked to therapy dose. It needs to be pre-ordered so that no manipulation of the activity is needed (nor allowed) in the hospitals. This is the same situation for TheraSphere. Only SIR-Spheres allows on-site manipulation of the activity. However, the one-day procedure is not routine clinical practice in the NHS, even when SIR-Spheres are used.

We refer to the nominated UK experts to provide feedback about whether single day SIRT procedure is standard practice in the UK for advanced HCC with Child-Pugh grade A liver impairment when conventional transarterial therapies are inappropriate.

b. **If this is not the case then please account for the additional costs associated with multiple hospital visits on QuiremSpheres™.**

QuiremSpheres™ treatment does not differ compared to the reimbursed Y-90 SIRT products regarding multiple hospital visits. No additional costs are associated.

B4. Priority question: Is the Q-Suite software required to calculate the required QuiremSpheres™ dose using ^{99m}Tc-MAA work-up? What are the costs associated with this software?

The Q-suite software is not required to calculate the required QuiremSpheres™ dose using the ^{99m}Tc-MAA work-up. Standard available software packages can be used to calculate the required QuiremSpheres™ dose using ^{99m}Tc-MAA work-up. Furthermore, Q-suite will be provided free of charge by Terumo as part of the hospital start-up process.

B5. Priority question: The manufacturer of SIR-Spheres claims that the work-up, SIRT procedure, and post-implantation imaging is typically undertaken in a single admission.

a. **Is this the case in settings where QuiremSpheres™ is already in use?**

A detailed answer to this question has been provided above (B3 a.). The major comment regarding this question is that the statement that a single day procedure is typical practice is not correct. However, when appropriate, a single admission for a SIRT procedure can be performed with all 3 SIRT products.

b. **Please calculate the average cost per patient associated with QuiremSpheres™ compared to the other technologies, if multiple hospital admissions are required.**

No multiple hospital admissions are required with QuiremSpheres™ compared to the other technologies.

B6. Priority question: Please present a comparison of average dose verification imaging costs for SPECT-CT/MRI and PET-CT (i.e. QuiremSpheres™ vs Y-90 SIRTs)

	Cost	Source
RN05A: Single Photon Emission Computed Tomography with Computed Tomography (SPECT-CT) of Two or Three Areas, 19 years and over	£234	HRG RN05A; Direct access and outpatient nuclear medicine services (Tariff varies according to age and the number of areas imaged, from 1 to >3. This is our assumption for SIRT)
RD01A: Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	£118	HRG RD01A; Direct access and outpatient diagnostic imaging services (Tariff varies according to age, use of contrast and number of areas imaged, from 1 to >3. This is our assumption for SIRT)
RN02A: Positron Emission Tomography with Computed Tomography (PET-CT) of Two or Three Areas, 19 years and over	£201 - £935	HRG RN02A is a listed procedure. As per 2023/25 NHS Payment Scheme several high cost drugs, devices and listed procedures, and MedTech Funding Mandate products are unbundled and excluded from the associated core payment mechanisms or prices. To identify an appropriate cost, we have looked at the latest set of Reference Costs 2021/22[3]. Unfortunately the cost for RN02A was not reported and we report the values

[3] https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/

		for RN01A (“one area”) and RN03A (3+ areas)
Note: we haven’t used 2021/22 Reference costs for all imaging methods as we found the data reliability a bit weak (due to the number of data submissions for some categories, higher costs for SPECT-CT with 1 area vs 2-3 areas, etc…)		

B7. Priority question: What is the company’s understanding of the market share of SIRT in this patient group in the NHS? Clinical advice to the EAG suggests that SoC is now atezolizumab + bevacizumab given its superiority to sorafenib and likely to SIRT by extension. What does the company believe determines whether a patient receives SIRT?

We believe that this question is out of the current evaluation’s scope ie the cost-comparison assessment of QuiremSpheres™ versus Y90-SIRT products.

Furthermore, we would like to refrain from making statements as a company for treatment decisions. Physicians should follow the recommendations as provided by NICE TA688. By recommending QuiremSpheres™, it would give physicians during MDT discussions another option to treat patients according to the recommendation in NICE TA688.

For completeness of the answer we provide below our understanding of the patients eligible for SIRT:

As mentioned in A7 a. since the evaluation of TA688 new understanding of the intermediate stage B population has become available and a better definition of TACE unsuitable (inappropriate) is present (see Figure 1). Therefore, intermediate stage B patients that are TACE unsuitable would be candidates for SIRT as they are considered inappropriate for conventional transarterial therapies. This is a distinct patient group to the one for which atezolizumab + bevacizumab provided evidence for.

Another part of the patient group is the advanced population corresponding to BCLC C for which atezolizumab + bevacizumab is now currently standard of care. Although BCLC C is considered a homogenous HCC patient population it consists of patients with portal invasion and/or extrahepatic spread or ECOG performance status 1-2. For patients with portal invasion and no extrahepatic spread, physicians could still consider the disease as locally advanced without systemic spread and refer the patient for SIRT as TACE is contra-indicated.

Furthermore, as SIRT is a well-tolerated treatment studies are ongoing to combine SIRT + immunotherapy. To this point, QuiremSpheres^{TM} is under investigation in the combination with atezolizumab and bevacizumab in the HolmBrave study. HolmBrave (NCT 05705791), more information is present in the original CS.

Section C: Textual clarification and additional points

C1. Priority question: Please provide protocols and clinical study reports (CSRs) for the four QuiremSpheres^{TM} studies where available.

We provide the RECORD clinical study report. Other CSRs are not available to Terumo.

C2. Please clarify and provide an update on the statement below regarding the Intervention in the Decision Problem (CS, Table 1, p7):

"It is in line with the scope. We are proposing a slight change of wording to be in line with TA688. We are awaiting NICE technical team feedback."

The title of the appraisal has changed to be in line with TA688 and is now *Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]*

C3. Please clarify why no clinical effectiveness results are provided for the outcome 'rates of liver transplant or surgical resection' listed within the NICE scope (Table 1, p8)

This decision was made based on the comment of the AG on the previous TA688 assessment:

The AG was advised that downstaging of patients with advanced HCC to transplant and other curative options is rare in UK clinical practice, with very few if any of these patients receiving curative therapies. It is also notable that the SIRveNIB trial,3 which recruited a similar population, makes no mention of any patients going on to receive curative therapy. Similarly, none of the previous TAs which assessed systemic cancer treatments for advanced HCC modelled the possibility of curative therapies. The AG is therefore concerned that the very sizable benefits resulting from curative therapy would not be realised in practice, and that the rarity of downstaging means any resulting incremental benefits are subject to very considerable uncertainty.

We agree with the statement made by the AG that the conversion to curative options is rare in clinical practice for patients with advanced disease.

C3. **Please add the number of patients on which results in Table 13 (CS, p49) are based, for each outcome within each study.**

Trial acronym	**ORR (CR/PR) %**	**Median PFS (95% CI) months**	**Median OS (95% CI) months**	**QoL at 3 months *(not used in the forest plots provided)***
QuiremSpheres™ studies				
HEPAR Primary (17)	54% (19/35%) **N=14/26 (5/9)**	NR	14.9 (10.4-24.9) **N=31**	Median 67% (IQR ~55-82%) EORTC QLQ C30 Global Health Status **N = NR**
RETOUCH (Manuscript submitted)	100% (79/21%) **N=14/14 (11/3)**	NR	NR	NR
RECORD (Manuscript submitted)	70.3% (mixed tumour response evaluation reported in the study, not used for the comparison) N=26/37	9.1 (7.1-14.0) **N=55**	14.7 (13.8-n.e.) **N=55**	NR

Jena Clinical Experience (18)	67% (8/58%) **N=8/12 (1/7)**	7.3 (5.5-15.7) **N=14**	22.1 (13.6-29.8) **N=NR**	NR
Y-90 SIRT studies				
SARAH (19)	RECIST 1.1 19% (3/16%) **N=36/190 (5/31)**	IIT 4.1 (3.8-4.6) **N=237**	Per protocol 9.9 (8.0-12.7) **N=185**	Per Protocol Mean ~60% (SD 35-85%) EORTC QLQ C30 Global Health Status N=169
SIRveNIB (20)	RECIST 1.1 23.1% (NR) **N=NR**	Treated 6.3 (5.9-8.3) **N=130**	Treated 11.3 (9.2-13.6) **N=130**	EQ 5D, mean ~75% (CI 70-83%)
DOSISPHERE-01 (21) Standard arm	RECIST 1.1 (according to EASL criteria; not used in the plots) 43% (21/21%) **N=12/28 (6/6)**	3.4 (2.8-8.5) **N=29**	10.7 (6.0-16.8) **N=29**	NR
DOSISPHERE-01 (21) Personalized dosimetry arm	RECIST 1.1 according to EASL criteria; not used for the naïve comparison 79% (18/61%) **N= 22/28 (5/17)**	6.0 (3.5-11.6) **N=31**	26.6 (11.7-NR) **N=31**	NR
CIRT (22)	NR	NR	16.5 (14.2-19.3) **N=422**	NR
TARGET (24)	mRECIST 61.7% **N=129/209** RECIST 1.1 34.4%	NR	20.3 (16.7-26.4) **N=209**	NR

	N=72/209			
RESiN HCC (23)	NR	Total cohort 11.2 (9.4-13.6) **N=352** BCLC C 6.3 (4.8-30.2) **N=41**	Total cohort 17.6 (14.7-21.8) **N=354** BCLC C 13.6 (6.2-21.8) **N=42**	NR

C4. Please provide an English translation of the report by the Dutch Healthcare Agency on its assessment of QuiremSpheres™ referred to in Appendix D.1.1 (CS, p72). This appears in the reference list as follows:

9. Nederland Z. Holmium-166 radioembolisatie bij hepatocellulair carcinoom. 2022. https://www.zorginstituutnederland.nl/publicaties/standpunten/2022/10/06/holmium-166-radioembolisatie-bij-hepatocellulair-carcinoom (english translation provided in the submission)

We provide an English version of the Dutch Healthcare agency report (translated through DeepL)

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	British Association for the Study of the Liver (BASL) / HCC-UK
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? No • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? No • Other (please specify): Responding on behalf of BASL / HCC-UK as the Radiology representative of the HCC UK Committee and nominated by BASL as a clinical expert – see submitted clinical expert form.
5. Brief description of the organisation (including who funds it).	British Association for the Study of the Liver is the National Association for hepatology. BASL is composed of interested individuals from clinical medicine, clinical and basic research and allied professions. BASL is funded through membership fees and organising and hosting an annual meeting and educational events. HCC-UK is a national cross-specialty group of clinicians with an interest in hepatocellular carcinoma (HCC) and a special interest group of BASL.
6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes - Sirtex Medical (comparator). BASL received £7,000 in sponsorship funding towards the HCC-UK Annual Conference that took place in March 2023. Yes - Boston Scientific (comparator) BASL received £7,000 in sponsorship funding towards the HCC-UK Annual Conference that took place in March 2023.

7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	• Compared to Yttium-90 Sirspheres and Theraspheres, QuiremSpheres contains 166Ho microspheres which are made of poly-l-lactic acid (PLLA), containing the isotope 166Ho. It emits high-energy beta radiation for therapy (same as the comparators) and also emits primary gamma photons that can be used for SPECT. • Unlike Sirspheres and Theraspheres which use 99mTc-MAA for work up evaluation, a scout dose of 250 MBq 166Ho microspheres (CE marked) can be used for work up in QuiremSpheres. By using identical microspheres for the therapy in the work up, it has the advantage of more accurate work up evaluation (liver uptake and extrahepatic shunt) and dosimetry calculation. 166Ho scout was shown to have a superior predictive value for intrahepatic distribution in comparison with the commonly used 99mTc-MAA (MLJ Smits et al Eur J Nucl Med Mol Imaging. 2020; 47(4): 798–806.) • Furthermore, being a lanthanide containing paramagnetic properties, it can be imaged by MRI (in addition to the standard SPECT-CT for Sirspheres and Theraspheres work up) to evaluate work up and treatment absorbed dose calculation. • Along with the same principle of Simplicit90YTM for Theraspehres, a dedicated software package (Q-suite™, Quirem BV, Deventer, The Netherlands) can be used for treatment planning and dose reconstruction for treatment evaluation in QuiremSpheres. • It also has a dedicated administration system. • Compared to Y-90 containing microspehres, 166Ho-containing microspheres have shorter half-life (26.8 and 64.1 h), potentially resulting in a higher tissue dose rate after delivery. • Its specific activity is between resin (lowest) and glass microspheres (highest). • As a result, the number of particles injected differs for each technology. It is approx. 5 million for TheraSphere, 20 million for Quiremspheres, and 50 million for SIR-Spheres. This means the relative embolic effect of Quiremshoperes is in between of the comparators. • The distribution of the microspheres (and the effect of radiation) in the liver is more heterogeneous when smaller number of microspheres are injected. The distribution is more homogeneous when a large number of microspheres are injected, each containing a low specific activity.

9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	• Currently there is no comparative date in clinical effectiveness between Quiremspheres and comparators. • So far phase 1 and 2 studies have low number of subjects (<50) primarily aimed to establish the safety and efficacy of the procedure for indications already evaluated for the comparators. • The Hepar primary phase 2 study (n=31) showed 166Ho-radioembolization is a safe treatment option for HCC patients with Unacceptable toxicity related to study treatment occurred in 10% of patients. Complete or partial response for 54% of the target liver lesions at 3-month follow-up and 84% of the target liver lesions at 6-month follow-up. Median overall survival was 14.9 months (Reinders-Hut et al Cardiovasc Interv Radiol. 2021;44(S1):1–64.)
10. What impact would the technology have on the current pathway of care?	• It would have the same clinical workflow as the comparators. • The indications and contraindications are expected to be similar.
11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	• The provision will be provided by specialist HCC units that also offer other treatment strategies e.g. transarterial treatment, ablations, liver resection, +/- liver transplantation.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• If this technology were to be funded, it will primarily be used in the NHS in the same way as its comparators.
13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	• Not that i am aware of.

14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	• It is not possible to draw a valid conclusion at this stage due to the limited data
15. Do the clinical trials on the technology reflect current UK clinical practice?	• Current studies on Holmium-166 assess the outcome on the same indications as for Y-90. The latter is now relatively well established in the UK so the clinical practice will largely remain the same. Further refinement on patient selection, techniques, and personalised therapy will need to be further evaluated.
16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	• It would be similar to its comparators.
17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	• Nil specific

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External Assessment Group Report

Cost comparison evaluation process

Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688)

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Contributions of authors

Eleonora Uphoff wrote the background (Section 2), critique of the decision problem (Section 3) and contributed to the critiques of the systematic review and clinical effectiveness evidence (Section 4).
Joseph Lord wrote the critique of the cost comparison (Section 5) and cost comparison results (Section 6).
Sumayya Anwer contributed to the background (Section 2), critique of the decision problem (Section 3) and critiques of the systematic review and clinical effectiveness evidence (Section 4).
Melissa Harden reviewed the systematic review searches and wrote sections of the report pertaining to the searches.
Mark Baker provided clinical expert advice relating to the mechanism of actions of selective internal radiation therapies and their use in the NHS.
Matthew Walton oversaw the review of the cost comparison and the report as a whole.
Sarah Nevitt oversaw the review of the clinical effectiveness evidence, wrote, and commented on drafts of the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted]

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List of abbreviations

AE	Adverse event
AG	Assessment Group
BCLC	Barcelona Clinic Liver Cancer
Bq	becquerel
CI	confidence interval
CIC	commercial-in-confidence
CON	confidential
CR	complete response
CRD	Centre for Research and Dissemination
CS	company submission
CT	computed tomography
CTT	conventional transarterial therapy
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
HCC	hepatocellular carcinoma
^{166}Ho	holmium-166
HRQoL	health-related quality of life
ICER	Incremental Cost Effectiveness Ratio
IPG	Intervention Procedure Guideline
IQR	interquartile range
ITT	intention-to-treat
MDT	Multi-Disciplinary Team
MRI	Magnetic Resonance Imaging
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence
NIH	National Institute for Health
NMA	Network Meta-Analysis
NR	not reported
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PET-CT	Positron emission tomography with computed tomography
PFS	progression-free survival
PLLA	poly-L-lactic acid
PR	partial response
PS	performance status
PVI	portal vein invasion
PVT	portal vein thrombosis
QALY	Quality-adjusted life year
REILD	radioembolization-induced liver disease
RCT	randomised controlled trial
SIRT	Selective Internal Radiation Therapy
SLR	systematic literature review
SPECT	single-photon emission computerised tomography
TACE	transarterial chemoembolization
TAE	transarterial embolization
TARE	transarterial radioembolization
^{99m}Tc-MAA	technetium-macroaggregated albumin
TTP	time-to-progression
^{90}Y	yttrium-90

EXTERNAL ASSESSMENT REPORT: COST COMPARISON EVALUATION PROCESS

1 EXECUTIVE SUMMARY

1.1 Summary of the decision problem

The company's decision problem broadly aligns with the final scope issued by the National Institute for Health and Care Excellence (NICE).

The population specified in the NICE scope for the current appraisal is adults with unresectable advanced hepatocellular carcinoma (HCC) with Child-Pugh grade A liver impairment when conventional transarterial therapies (CTTs) are inappropriate, which was the population that selective internal radiation therapy (SIRT) treatments SIR-Spheres® and TheraSphere® were recommended for in TA688.[1]

The population considered in the clinical and economic evidence for the indicated population within TA688 was more inclusive in terms of Barcelona Clinic Liver Cancer (BCLC) staging, with both intermediate (BCLC B) and advanced (BCLC C) included. Clinical advice to the evidence assessment group (EAG) and company in intervening TA666 of atezolizumab with bevacizumab,[2] suggested that BCLC B patients not amenable to locoregional therapies (i.e., CTT) are not easily clinically distinguishable from BCLC C patients and thus atezolizumab with bevacizumab was recommended for both BCLC B and BCLC C patients.

The EAG considers that the relevant indicated population for this current appraisal should be primarily determined by ineligibility for surgical resection or CTT, i.e., adult patients who are not eligible for CTT *or* surgical resection *and* have BCLC B *or* BCLC C HCC with Child-Pugh grade A liver impairment are relevant to the decision problem. This reflects the company's proposed position of QuiremSpheres and aligns with how SIR-Spheres and TheraSphere are currently used within NHS clinical practice according to clinical advice to the EAG.

1.2 Summary of the clinical evidence

The clinical evidence in the company submission (CS) focuses on three prospective single arm studies (HEPAR Primary, 31 treated patients; Jena Clinical Experience, 14 treated patients; RETOUCH, 15 treated patients) and one retrospective single arm study (RECORD, 55 treated patients) of QuiremSpheres®.

The company have conducted a naïve visual comparison of treatment estimates of QuiremSpheres and comparators (six studies of SIR-Spheres or TheraSphere). The EAG considers that this approach is acceptable given the anticipated observational nature of the relevant studies. The EAG considers that an additional three comparator studies (SIR-Spheres or TheraSphere) provide relevant outcome data for a cohort of patients the majority of whom align with the population relevant to the decision problem and that the cohort recruited to the RETOUCH study is not reflective of the relevant population. Therefore, the EAG includes three QuiremSpheres studies and nine comparator studies in a naïve comparison.

The EAG considers that there is no evidence of any important differences in terms of overall survival (OS), progression free survival (PFS) or objective response rate (ORR) between QuiremSpheres and SIR-Spheres or TheraSphere. There is also no evidence of any important differences in the safety profile of QuiremSpheres compared to SIR-Spheres or TheraSphere. Health-related quality of life (HRQoL) data available are too limited to draw any meaningful comparisons between QuiremSpheres and comparators.

1.3 Summary of the cost comparison evidence

The company's cost comparison analysis assumes equivalence of QuiremSpheres in terms of overall health outcomes as well as healthcare resource use, treatment and administration costs including dose-verification imaging and adverse event costs relative to the comparator technologies SIR-Spheres and TheraSphere. Therefore, only the acquisition costs of the technologies (i.e. the cost per SIRT procedure performed) are included in the cost comparison analysis. The EAG considers this approach to be appropriate and it is plausible that the addition of QuiremSpheres, using ^{99m}Tc-MAA (technetium-macroaggregated albumin) work-up product, as an alternative to SIR-Spheres or TheraSphere could be cost-neutral in this position.

1.4 EAG critique of cost comparison approach to this technology assessment

The EAG considers that a cost comparison approach is an appropriate method to assess this technology. The technical characteristics presented and clinical advice to the company and to the EAG suggest that it is reasonable to consider QuiremSpheres as a technical variant to SIR-Spheres and TheraSphere.

NICE requires that for acceptance of the cost comparison case, sufficient evidence in support of similarity between the intervention and comparator technologies, in terms of overall health outcomes must be presented. The EAG considers that these conditions have broadly been met given the circumstances, and that there is no evidence of any difference in health outcomes or safety profiles between QuiremSpheres and SIR-Spheres or TheraSphere.

Uncertainties remain, relating to low quality evidence provided by observational, retrospective, and non-comparative studies, heterogeneity of study and patient characteristics across studies and generalisability of results of the studies of SIRTs which include patients who would not be eligible to receive SIRT treatment in NHS clinical practice.

The availability of QuiremSpheres is not expected to change the clinical pathway for treating advanced unresectable HCC, as the proposed position of QuiremSpheres is as an alternative SIRT treatment alongside SIR-Spheres or TheraSphere.

Since the appraisal of SIR-Spheres and TheraSphere within TA688, the immunotherapy combination atezolizumab with bevacizumab has been recommended for treating advanced or unresectable HCC, replacing sorafenib as the first-line standard of care for this population in the NHS. The EAG considers that there is insufficient robust clinical effectiveness evidence available to inform a cost-effectiveness analysis of QuiremSpheres compared to SIR-Spheres or TheraSphere, or to atezolizumab with bevacizumab, the current standard of care in NHS practice for treating unresectable or advanced HCC.

2 BACKGROUND

2.1 Introduction

This Evidence Assessment Group (EAG) report is a critique of the company's submission (CS) from Terumo which informs the National Institute for Health and Care Excellence's (NICE's) part review of health technology guidance TA688 'Selective internal radiation therapies for treating hepatocellular carcinoma', published in March 2021.[1]

The Multiple Technology Appraisal (MTA) of selective internal radiation therapies (SIRTs) for hepatocellular carcinoma (HCC) included the appraisal of evidence from SIR-Spheres® (manufactured by Sirtex), TheraSphere® (manufactured by Boston Scientific), and QuiremSpheres® (manufactured by Terumo, and Quirem Medical before its acquisition by Terumo in 2020), for early, intermediate, and advanced HCC. After appraisal by the University of York assessment group (AG), the NICE committee recommended SIR-Spheres and TheraSphere for treating unresectable advanced HCC for people with Child-Pugh grade A liver impairment when conventional transarterial therapies (CTTs) are inappropriate. Although clinical trial data were limited, and compared SIRTs only to sorafenib (the standard of care at the time), the committee recommended SIR-Spheres and TheraSphere on the basis of cost savings and potentially reduced side effects. QuiremSpheres was not recommended as it was considered less effective and costlier than sorafenib.

The CS for the current appraisal reports on the clinical effectiveness and cost comparison of SIRT with QuiremSpheres within its marketing authorisation for treating unresectable advanced HCC. Comparators are the previously recommended SIR-Spheres and TheraSphere. QuiremScout®, a product which uses the same microspheres for the workup procedure of QuiremSpheres, which was included within the cost of QuiremSpheres for TA688, is not included as part of the current appraisal.

The company performed an update of the systematic literature review of SIRT for HCC conducted to inform TA688. In the CS, evidence is presented from four single-arm studies on QuiremSpheres (two unpublished, and all conducted subsequent to the submission of evidence for TA688), and six comparator studies (two of which were included within TA688). Updated costs for QuiremSpheres are also presented.

Two clinical experts, a consultant hepatologist and a Principal Clinical Scientist (medical physicist), advised the EAG during the writing of this report. Clarification on some aspects of the CS were requested from the company by the EAG via NICE on 30th January 2023, and a response was received by the EAG on 14th of February 2023.

2.2 Epidemiology and staging of HCC

Epidemiology of HCC in England, including common causes, is described in the CS (Section B1.3, pp. 12-13). The Barcelona Clinic Liver Cancer (BCLC) staging system, which is used to establish prognosis and enable the selection of appropriate treatment based on underlying liver dysfunction, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and cancer stage, is also presented in the CS (Figure 1, p. 13).

In 2017, 79% of patients diagnosed with HCC in England were men and 21% were women,[3] with most cases occurring in adults over the age of 60. In the HCC BRIDGE study, the mean age of diagnosis of patients across Europe was 65 and 72% were classed as having Child-Pugh grade A liver impairment at diagnosis, indicating normal liver function.[4]

An audit of 11 UK centres between January 2018 and August 2020 reported on patients with advanced HCC suitable for systemic therapy, as determined in a Multi-Disciplinary Team (MDT) meeting and with a subsequent assessment in a local clinic.[5] Out of 361 patients with Child-Pugh grade A liver impairment, 82% were men and the median age at assessment was 68. Cirrhosis, identified by the EAG's clinical advisor as a key predictor of prognosis, was present in 66% of patients. Most patients experienced some limitations to their daily activities; 21% with ECOG PS 0, 62% with ECOG PS 1 and 17% with ECOG PS 2. 57% of patients had received no prior treatments and 34% of patients had received prior CTT therapies of transarterial chemoembolization (TACE) or transarterial embolization (TAE).

2.3 Description of SIRT treatment

2.3.1 Clinical pathway

Since the MTA of QuiremSpheres, SIR-Spheres, and TheraSphere for HCC (TA688) began in 2019, the clinical pathway for patients with advanced HCC has changed. The combination of immunotherapies, atezolizumab with bevacizumab, has been recommended by NICE for treating advanced or unresectable HCC only for adults who have not had previous systemic treatment and have Child-Pugh grade A liver impairment and an ECOG PS of 0 or 1 (TA666)[2]. This replaced sorafenib as the first-line systemic therapy in the NHS. Durvalumab with tremelimumab has also been shown to be superior to sorafenib in terms of overall survival (OS) for patients with unresectable HCC;[6] however, durvalumab with tremelimumab is yet to undergo NICE appraisal so is not yet available for patients in the NHS.[7]

The clinical pathway of care in HCC is described in the CS (pp. 13-15, Figure 1, and Figure 2). CS, Figure 1 outlines proposed treatment strategies for different BCLC stages of HCC. It should be noted

that SIRTs, including QuiremSpheres, are not represented on this figure and the availability of systemic treatments for NHS patients is subject to NICE recommendation.

The company's proposed position for QuiremSpheres in NHS clinical practice is described in response to clarification question A1 as an alternative to SIR-Spheres and TheraSphere, for patients with intermediate stage HCC (BCLC stage B) when TACE is not feasible or inappropriate; defined as those with a combination of large tumours (>6 cm), a large number of tumour nodules (≥ 7), and bilobar, multifocal tumours (response to clarification question A7a). QuiremSpheres is also positioned for patients with BCLC stage B HCC when diffuse, infiltrative, extensive bilobar liver involvement is present, or for patients with advanced HCC (BCLC stage C) as an alternative to systematic therapy (response to clarification question A1). The company have also indicated a role for QuiremSpheres in treating advanced stage HCC with portal invasion and no extrahepatic spread (response to clarification question B7). The company's proposed position of QuiremSpheres is outlined in Table 1.

Table 1 Proposed position of QuiremSpheres in NHS clinical practice

HCC BCLC stage	Patient / Tumour characteristics	Recommended first-line treatment	Potential role for QuiremSpheres?
Very early stage (0)	No role for QuiremSpheres		
Early stage (A)	No role for QuiremSpheres		
Intermediate stage (B)	Meeting liver transplant criteria	Transplant	No
	Well defined nodules, preserved portal flow, selective access.	TACE	No
	Diffuse, infiltrative, extensive bilobar liver involvement. No portal invasion. No extrahepatic spread.	Atezolizumab with Bevacizumab	Yes, if Child-Pugh grade A (normal liver function).
Advanced stage (C)	Portal vein invasion and/ or extrahepatic spread.	Atezolizumab with Bevacizumab	Yes, if Child-Pugh grade A (normal liver function).
Terminal stage (D)	No role for QuiremSpheres.		

Abbreviations: TACE: transarterial chemoembolization.

2.3.2 Case for cost comparison: mechanism of action

The NICE guide to the methods of technology appraisal states that "for the acceptance of a cost comparison case, evidence in support of similarity between the intervention and comparator technologies, in terms of overall health outcomes, must be presented."[8]

Evidence to support similarity of QuiremSpheres with SIR-Spheres and TheraSphere presented in the CS includes:

- A comparison of the technical characteristics and mechanisms of action of the SIRTs, including a description of the technical advantages of QuiremSpheres (CS, Section B.1.3, pp11-19)
- Clinical Expert Validation (CS, pp. 62-65)
- Dutch health technology assessment agency (Zorginstituut) guidance[9] and NICE Intervention Procedure Guidelines (IPGs) for SIRTs (CS, p12)
- Naïve comparisons of clinical effectiveness outcomes (OS, PFS and ORR) and safety from studies of QuiremSpheres, SIR-Spheres, and TheraSphere (CS, Section B.3.9)

2.3.2.1 Technical characteristics and mechanisms of action of SIRTs

During a SIRT procedure, radioactive forms of chemical elements (yttrium-90 for SIR-Spheres and TheraSphere, and holmium-166 for QuiremSpheres) are administered into the hepatic artery via a catheter as microspheres (microscopic beads) to deliver radiation to the tumour tissue. Microspheres remain in the capillary bed of the liver tumour(s), from where radiation is emitted in higher doses to tumour tissue than to healthy liver issue.

Table 2 describes the technical specifications, mechanisms of action and treatment procedures associated with QuiremSpheres, SIR-Spheres and TheraSphere, supplementing the information presented in the CS (Table 2, Table 3 and Section B.1.3) with additional information submitted by the companies for TA688.[1]

QuiremSpheres uses poly-L-lactic acid (PLLA) microspheres containing holmium-166(^{166}Ho), whereas SIR-Spheres and TheraSphere use resin and glass microspheres respectively containing yttrium-90 (^{90}Y). While the therapeutic mode (i.e. tumour cell death induced by beta radiation) is the same, QuiremSpheres allow for potentially better visualisation of the microspheres using single-photon emission computed tomography due to its gamma emission (compared to bremsstrahlung imaging for ^{90}Y). ^{166}Ho is also paramagnetic, allowing for imaging of the microspheres via magnetic resonance imaging (MRI) technology.

Table 2 Characteristics of QuiremSpheres, SIR-Spheres and TheraSphere (adapted from CS Table 3, pp18-19)

Characteristics	QuiremSpheres	SIR-Spheres	TheraSphere
TECHNICAL CHARACTERISTICS			
Isotope	^{166}Ho	^{90}Y	^{90}Y
Half-life	26.8 hours	64.1 hours	64.1 hours
Time to 90% of dose deposited	4 days	11 days	11 days
Activity per microsphere	200-400 Bq	50 Bq	2500 Bq
Penetration range in soft tissue	max 8.7 mm, mean 2.5 mm	max 11 mm, mean 2.5 mm	max 11 mm, mean 2.5 mm
Radiation emitted	Beta radiation (therapeutic mode of action); gamma radiation (post-treatment evaluation	Beta radiation (therapeutic mode of action)	Beta radiation (therapeutic mode of action)
Material of microsphere	PLLA (biodegradable)	resin (non-biodegradable)	glass (non-biodegradable)
Mean diameter of microsphere	25-35 µm	20-60 µm	20-30 µm
Typical number of microspheres administered (x million)	20-30	40-60	1.2-8
TREATMENT PROCEDURE			
Work-up imaging surrogate	^{99m}Tc-MAA or ^{166}Ho (QuiremScout)	^{99m}Tc-MAA	^{99m}Tc-MAA
Work-up imaging technology	SPECT/CT	SPECT/CT	SPECT/CT
Product supplied	Patient specific vials (up to 3 vials) ordered following work-up. Available in all increments with 2 decimals. No preparation needed	Mother vial Requires preparation of patient specific dose	Patient specific vial ordered following work-up. Available in 0.5 GBq increments between 3 GBq-20 GBq. No preparation needed
Calculation of required dose	Standard dosimetry or based on dose simulation using QuiremScout® or ^{99m}Tc-MAA.	Standard dosimetry or based on dose simulation using ^{99m}Tc-MAA.	Standard dosimetry or based on dose simulation using ^{99m}Tc-MAA.
Post-treatment imaging	SPECT/CT or MRI	SPECT/CT or PET-CT	SPECT/CT or PET-CT
Hospital visit(s) required	Minimum one day hospital appointment for work up and separate day / visit for treatment	Minimum one day / visit hospital appointment for work up and treatment	Minimum one day hospital appointment for work up and separate day/ visit for treatment

Abbreviations: Bq: becquerel; CT: computed tomography; ^{166}Ho: Holmium-166; MRI: magnetic resonance imaging; PET-CT: positron emission tomography- computed tomography; PLLA: poly-L-lactic acid; SPECT: single-photon emission computed tomography; ^{99m}Tc-MAA: ^{99m}Tc-macroaggregated albumin; ^{90}Y: Yttrium-90.

The company consider the possibility of MRI imaging to be a technical advantage of QuiremSpheres (CS, p16). Clinical advice to the EAG is that imaging using MRI for work-up and post-treatment may result in improved images of radiation and may have advantages for dosimetry during work-up; however, logistically, SPECT-CT more likely to be the preferred option dependent on the capacity of the treatment centre.

The difference in radioactive isotope means QuiremSpheres differs from the SIR-Spheres and TheraSphere with regards to its half-life, time taken to deposit 90% of the dose, and penetration range into tissue. There are also differences between the three SIRTs in the size and number of microsphere beads administered (Table 2).

Clinical advice to the EAG is that the lower maximum penetration rate is due to the lower beta-energy emitted by ^{166}Ho compared to ^{90}Y. This lower penetration range of QuiremSpheres in soft tissue may mean it is less likely to damage healthy liver tissue, but it may also affect the ability of the radiation to effectively reach all tumour tissue.

The number of microspheres per administration is higher for SIR-Spheres and lower for TheraSphere compared to QuiremSpheres (Table 2). Clinical advice to the EAG is that a higher number of microspheres may lead to a better, more uniform delivery of the radiation, whilst a lower number of microspheres may reduce the risk of vascular stasis and thus allow subsequent SIRT procedures.

Prior to administering any SIRT, a work-up procedure is required for treatment planning, to occlude vessels which may carry microspheres away from the liver, and to determine patient eligibility for the full SIRT procedure; a high level of lung shunt or extra-hepatic uptake would contraindicate SIRT. The work-up also allows a more exact calculation of the patient-specific treatment dose for eligible patients compared to standard dosimetry.

The work-up procedure of QuiremSpheres and TheraSphere are patient-specific, meaning that a personalised dose is ordered following dosimetry calculations based on imaging and delivered to the treatment centre. For SIR-Spheres, the dose is prepared on site upon receipt of a mother vial, which means that in principle, the work-up and treatment could be completed in one visit.[10]

However, clinical advice to the EAG is that it is very unlikely that work-up and SIRT treatment would be completed in a single visit on a single day for any of the SIRTs due to the complexity of the work-up, the number of procedures and departments involved in the work-up, dose preparation, and administration of SIRTs, and the potential risk of wastage if a patient cannot received a treatment ordered in advance. In practice, a patient would likely undergo the SIRT procedure several days after work-up, depending on availability of the radiology suite at the treatment centre.

Clinical advice to the EAG is that the shorter half-life of ^{166}Ho, meaning that the therapeutic radiation level within the spheres drops sooner, has advantages as highlighted by the company in the CS (p17) but this may also have practical disadvantages in the event of any delays to the delivery of a patient-specific dose for the SIRT procedure following work-up.

Work-up procedures are performed with a surrogate marker (^{99m}Tc-macroaggregated albumin [^{99m}Tc-MAA]) injected into the hepatic artery using the same catheter position as would be used for a SIRT procedure. The work-up procedure for QuiremSpheres can also be performed using a lower dose of ^{166}Ho (QuiremScout) rather than a ^{99m}Tc-MAA based surrogate marker, but this is not being proposed as part of the current appraisal.

For two of the studies[11, 12] of QuiremSpheres submitted for the current appraisal, all patients received work-up with QuiremScout prior to treatment with QuiremSpheres. In the Jena Clinical Experience study[13], both QuiremScout and ^{99m}Tc-MAA were used for work-up, but the proportions of each surrogate marker used were not reported and in the RECORD study[14], QuiremScout was used in 63.7% of patients and ^{99m}Tc-MAA in 36.3% of patients. The company state that the choice between QuiremScout and ^{99m}Tc-MAA in these studies is based on hospital preference and access to the products and that there were no significant differences in the visually graded targets of the work-up products used for therapy decision (response to clarification question A8).

2.3.3.2 Clinical expert validation and HTA guidance

The company provide clinical expert validation of similarity of clinical efficacy and adverse events between QuiremSpheres and ^{90}Y SIRTs, and the anticipated position of QuiremSpheres in the clinical pathway as an alternative to ^{90}Y SIRTs (CS, pp. 64-65). The Dutch Zorginstituut reassessed the evidence for QuiremSpheres for HCC in 2022[9], after publication of the HEPAR Primary study[11]. They concluded that, whilst there are technical differences between the three SIRTs, the limited evidence available appears to suggest that clinical outcomes are comparable and that holmium-166 microspheres are a "technical variant" of ^{90}Y microspheres.

Clinical advice to the EAG agrees with the clinical expert validation provided to the company and that QuiremSpheres can be considered as a 'technical variant' of SIR-Spheres and TheraSphere due to the similar administration methods and same therapeutic mode of action. However, the emission of gamma-radiation and the implications for imaging are technical differences which could provide technical advantages or practical disadvantages for QuiremSpheres. The company also provide clinical expert validation regarding the feasibility of 'switching' current patients currently receiving ^{90}Y SIRTs to QuiremSpheres (CS, p65). Clinical advice to the EAG suggests that a choice between QuiremSpheres and ^{90}Y SIRTs or switching patients currently receiving ^{90}Y SIRTs to QuiremSpheres may not be necessary in NHS practice and that if approved, treatment centres may offer both

QuiremSpheres and ^{90}Y SIRTs, with the choice between SIRTs made based on clinician preference and familiarity with a specific SIRT.

The company refer to two published NICE Interventional Procedure Guidelines (IPGs) of SIRT for unresectable primary intrahepatic cholangiocarcinoma and unresectable colorectal metastases in the liver[15, 16] and one IPG in development of SIRT for neuroendocrine tumours that have metastasised to the liver.[17] These IPGs do not make any distinction between the clinical effectiveness of QuiremSpheres, SIR-Spheres and TheraSphere. The EAG notes that NICE recommends SIRTs for these indications only under special arrangements, such as for research, due to limited evidence of effectiveness and safety and considers that these IPGs do not provide supportive evidence of similarity between QuiremSpheres and the ^{90}Y SIRTs for the population outlined in the NICE scope for the current appraisal.

2.3.3.3 EAG commentary on mechanism of action of SIRTs

There are differences between QuiremSpheres, SIR-Spheres and TheraSphere in terms of technical characteristics, work-up, imaging and administration. While some of these differences may offer technical advantages for QuiremSpheres as described by the company (CS, pp. 16-17), the EAG is not aware of any evidence that these technical advantages translate into improved clinical outcomes for patients. Furthermore, these differences may also result in some practical disadvantages of QuiremSpheres, as described by the clinical advisors to the EAG.

Clinical advice to the EAG is that technical differences in half-life, penetration range, size and number of microspheres, work-up product and imaging technology are unlikely to significantly impact on clinical outcomes. Therefore, the EAG considers that it is reasonable to consider QuiremSpheres as a technical variant to SIR-Spheres and TheraSphere.

The EAG emphasises that the use of QuiremScout is associated with an additional procurement cost, which does not form part of the QuiremSpheres procedure for the present cost comparison. The QuiremSpheres procedure under cost comparison for the current appraisal must be assumed to use the ^{99m}Tc-MAA work-up product.

The EAG critique of the naïve comparisons of clinical effectiveness outcomes and safety from studies of QuiremSpheres, SIR-Spheres, and TheraSphere is provided in section 4.

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The company's decision problem broadly aligns with the final scope issued by NICE (Table 3). The EAG comments below on the definition of the population within the NICE scope and the outcome data provided in the CS and in response to clarification.

Table 3 Summary of the decision problem (adapted from CS Table 1, pp7-8)

	Final NICE scope	Company's decision problem	EAG comments
Population	Adults with unresectable advanced HCC with Child-Pugh grade A liver impairment when CTT are inappropriate.	Same as final scope issued by NICE.	The EAG considers that the relevant population is adult patients who are not eligible for CTT or surgical resection and have BCLC B or BCLC C HCC with Child-Pugh grade A liver impairment. Clinical evidence provided in CS and in clarification reflects a broader population than the relevant population defined above
Intervention	QuiremSpheres	Same as final scope issued by NICE.	No concerns.
Comparators	SIR-Spheres and TheraSphere.	Same as final scope issued by NICE.	No concerns.
Outcomes	• Overall survival, • Progression-free survival, • Time-to-progression, • Response rates, • Rates of liver transplant or surgical resection • Adverse effects of treatment • Health-related quality of life.	Same as final scope issued by NICE.	The outcomes in the CS are appropriate and match the scope with the following exceptions: • No clinical effectiveness results are provided for 'rates of liver transplant or surgical resection' The EAG considers this to be appropriate. • Limited data presented for health-related quality of life, therefore equivalence of QuiremSpheres with comparators in terms of this outcome is very uncertain
Economic analysis	Cost comparison	Same as final scope issued by NICE.	No concerns.

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; CTT: conventional transarterial therapies; EAG: Evidence Assessment Group; HCC: hepatocellular carcinoma.

3.1 Population

The population specified in the NICE scope for the current appraisal is adults with unresectable advanced HCC with Child-Pugh grade A liver impairment when CTT are inappropriate, which was the population that SIR-Spheres and TheraSphere were recommended for in TA688.

The trial and economic evidence considered in the Assessment Group (AG) report for TA688 was based on a population defined as patients:

- with unresectable intermediate (BCLC B) or advanced (BCLC C) HCC.
- who are ineligible for any CTT.
- who have no extrahepatic disease.

The resulting indicated population in the TA688 FAD is restricted to advanced HCC, presumably to align with the guidance for sorafenib, the main comparator to the SIRT treatments in TA688, which is indicated for advanced HCC only (TA474).[18] Therefore, the population defined in the TA688 AG report is more inclusive in terms of BCLC staging than implied in the resulting guidance and the scope for the current appraisal, but also excludes those with extrahepatic disease who would be eligible for systemic therapies. In intervening TA666 of atezolizumab with bevacizumab,[2] conducted since the MTA for TA688 began, the guidance includes ‘advanced *or* unresectable HCC', and is inclusive of patients 'not amenable to locoregional therapies', i.e. CTT. Clinical advice to EAG and company within TA666 suggested that BCLC B patients not amenable to locoregional therapies are not easily clinically distinguishable from BCLC C patients. Furthermore, it was not possible to present separate incremental cost-effectiveness ratios (ICERs) by subpopulation in TA666.

Whilst not in alignment with the population sorafenib is recommended for in TA474, it was accepted in TA666 that sorafenib and lenvatinib were standard of care in this BCLC B CTT-ineligible population, and thus atezolizumab with bevacizumab was recommended for both BCLC B and BCLC C patients.

The EAG, therefore, considers that the relevant indicated population for this current appraisal should be primarily determined by ineligibility for surgical resection or CTT. The EAG considers that clinical evidence for SIRT treatment in adult patients who are not eligible for CTT or surgical resection and have BCLC B or BCLC C HCC with Child-Pugh grade A liver impairment is relevant to the current decision problem.

The EAG acknowledges that the eligibility of a patient for CTT is based on multiple factors and therefore a CTT-ineligible population may be difficult to define or to identify retrospectively within a clinical study. The company defines, according to the Asia-Pacific Primary Liver Cancer Expert Consensus Statements,[19] that TACE is inappropriate for tumours which are large in size (> 6cm) and/or large in number (≥ 7 nodules), or large in number and bilobar multifocal (response to clarification question A7a).

The EAG notes that a wider range of HCC patients are included in the studies of QuiremSpheres, SIR-Spheres and TheraSphere than would be relevant to the current decision problem. The implication is that a substantial proportion of patients within some of the studies would not receive SIRT treatment in NHS practice. This introduces uncertainty into the clinical effectiveness results for QuiremSpheres and also into the comparative clinical effectiveness of QuiremSpheres compared to SIR-Spheres and TheraSphere. Further discussion is provided in Section 4.2.1.

3.2 Outcomes

No clinical effectiveness results are data are provided for the outcome rates of liver transplant or surgical resection. The company and the EAG consider that surgical resection is not a relevant outcome for a population with unresectable HCC. Clinical advice to the AG during TA688 was that downstaging of patients with advanced HCC to transplant and other curative options is rare in UK clinical practice, with very few if any of these patients receiving curative therapies. The company agree with this clinical advice (response to clarification question C3), and clinical advice to the EAG for this current appraisal is that rate of transplant is not a relevant outcome for this population.

Very limited data are available for health-related quality of life (HRQoL) from the studies of QuiremSpheres and of SIR-Spheres and TheraSphere included in the CS (Table 13 and response to clarification question A12). The EAG therefore considers that the case for equivalence of HRQoL outcomes for QuiremSpheres compared to SIR-Spheres and TheraSphere to be very uncertain (see Section 4.3.4).

4 SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

4.1 Critique of the methods of the literature review

4.1.1 Summary of systematic literature review (SLR) conducted for TA688

The SLR conducted by the AG to inform TA688 identified studies including patients with early, intermediate, and advanced stage HCC treated with SIRTs and relevant comparators, in line with the NICE scope for TA688. The SLR included 26 comparative studies of SIR-Spheres and/or TheraSphere and one non-comparative study of QuiremSpheres.[20] A network meta-analysis (NMA) of patients with unresectable HCC who are ineligible for CTTs was performed with two RCTs comparing SIR-Spheres to sorafenib (SARAH[21], SIRveNIB[22]), an RCT comparing sorafenib and lenvatinib[23] and two retrospective studies comparing SIR-Spheres and Therasphere.[24, 25] No comparisons of QuiremSpheres to other therapies, direct or indirect, could be made in TA688.

4.1.2 SLR conducted for the current appraisal

The clinical effectiveness SLR conducted by the company to inform the current appraisal is outlined in response to clarification questions A2 and A3.

4.1.2.1 Searches

An EAG critique of the clinical effectiveness searches is provided in Appendix 1, Table 11.

The search strategies for the identification of studies on the clinical effectiveness of QuiremSpheres, SIR-Spheres and TheraSphere for treating unresectable advanced HCC were not supplied in the CS nor in the clarification response. Therefore, it was not possible for the EAG to check and verify the strategies used for the identification of the evidence for the clinical effectiveness SLR.

The company supplied a description of the searches in their response to clarification question A2. The company partially updated the searches from the previous SLR of SIRT treatments for HCC conducted to inform TA688[26] to identify any studies in the MEDLINE database, published between 25th January 2019 and 1st December 2023. As the company only searched MEDLINE, relevant studies in other databases and resources would not have been identified by this approach. In addition, inappropriate limits were applied to the search of MEDLINE which further reduced the comprehensiveness of the search: a limit to English language studies only, and a further restriction to those studies with available full text. Searches for unpublished studies, ongoing studies and grey literature were not reported. Therefore, the EAG cannot be certain that all potentially relevant studies, both published and unpublished, were identified in the company searches.

4.1.2.2 Study selection

Eligibility criteria and study selection methods used by the company in the SLR are outlined in response to clarification questions A2 to A4.

The company have selected studies with the aim of conducting a naïve visual comparison of treatment estimates of QuiremSpheres and comparators (SIR-Spheres and TheraSphere). The EAG considers that this approach is acceptable given the anticipated observational nature of the relevant studies. The EAG agrees that a mixed treatment comparison using formal synthesis methods, such as an unanchored matching adjusted indirect comparison would be subject to great uncertainty and would not provide any meaningful evidence in addition to a naïve comparison. Nonetheless, a treatment comparison, whether via synthesis or a naïve visual comparison should include all relevant evidence to the decision problem. The EAG considers that study selection has not been conducted[27] nor reported[28] according to systematic review standards.

Selection criteria provided are ambiguous, such as the cohort must be of a 'reasonable size' and the study must be of an 'appropriate design for allowing comparison with available data for QuiremSpheres' without further defining sample sizes that would be considered reasonable or designs that would be considered appropriate (response to clarification question A2).

The company PRISMA flowchart (response to clarification question A3b) indicates that out of 120 studies which 'met broad inclusion criteria,' 108 studies were excluded at full text screening. A list of these 108 studies has not been provided by the company, therefore the EAG is unable to verify the relevance of these studies to the decision problem (Table 3).

The remaining 12 studies identified in the company search were 'included in the final evaluation' for the naïve comparison. Two unpublished QuiremSpheres studies (RECORD[14] and RETOUCH[12]) and the two RCTs comparing SIR-Spheres to sorafenib (SARAH[21] and SIRveNIB[22]) which were included in TA688 were also included in this final evaluation. These four studies identified from other sources are not reflected on the PRISMA flowchart (response to clarification question A3b). Out of these 16 studies evaluated, the company excluded six comparator studies[29-35] identified in the search (response to clarification question A3c) and included four QuiremSpheres studies[11-14], four SIR-Spheres studies[21, 22, 36, 37] and two TheraSphere studies[34, 38] in the naïve comparisons (CS, Section B3.9).

The EAG has assessed eligibility of the 16 studies considered for inclusion in the naïve comparison according to the population, intervention, comparators, and outcomes outlined in the decision problem (Table 3). The company and EAG assessments of eligibility are presented in

Table 4; see Appendix 2, Table 12 and Table 13 for further details of patient baseline characteristics and

Table 14 for clinical effectiveness results extracted by the EAG from the QuiremSpheres and comparator studies.

Table 4 Company and EAG eligibility assessment for naïve comparison of QuiremSpheres and comparators (SIR-Spheres and TheraSphere)

Trial	SIRT interventions	Source	Included in naïve comparison		EAG comments on eligibility
			Company	EAG*	
Reinders 2022 (HEPAR Primary)[11]	QuiremSpheres	Company SLR; study known to the company	Yes	Yes	The majority of the cohort aligns with the relevant population (all treated patients BCLC stage B or C, 90% Child-Pugh grade A liver impairment). Cirrhosis was present in 65% of the cohort, which is lower than would be expected in NHS clinical practice according to the clinical advice. Relevant outcome data are reported (OS, ORR and AEs).
Drescher 2023 (Jena Clinical Experience) [13]	QuiremSpheres	Company SLR; study known to the company	Yes	Yes	The majority of the HCC cohort (n=14) aligns with the relevant population (78% of patients BCLC stage B or C, and 93% Child-Pugh grade A liver impairment). Five patients (36%) received active treatment after QuiremSpheres, which suggests they would not have been eligible for SIRT in the NHS (2 received TACE, 1 resection, and 2 liver transplantations). Relevant outcome data are reported (OS, PFS, ORR and AEs).
RECORD[14]	QuiremSpheres	Unpublished study known to the company	Yes	Yes	The majority of the HCC cohort aligns with the relevant population (78% of patients BCLC stage B or C, and 65.5% Child-Pugh grade A liver impairment). BCLC stage was missing for 13% of patients and 34.5% of patients had Child Pugh grade B or C liver impairment so would not have been eligible for SIRT in the NHS. In the full cohort, treatment was intended to be palliative in only 66.4% of the cases. Relevant outcome data are reported (OS, PFS, ORR and AEs).
RETOUCH[12]	QuiremSpheres	Unpublished study known to the company	Yes	NO*	The majority of the cohort does not align with the relevant population (73% of patients BCLC stage A and 80% with solitary tumours, QuiremSpheres used as downstaging or bridging-therapy).
Vilgrain 2017 (SARAH)[21]	SIR-Spheres	Included in TA688	Yes	Yes	The majority of the cohort aligns with the relevant population (96% of patients BCLC stage B or C, and 87.9% Child-Pugh grade A liver impairment). Relevant outcome data are reported (OS, PFS, ORR and AEs).
Chow 2018 (SIRveNIB)[22]	SIR-Spheres	Included in TA688	Yes	Yes	The majority of the cohort aligns with the relevant population (all patients BCLC stage B or C, and 90.0% Child-Pugh grade A liver impairment and 'not amenable to curative treatment modalities.' Relevant outcome data are reported (OS, PFS, ORR and AEs).
Frantz 2021 (RESiN)[36]	SIR-Spheres	Company SLR	Yes	Yes	The majority of the cohort aligns with the relevant population (74% of patients BCLC stage B or C, and 99% Child-Pugh grade A liver impairment). A small proportion of patients (4.5%) received treatment with the intend of bridging (if BCLC stage A) or downstaging to transplant (if BCLC stage B), and 0.8% received resection after treatment with SIR-Spheres. Relevant outcome data are reported (OS, PFS, ORR and AEs).
Helmberger 2021 (CIRT)[37]	SIR-Spheres	Company SLR	Yes	Yes	BCLC stage not reported. Majority of the cohort Child-Pugh grade A liver impairment (80.9%). After treatment with SIR-Spheres, 8.1% of patients with HCC received TACE, and 3.3% resection or ablation. Relevant outcome data are reported (OS and AEs).

Van Thai 2021[35]	SIR-Spheres	Company SLR	No	YES*	The majority of the cohort aligns with the relevant population (all patients BCLC stage B or C, 94% Child-Pugh grade A liver impairment and 'unsuitable for radical treatments [surgery, liver transplantation, or percutaneous ablation] or chemoembolization as a result of the presence of PVT or extensive tumour burden'). Relevant outcome data (OS, ORR and AEs) are reported.
Casáns-Tormo 2023[30]	SIR-Spheres TheraSphere	Company SLR	No	YES*	The majority of the cohort aligns with the relevant population (all patients Child-Pugh grade A liver impairment, 92% BCLC stage B or C, 83% SIRT treatment palliative, median tumour size 63 [range 9-150]) and relevant outcome data (OS, ORR and AEs) are reported.
Hur 2023[31]	SIR-Spheres TheraSphere	Company SLR	No	YES*	All patients have advanced HCC with PVT. The company have indicated a role for QuiremSpheres in this population. Relevant outcome data are reported (OS, PFS, ORR and AEs).
Garin 2020 (DOSISPHERE-01)[38]	TheraSphere	Company SLR	Yes	Yes	All patients BCLC stage B or C, 79% of patients Child-Pugh grade A5 liver impairment (remaining 21% grade A6 or B7). One of the inclusion criteria was 'not amenable to surgery or local ablative treatment'. Relevant outcome data are reported (OS, PFS, ORR and AEs).
Lam 2022 (TARGET)[34]	TheraSphere	Company SLR	Yes	Yes	The majority of the cohort aligns with the relevant population (87.0% of patients BCLC stage B or C, 89.5% of patients Child-Pugh grade A liver impairment).
Makary 2023[29]	^{90}Y SIRTs	Company SLR	No	No	Agree with company reason for exclusion; 77% of the cohort could be downstaged to or maintained within the Milan criteria which does not reflect the relevant population for this appraisal.
Dhondt 2022[32]	TheraSphere	Company SLR	No	No	Agree with company reason for exclusion; the study includes patients who are eligible for CTT.
Salem 2021[33]	TheraSphere	Company SLR	No	No	Agree with company reason for exclusion; the study includes patients who are eligible for CTT.

*Indicates a different judgment to the company of study eligibility for inclusion in the naïve comparison

Abbreviations: AEs: adverse events; BCLC: Barcelona Clinical Liver Cancer; CTT: conventional transarterial therapies; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PVT: portal vein thrombosis; SIRT: selective internal radiation therapies; SLR: systematic literature review, TACE: transarterial chemoembolization; ^{90}Y: yttrium-90.

The patient populations recruited to the 16 studies are broader than the population the EAG deems relevant for the decision problem (Section 3.1). The company further describes the relevance of the patient cohorts recruited to the four QuiremSpheres studies to the population defined in the decision problem (response to clarification question A7a and A7b). The EAG acknowledges the difficulty of assessing eligibility of the patient cohorts, particularly in terms of suitability for CTT which is determined by multiple factors (Section 2.3.1). Therefore, the EAG has adopted an inclusive approach and has included all studies of QuiremSpheres and comparators in which the majority of patients receiving SIRT align with the relevant population, or where outcome data for the relevant population are presented separately.

The EAG also considers studies which report relevant outcome data in any format to be eligible for inclusion in the naïve comparison. While studies which report the same summary statistics (e.g., median and 95% confidence intervals [CIs] for OS and PFS) may be more readily comparable in a visual format such as a forest plot, studies which provide alternative summary statistics for relevant outcomes (e.g., mean OS or PFS) should also be included in the naïve comparison. Therefore, the EAG has included three studies of comparators that were excluded by the company (Casáns-Tormo 2023[30], Hur 2023[31], Van Thai 2021[35]) in which the majority of patients receiving SIRT align with the relevant population, and relevant outcome data are reported. The EAG has also excluded one of the QuiremSpheres studies (RETOUCH[12]) from the naïve comparison, in which the majority of patients receiving SIRT did not align with the relevant population (Table 4).

4.2 Included studies

4.2.1 Patient and disease characteristics

Study characteristics and patient baseline characteristics of the four QuiremSpheres studies included by the company are presented in CS (Table 8 and Table 9 respectively). Patient baseline demographic characteristics and disease characteristics in the three QuiremSpheres studies and nine comparator studies included in the EAG naïve comparisons are presented in Appendix 2, Table 12 and Table 13.

Patients recruited into the studies of QuiremSpheres, ranging from a median age of 66.2 years[14] to 73 years[11, 13], were on average slightly older than patients recruited into the studies of comparators, ranging from a mean or median age of 59.4 years [31] to 66.3 years[21]. Cohorts recruited to the studies of QuiremSpheres and of comparators were majority male (67.8% to 93%) and where reported, cirrhosis, an important prognostic factor in HCC, was present in the majority of patients (65% to 97%). Of note, the QuiremSpheres HEPAR Primary study[11] recruited the lowest proportion of patients with cirrhosis (65%), which is lower than would be expected in NHS clinical practice, according to clinical advice to the EAG.

The proportion of patients with portal vein thrombosis (PVT) or invasion (PVI) present, a characteristic which contraindicates CTT, was variable across studies ranging from 10.9%[14] to 100%[31]. In most studies of QuiremSpheres and of comparators, the majority of the cohort had an ECOG PS of zero, indicating no restrictions in daily activities, with the exceptions of comparator studies DOSISPHERE-01[38] (48% with ECOG PS 0) and van Thai[35] (14% with ECOG PS 0). Despite the majority of the cohort aligning with the relevant population of the decision problem, the combination of restrictions to daily activities (85.6% of the cohort with ECOG PS 1 or 2), cirrhosis (97%), and PVT (63%) present suggests a worse prognosis for the cohort recruited to the van Thai study[35] compared to the other studies of QuiremSpheres and comparators.

Across all studies, the majority of the cohort were classified as having Child-Pugh grade A liver impairment at diagnosis (normal liver function) and were intermediate (BCLC stage B) or advanced (BCLC stage C) HCC and would therefore potentially be eligible to receive SIRT treatment with QuiremSpheres in NHS clinical practice within the position proposed by the company (Table 1).

All except one study[30] included a minority (up to 30.9%[14]) of patients with Child Pugh score B7 indicating mild to moderate liver damage and three studies[14, 37 36] included one or two patients with Child-Pugh grade C liver impairment, indicating severe liver damage which may limit treatment options. Two QuiremSpheres studies[13, 14] and two comparator studies[36 34] included between 5.5% and 19% of patients with early stage HCC (BCLC stage A) and one QuiremSpheres study[14] included 3.6% of patients with very early stage HCC (BCLC stage 0). One comparator study included 7% of patients with end-stage HCC (BCLC stage D)[36] and one comparator study did not report BCLC stages[37]. All of these patients within these studies would likely not be eligible to receive SIRT treatment in the NHS (Table 1), which limits the generalisability of the results of these studies to NHS clinical practice.

Where reported, a minority of patients included in the studies had received prior treatments including systemic therapies, TACE, resection, and radiotherapies. The distribution of tumour involvement (unilobar vs bilobar) and the number of tumours present (one or multiple tumours, including over ten up to an uncountable number of tumours) varied greatly across the studies. The impact of these variations in patient baseline characteristics on the treatment effect estimates should be considered when drawing conclusions from the naïve comparisons of the QuiremSpheres studies to the comparator studies.

4.2.2 Quality assessment

Quality assessment of the four QuiremSpheres studies is presented in CS, Table 11, and Appendix D1.3. Quality assessment of the four of the comparator studies[34, 36-38] are presented in response to clarification question A6. The company refer to the quality assessment conducted of the SARAH[21] and SIRveNIB[22] studies within TA688.

The EAG believes that the company used the National Institute of Health (NIH) Quality Assessment Tool for before-after studies with no control group[39] for the quality assessments presented in CS Appendix D.1.3 and in response to clarification question A6 (rather than the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies as described in response to clarification question A5). The company did not use a specific tool for the quality assessments presented in CS, Table 11 (response to clarification question A5).

The EAG considers that aside from general limitations associated with observational evidence from single arm studies without control groups[27], the main limitations of the QuiremSpheres studies and the studies of SIR-Spheres and TheraSphere are the generalisability of the populations in these studies to patients who would receive SIRT treatment in NHS practice (Section 4.2.1), small sample sizes of some of the studies and the exclusion of data from patients lost to follow-up in some of the studies. The EAG has not performed a formal quality assessment of the three additional studies included within the EAG naïve comparisons[30, 31, 35], but considers that these studies are associated with similar limitations as those included in the company naïve comparison.

4.3 Clinical effectiveness evidence for QuiremSpheres

Table 7 of the CS describes four QuiremSpheres studies submitted as evidence by the company:

- The HEPAR Primary Study, a multi-centre, interventional, non-randomized, non-comparative, early Phase II trial[11]
- RETOUCH, a prospective, non-randomized, single-center pilot study[12]
- RECORD, a real-world, multicenter, retrospective registry[14]
- Jena Clinical Experience, a prospective single center observational study[13]

CS, Sections B3.2 to B 3.5 summarise the design, characteristics, and methodology of four QuiremSpheres studies and Section B.3.6 describes the clinical effectiveness results of these studies.

The company's naïve visual comparison of treatment effect estimates from QuiremSpheres studies and comparator studies is presented in Section B.3.9 of the CS. The company conclude that the results of the naïve comparison demonstrate that the OS, PFS and ORR outcomes for patients receiving QuiremSpheres are similar to those for patients receiving SIR-Spheres or TheraSphere.

The EAG does not consider the RETOUCH study[12] to be eligible for inclusion in the naïve comparison of QuiremSpheres and comparators (see Section 4.1.2.2). Appendix 2, Table 14 presents OS, PFS and ORR results extracted by the EAG from the QuiremSpheres studies and comparator studies included in the EAG naïve comparison. Figure 1 and

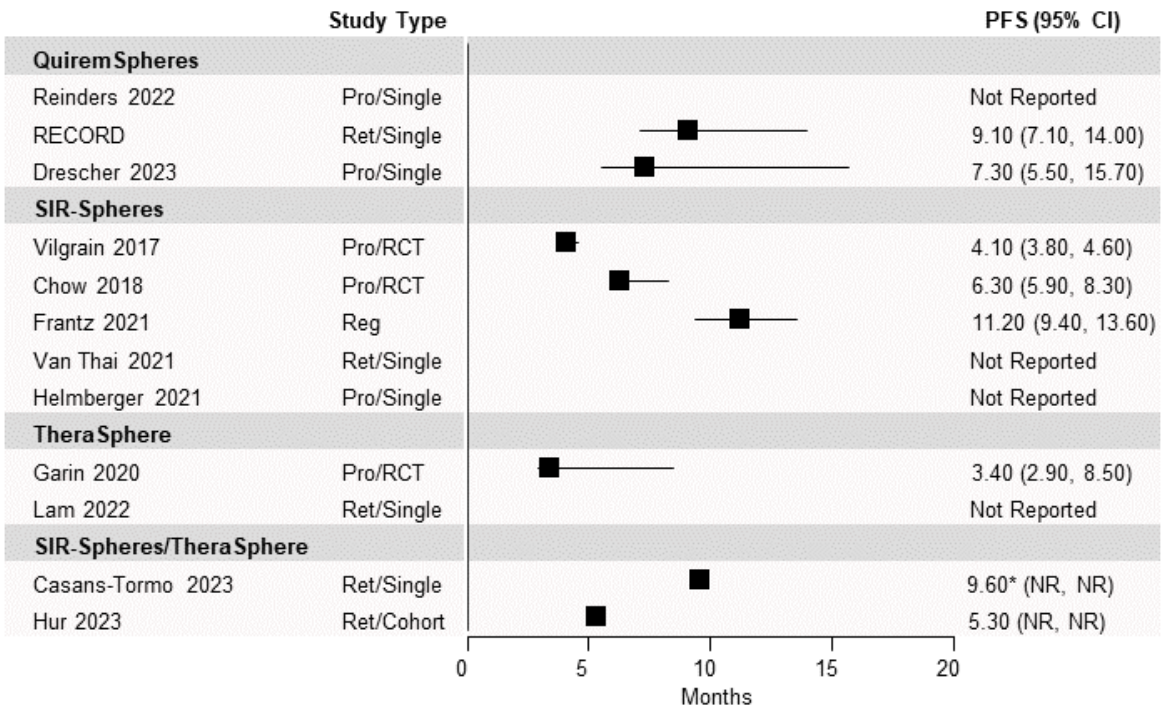

Figure 2 also visually display OS and PFS results of the EAG naïve comparison.

The study designs, the range of follow-up, and how the extent of follow-up was reported, varied across the QuiremSpheres studies and comparators studies. The comparability of OS and PFS results from studies with shorter follow-up, such as the RECORD study[14] of QuiremSpheres with a median of 7.1 months follow-up to longer term comparator registry studies RESiN[36] and CIRT[37] with two to four years of follow-up, must be considered when making naïve comparisons.

4.3.1 Overall survival (OS)

The estimates for median OS vary between 14.7 and 22.1 months for QuiremSpheres, and between 9.9 months and 28.2 months for comparator studies. Notably, the three RCTs of comparator treatments, SIR-Spheres (SARAH, [21] SIRveNIB[22]) and TheraSphere (DOSISPHERE-01[38]), showed the lowest median OS ranging from 9.9 to 11.3 months (Figure 1).

4.3.2 Progression free survival (PFS)

The estimates for median PFS were 8.8 months and 9.1 months for QuiremSpheres, PFS was not reported for in the HEPAR Primary study.[11] Where reported, median PFS ranged from 3.4 months to 10.6 months (for patients with Child-Pugh grade A liver impairment and intermediate BCLC stage B HCC[36]). Similar to OS, the PFS values observed in the three RCTs are amongst the lowest (

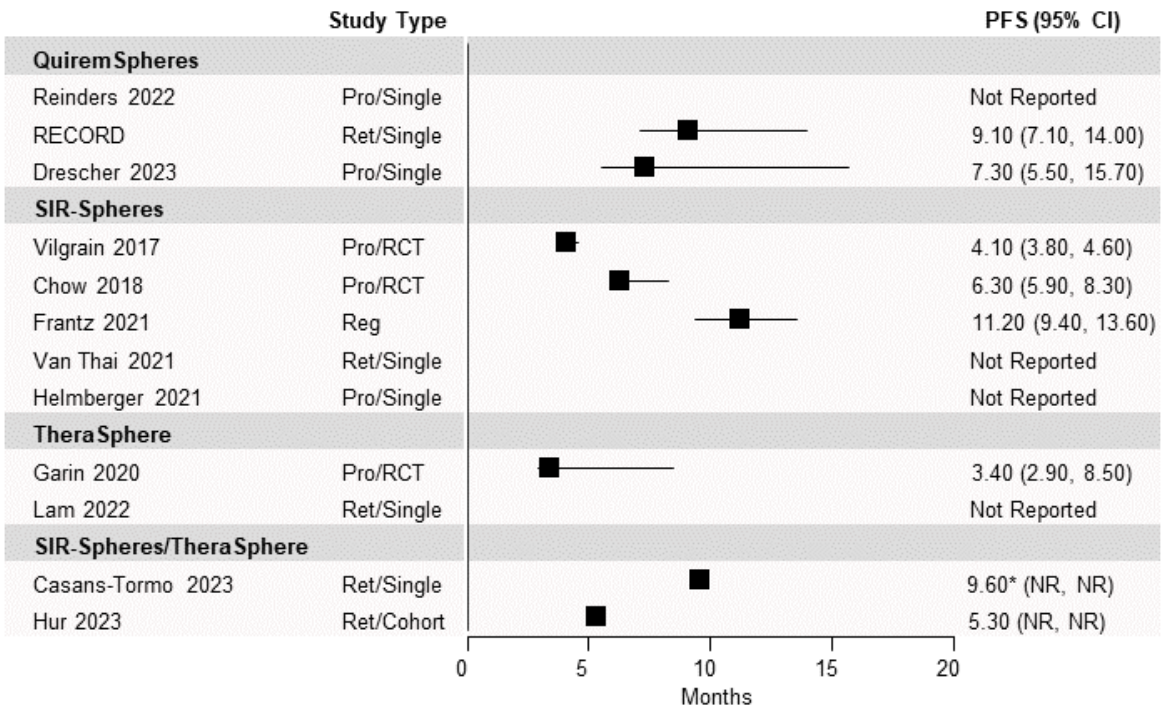

Figure 2). The EAG notes that the definition of progression events and censoring approaches varied across studies and different criteria were used to assess progression (RECIST 1.1 or mRECIST). These differences must be considered when making naïve comparisons of PFS treatment effect estimates.

4.3.3 Objective response rate

Response was evaluated using RECIST 1.1 criteria or mRECIST criteria. The mRECIST criteria were developed for HCC due to limitations of conventional RECIST guidelines which measure tumour size as an indicator of response.[40] However, the mRECIST criteria which consider target and non-target lesion response as well as liver response, and occurrence of new lesions may also have limitations and 'response' as indicated by mRESIST criteria may not correlate with with overall survival.[11]

The EAG considers that due to the difference in definitions of 'complete' and 'partial' response according to the two criteria,[40] ORR rates calculated using the two different criteria are not comparable. Specifically, ORR rates calculated using mRECIST criteria are generally higher than those calculated using RECIST 1.1. This is particularly evident from the results of the TARGET study,[34] where both criteria were used.

Restricting to ORR rates calculated using the mRECIST criteria only; ORR rates ranged from 53% to 84% for QuiremSpheres and from 54.7% to 69.2% for comparators. It should also be noted when making naïve comparisons that ORR rates are calculated at different time points and based on numbers of evaluable patients, which varied across the studies.

4.3.4 Health-related quality of life (HRQoL)

CS, Table 13 reports HRQoL results from the HEPAR Primary study[11] (median and IQR of EORTC QLQ C30 Global Health Status score) and from comparator studies SARAH[21] (mean and standard deviation EORTC QLQ C30 Global Health Status score) and SIRveNIB [22](mean and 95% CI of EQ 5D score). Additional results relating to EORTC QLQ C30 functional and symptom scales from the HEPAR Primary study[11] are provided in CS, Figure 5. The EAG considers that the available HRQoL data is too limited to draw meaningful comparisons between QuiremSpheres and comparators.

4.4 Adverse events

Adverse events (AEs) for reported in the HEPAR Primary[11] and RETOUCH[12] studies of QuiremSpheres are presented in Section B.3.10 of the CS (Table 14 and Table 15).

In the HEPAR Primary study, the most commonly observed grade 1/2 AEs were fatigue (54% of patients), abdominal pain (19%) and ascites (29%). Of the 19 serious AEs that occurred, 4 events (in 3 patients) which were deemed to be related or possibly related to treatment: 2 patients experienced spontaneous bacterial peritonitis (of which one case was fatal), and one patient experienced radiation-induced cholecystitis and cholangitis. In RETOUCH, grade 1/2 fever (observed in 20% of patients) and grade 1/2 fatigue (in 27% of the patients) were the most commonly observed AEs.

A comparison of AEs reported in the HEPAR Primary[11] and RETOUCH[12] studies to AEs reported in the SARAH[21] and SIRveNIB[22] RCTs of SIR-Spheres and the DOSISPHERE RCT[38] personalised versus standard dosimetry with TheraSphere are presented in CS, Table 16. The EAG considers that the types and frequency of AEs reported within the interventional studies of QuiremSpheres are in line with those reported in the interventional studies of SIR-Spheres and TheraSphere.

The EAG acknowledges that recording of AEs differs in observational and retrospective designed studies to the prospective recording within interventional studies and that rates of AEs reported across differing study designs may not be directly comparable. Nonetheless, observational studies such as registry studies often provide extended follow-up of patients compared to interventional studies to monitor for delayed or longer-term AEs. The EAG summarises the AEs reported in the observational and retrospective studies of QuiremSpheres and comparators.

Within the retrospective RECORD study of QuiremSpheres[14], 5 (3.4%) patients experienced at least one AE of special interest, including gastric ulceration in 3 patients (2.1%). Three of the five fatal AEs were considered related to device or procedure: one case of cholecystitis (related to procedure and device), one case of renal failure (related to the procedure), and one case of radioembolization induced liver disease (REILD) (related to the procedure and potentially related to the device).

Limited AE data were reported in the Jena Clinical Experience study[13] of QuiremSpheres; significant deterioration of liver function in two patients which may have been related to the procedure, and three cases of periprocedural abdominal pain.

A retrospective study of SIR-Spheres[35] reported gastrointestinal disorders and constitution symptoms at a similar rate to the interventional studies of SIRT, as well as one case of radiation pneumonitis. The retrospective TARGET study of TheraSphere also reported Grade 3 and 4 gastrointestinal and liver disorders, and constitutional symptoms at a similar rate to the interventional studies of SIRT. One retrospective study of SIRT (SIR-Spheres or TheraSphere)[31] reported treatment related AEs including gastrointestinal disorders and liver disorders as well as two cases of radiation pneumonitis and six cases of REILD. Another retrospective study of SIRT[30] reported limited adverse data for the entire study cohort which also included patients with liver metastases and cholangiocarcinoma.

Retrospective registry studies RESiN[36] and CIRT[37] of SIR-Spheres, reported Grade 3 and 4 liver and gastrointestinal disorders, constitution symptoms and AEs attributed to procedure at a similar rate to the interventional studies of SIRT. Three cases of REILD were reported in the CIRT registry study.[37]

Considering all of the relevant evidence, the EAG agrees with the company conclusion that the adverse event profile of QuiremSpheres when used to treat HCC is very similar to the adverse event profiles of SIR-Spheres and TheraSphere for treating HCC.

4.5 Summary

The EAG considers that there is no evidence of any important differences in terms of OS, PFS, ORR or adverse events between QuiremSpheres and SIR-Spheres or TheraSphere. However, uncertainty in the comparisons remains due to:

- Differences in study designs and distributions of patient baseline characteristics across the studies of QuiremSpheres, SIR-Spheres and TheraSphere.
- Limitations associated with observational, retrospective, and non-comparative evidence, as well as small sample sizes and losses to follow-up within some studies.
- The generalisability of the results of the QuiremSpheres and comparator studies all of which include patients who would not be eligible to receive SIRT treatment in NHS clinical practice.
- HRQoL data available is too limited to draw meaningful comparisons.

Although no robust, high quality, comparative evidence is available for QuiremSpheres, nor to inform direct or indirect treatment comparisons between QuiremSpheres, SIR-Spheres, and TheraSphere, the EAG believes that these interventions are likely to be broadly similar in terms of overall health outcomes and that the case for a cost comparison has been met.

5 SUMMARY OF THE EAG'S CRITIQUE OF COST COMPARISON EVIDENCE SUBMITTED

The EAG's critique of the economic evidence submitted by the company assumes that the clinical evidence provided is sufficient to support a case for the similarity in terms of overall health outcomes of QuiremSpheres compared to SIR-Spheres and TheraSphere (see Section 4).

The EAG considers a comparison of the costs of QuiremSpheres with SIR-Spheres and TheraSphere within the scope of NICE's part-review of TA688. The following critique focusses on addressing the question of whether QuiremSpheres is likely to be cost-saving or -neutral relative to SIR-Spheres and TheraSphere, although, it should be noted that these options may not represent the current standard of care in the population relevant to the decision population (see Section 2.3.1 and Section 3.1).

The evidence presented by the company sought to address the committee's concerns which led to QuiremSpheres not being recommended for routine use in TA688, namely, that QuiremSpheres lacked clinical evidence and was associated with higher costs than the other two SIRT technologies. The additional costs of QuiremSpheres were driven primarily by the use of the proprietary QuiremScout work-up, which does not form part of the QuiremSpheres procedure for the purposes of this cost comparison. With the omission of QuiremScout, the company argue that all remaining resource use remains equivalent to approved SIRT technologies. The CS therefore largely comprises a comparison with the committee's preferred assumptions for SIR-Spheres and TheraSphere in TA688.

5.1 Summary of costs and assumptions

The company present a cost comparison analysis which assumes equivalence of QuiremSpheres in terms of costs and resource use relative to the comparator technologies. Under the assumption that QuiremSpheres is a clinically equivalent 'technical variant' of the ^{90}Y SIRTs, the company argue that there are no differences in resource use across the three technologies, and thus only the relative acquisition costs are relevant to the cost comparison.

The company present resource assumptions agreed upon in TA688 in the CS (Table 18, pp61-62). The company assume that resource use items such as proportion of work-ups leading to SIRT, mean number of work-ups required, and mean number of SIRT procedures, are equivalent to the modelled values for SIR-Spheres and TheraSphere in the TA688 AG model. The company note that the only cost differences in the assumptions agreed upon in TA688 were the price of the technologies.

The company did not perform a systematic literature review to identify relevant cost-effectiveness evidence against SIR-Spheres and TheraSphere, but the company describe how, to their knowledge, no economic studies have been published comparing QuiremSpheres to comparators (response to

clarification question B1). The EAG have also identified no such studies following a limited online search for cost-effectiveness studies of the named QuiremSpheres technology, appearing to confirm that there have been no more relevant analyses published since TA688.

5.2 EAG critique of cost comparison analysis

The EAG critiques the key assumptions of the company analysis described above related to verifying the assumed equivalence of QuiremSpheres with comparators according to the following parameters:

- Acquisition costs
- Healthcare resource use
- Treatment costs
- Adverse event costs

Given that comparator acquisition costs inclusive of Patient Access Scheme (PAS) discount are unknown to company, and the PAS applied to QuiremSpheres may be subject to change, we consider the appropriateness of the company's analysis which is based solely on acquisition costs. To allow us to consider only the relative acquisition costs of each technology in the cost comparison (in line with the company's analysis), the EAG considers the plausibility of equivalence between the technologies in terms of each of these key aspects of resource use (excluding acquisition costs) relative to the accepted values in TA688, making use of any available trial evidence made available following TA688.

5.2.1 Acquisition costs

The acquisition costs of the technologies as confirmed by the manufacturers are presented in Table 5.

Table 5 Acquisition prices of QuiremSpheres, SIR-Spheres, and TheraSphere

Technology	Price	Source
QuiremSpheres	[redacted]	Company submission
SIR-Spheres	£8,000	Sirtex
Therasphere	£20,000	Boston Scientific

The company have proposed a [redacted] The EAG notes that there are confidential pricing arrangements in place for both comparator technologies, which are not known to the company. Details of all confidential commercial arrangements for QuiremSpheres, SIR-Spheres, and TheraSphere are provided in the confidential appendix to this report. These prices were correct as of 9th February 2024. The acquisition costs discussed in the CS and the EAR include only the proposed pricing arrangements for QuiremSpheres.

The company state that the company's proprietary Q-suite dosimetry software will be provided free of charge by Terumo as part of the hospital start-up process (response to clarification question B4); they also state that the Q-suite software is not required for administration of QuiremSpheres, and that standard software packages can be used to calculate personalised QuiremSpheres dosing.

5.2.2 Healthcare resource use

The original AG model developed for TA688 relied on a number of key resource use parameters for SIRT. The company, as part of this appraisal, assume that QuiremSpheres is equivalent to comparators in terms of these key resource use parameters in line with the committee's preferred assumptions in TA688 (Table 18, pp61-62).

The assumption of equivalence of resource use parameters for QuiremSpheres with SIR-Spheres and TheraSphere was made in TA688 due to the lack of study data available for QuiremSpheres at that time. The EAG considers that any data collected in the intervening years should now be used to support the assumption of equivalent resource use. For example, if QuiremSpheres were more likely than the comparators to require repeat procedures to achieve full coverage of the liver, it may be inappropriate to consider only acquisition costs in the cost comparison without adjustment for the rate of repeat procedures. The company provided resource use data from the four QuiremSpheres studies submitted as evidence for this current appraisal in response to clarification question B2 (Table 6).

Table 6 Comparison of trial resource use values to MTA values

Resource use parameter	**TA688 value (SARAH [n=237*])**	**HEPAR Primary (n=41*)**	**Jena Clinical Experience (n=20*; HCC: n=14*)**	**RETOUCH (n=20*)**	**RECORD (n=157*; HCC: n=55*)**
Proportion of work-ups leading to SIRT	**81.4% (184/226)**	96.6% (31/32)	NR	75% (15/20)	97.7% (167/171) (entire population)
Mean number of work-ups per patient	**1.09**	NR	NR	1.13	1.25 (HCC population)
Mean number of SIRT procedures per patient	**1.28**	NR	1.5 (HCC population)	1.13	1.14 (entire population) 1.22 (HCC population)

*assigned to receive SIRT
Abbreviations: HCC: hepatocellular carcinoma; MTA: multiple technology appraisal; NR: Not reported; SIRT: selective interval radiation therapy.

The EAG consider the QuiremSpheres study data provided to be broadly similar to the accepted values in TA688. As might be expected due to the small sample sizes it is not possible to conclude equivalence with any certainty. However, on the basis of the information available, the EAG are satisfied that these parameters of healthcare resource use are unlikely to be significantly different across QuiremSpheres and the comparators.

5.2.3 Treatment costs

The company assumes that the costs incurred by QuiremSpheres are equivalent to the values applied in the AG model developed as part of TA688 for the two comparators, comprising work-up costs and procedure costs (CS, Table 18, pp. 61-62). The costs applied in the company's analysis are described in Table 7.

Table 7 Treatment costs

Treatment costs	Company value (TA688)	Source
Work-up costs	£860.32	Based on values elicited from the Christie NHS Foundation Trust using micro-costing approach
SIRT procedure costs	£2,790.00	NHS reference costs for 2017-18 for YR57Z - average cost of 'Percutaneous, Chemoembolisation, or Radioembolisation, of Lesion of Liver'
Total	**£3,650.32**	

The company's position in TA688 was that QuiremSpheres required the use of the QuiremScout work-up procedure. The list price of QuiremScout was £4,372, which drove the higher total costs of QuiremSpheres compared to all other treatment strategies and contributed to the negative committee decision. QuiremScout has not been proposed by the company as part of the present cost comparison, instead assuming that all patients use ^{99m}Tc-MAA work-up product.

Same-day vs multi-day procedure

In response to the scope for this appraisal,[41] Sirtex Medical describe how due to improvements to logistical set-up following the publication of TA688, the entire SIR-Spheres work-up and administration process now requires only a single hospital admission where patients are commonly discharged on the same day or a subsequent day. Sirtex also argue that QuiremSpheres would require either three separate hospital admissions (work-up, implantation, post-implantation imaging), or 1-2 lengthy admissions. As a result, QuiremSpheres may result in the health system incurring greater costs associated with the procedure compared with SIR-Spheres.

The company state in the CS (p. 59) that the complete work-up and SIRT procedure can be performed either in a single day or across multiple days. They describe how in HEPAR I and HEPAR II studies,[42, 43] a same-day procedure was used but described how additional costs may be incurred (related to additional hospital admissions) if the procedure were to be administered over multiple days. The company stated that they anticipated that a multi-day procedure would be used in line with current clinical practice in the NHS (response to clarification question B3).

Clinical advice to the EAG confirms that SIRT technologies used in current NHS practice are most likely to be administered according to a multi-day procedure as imaging and dosimetry and radio-pharmacy would take most of the day and would not necessarily be less resource-intensive than if a

patient were invited back another day for the SIRT procedure. The EAG consider it unclear which of the single- and multi-day procedure approaches are typically less resource intensive from an NHS perspective, and that it is likely that they incur similar costs on average. There may, however, be a patient preference for the full procedure to be done in a single day, particularly in cases where the treatment centre is a long distance from home. Conversely, as a single day procedure would necessarily begin very early and end very late, it is likely that hotel stays would be required and therefore there may be preference among some patients for multiple hospital visits, separated by several days, which would allow patients to return home in between procedures.

The EAG are satisfied that QuiremSpheres would likely be equivalent in terms of treatment costs compared to comparators.

5.2.4 Dose verification imaging

In the CS (p16), the company describe how an advantage of QuiremSpheres is that SPECT-CT and high-resolution MRI can be used for dose verification. The company state that this differs from PET-CT currently used in clinical practice for ^{90}Y SIRT. They argue that the use of SPECT-CT offers benefits in the form of more accurate and flexible use across clinical settings. As a result, the EAG considered whether the different imaging technologies may result in different costs for QuiremSpheres against comparators. The latest NHS reference costs (21/22 – total Healthcare Resource Group (HRG)) are presented in Table 8 for each of the procedure codes provided by the company in response to clarification question B6.

Table 8 NHS reference costs for SPECT-CT, MRI and PET-CT

Procedure	Value – NHS 21/22 reference costs (total HRG)
RN05A: SPECT-CT of Two or Three Areas, 19 years and over	£659
RD01A: MRI Scan of One Area, without Contrast, 19 years and over	£197
RN02A: PET-CT of Two or Three Areas, 19 years and over	£703

Abbreviations: HRG: Healthcare Resource Group; MRI: Magnetic Resonance Imaging, PET-CT: Positron Emission Tomography with Computed Tomography; SPECT-CT: Single Photon Emission Computed Tomography with Computed Tomography

The costs associated with SPECT-CT appear slightly less than the equivalent cost for PET-CT. MRI costs appear significantly less than the other procedures. However, clinical advice to the EAG suggests that due to the demand for MRI at most treatment centres, it would typically be unlikely to be made available for the purpose of dose verification where SPECT-CT is available. Due to inconsistencies in the data described by the company in their clarification response, the EAG prefers the 'Total HRG' cost rather than the more granular data from nuclear medicine/diagnostic imaging. The EAG consider that any cost differences as a result of different dose verification imaging techniques are likely to be inconsequential.

5.2.5 Adverse event costs

The original AG model incorporated costs associated with management of adverse events (AEs) derived from previous TAs (2018 cost year) and weighted them according to AE incidence rates from the SIR-Spheres arm of the SARAH trial. This resulted in a total cost applied to each technology of £477.69 which is the value applied by the company in this analysis.

The equivalence of QuiremSpheres to comparators in terms of AEs is discussed further in Section 4.4**Error! Reference source not found.**. The EAG consider that it is reasonable to assume that adverse event costs are broadly equivalent between QuiremSpheres and the comparators.

5.3 Summary

Under the assumption that the clinical evidence presented is sufficient to demonstrate similarity in terms of overall health outcomes of QuiremSpheres compared to the other SIRT technologies, the EAG consider it plausible that the addition of QuiremSpheres in this position could be cost-neutral. As a result, the EAG consider it appropriate to compare only the acquisition costs of the technologies. In order for this to be the case inclusive of acquisition costs, currently available PAS discounts for TheraSphere and SIR-Spheres will have to be accounted for.

6 COMPANY AND EAG COST COMPARISON RESULTS

The following section details the results of the company's base case and the EAG's preferred base case (Table 9). All comparator acquisition costs are based on list prices, while the proposed PAS price for QuiremSpheres is inclusive of PAS. This analysis does not consider the use of QuiremScout in the workup procedure and assumes that all patients use ^{99m}Tc-MAA work-up product.

Given that the company assumed that QuiremSpheres is equivalent in terms of healthcare resource use and adverse event costs, the only relevant costs for the purpose of the cost comparison are the acquisition costs of the SIRT technologies themselves. The results in Table 9 (exclusive of PAS discounts) indicate that at list price, TheraSphere is the most costly option. The analysis inclusive of PAS prices is presented in the confidential appendix to this report.

Table 9 Company base case results (adapted from CS, Table 19)

Technologies	Acquisition cost (£)
QuiremSpheres*	[redacted]
TheraSphere	£20,000
SIR-Spheres	£8,000

*performed with ^{99m}Tc-MAA work-up (i.e., excl. QuiremScout)

6.1 EAG-preferred base case

The EAG accepts the company's assumptions included in their base case analysis; namely the equivalence of QuiremSpheres in terms of costs except acquisition costs.

7 EQUALITIES AND INNOVATION

The company does not present any equality issues (CS section B.1.4).

Clinical advice to the EAG is that SIRT can only be performed at specialist treatment centres which have clinical expertise combined with departments of nuclear medicine and interventional radiology. It is therefore likely that patients would only receive QuiremSpheres or ^{90}Y SIRTs in larger hospitals, which may impede access for those living further away from these specialist centres.

EAG critique of the "Technical advantages of QuiremSpheres supporting the unmet need" (CS, pp. 16-17) is provided in Section 2.3.2.1.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Conclusions

The EAG considers that the case for a cost comparison approach for SIRT with QuiremSpheres for treating unresectable advanced HCC has been met.

Although there are technical differences between the SIRTs, for example in the radioactive isotope, the size and number of spheres, and the workup and imaging requirements, there is no evidence to suggest that these differences would have an impact on clinical outcomes. This view is supported by two clinical advisors consulted by the EAG, and the EAG considers that it is reasonable to consider QuiremSpheres as a technical variant to SIR-Spheres and TheraSphere.

The evidence on the effectiveness of QuiremSpheres and comparators submitted in the CS is of low quality, high heterogeneity, and is limited in terms of its application to NHS clinical practice. The evidence for QuiremSpheres comes from four relatively small single-arm studies. None of the QuiremSpheres or comparator studies are based within UK healthcare settings, and all of the studies include patients who would not be eligible to receive QuiremSpheres (or other SIRTs) within the NHS currently or under the company's proposed position of QuiremSpheres.

Despite the lack of robust, high-quality evidence, there are no clear differences between the OS, PFS and ORR estimates between QuiremSpheres and comparators, nor any evidence of differences between the safety profiles of QuiremSpheres, SIR-Spheres and TheraSphere.

The EAG considers that there is insufficient robust clinical effectiveness evidence available to inform an updated cost-utility analysis of QuiremSpheres compared to SIR-Spheres or TheraSphere, or to atezolizumab with bevacizumab, the current standard of care in NHS practice for treating unresectable or advanced HCC.

8.2 Areas of uncertainty

Table 10 summarises areas of uncertainty, which could be addressed in future research and through monitoring of the use of SIRTs in UK clinical practice.

Table 10 Outstanding areas of uncertainty

No.	Issue	Description	Report section
1	Technical equivalence	It is possible that technical differences between the SIRTs impact on clinical outcomes, for example through differences in the dosimetry, imaging, or embolic effect of microspheres. The potential advantages or disadvantages of the QuiremScout workup were not considered as part of this appraisal.	2.3.2
2	Implementation in clinical practice	It is unclear how differences between SIRTs such as the workup, dosimetry, and length / number of hospital visits would affect preferences for one SIRT over another, and any associated costs to the NHS.	2.3.2, 5.2
3	Relevant population	To align with related NICE guidance, and to reflect the current use of SIRT treatment within NHS clinical practice, the EAG considers that the relevant population for this appraisal should be adult patients who are not eligible for CTT or surgical resection and have BCLC B or BCLC C HCC with Child-Pugh grade A liver impairment	3.1
4	Literature review and study selection	Search of the literature appears to be incomplete, and the process of identifying studies lacks transparency; selection criteria were not specific. It is possible relevant recent publications were not included.	4.1
3	Evidence does not match population in scope	No evidence from UK based treatment settings. Patient cohorts of QuiremSpheres studies and comparator studies vary with regard to their fit with the population relevant to the decision problem.	4.2.1
4	Lack of robust evidence	Four relatively small single-arm studies of QuiremSpheres; naïve comparisons made to non-comparative studies of SIR-Spheres and TheraSphere. Heterogeneity of study and patient characteristics, and of outcomes definitions such as response rates and adverse events. Insufficient HRQoL data to allow a meaningful comparison	4.3
5	Resource implications of same-day vs multi-day procedure	The work-up and administration process for SIR-Spheres is plausibly completed by SIRT centres in a single day, whilst this is very unlikely to be possible with QuiremSpheres. The resource implications from an NHS perspective of each approach are uncertain, as is the extent to which a same-day approach has been adopted across the NHS.	5.2.3

Abbreviations: BCLC: Barcelona Center Liver Cancer; CTT: conventional transarterial therapy
HCC: hepatocellular carcinoma; HRQoL: health-related quality of life; SIRT: selective internal radiation therapy

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43. Prince JF, van den Bosch M, Nijsen JFW, Smits MLJ, van den Hoven AF, Nikolakopoulos S, et al. Efficacy of Radioembolization with (166)Ho-Microspheres in Salvage Patients with Liver Metastases: A Phase 2 Study. *J Nucl Med* 2018;**59**:582-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28916623

APPENDICES

APPENDIX 1. SYSTEMATIC LITERATURE SEARCHES

Table 11 EAG appraisal of company searches

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	NO	Search strategies missing from Appendix D of the company submission and not supplied in the company response to the clarification questions A2 and A3.
Were appropriate sources searched?	NO	Search of MEDLINE only.
Was the timespan of the searches appropriate?	YES	Update of a previous review, covering the period 25th January 2019 to 1st December 2023.
Were appropriate parts of the PICOS included in the search strategies?	UNCLEAR	The search strategy run by the company in MEDLINE was not provided, so could not be checked by the EAG.
Were appropriate search terms used?	UNCLEAR	The search strategy run by the company in MEDLINE was not provided, so could not be checked by the EAG.
Were any search restrictions applied appropriate?	NO	Searches were limited to English language articles, therefore language bias is possible. Searches were limited to those studies with full text available.
Were any search filters used validated and referenced?	UNCLEAR	The search strategy run by the company in MEDLINE was not provided, so could not be checked by the EAG.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 2. STUDIES INCLUDED IN EAG NAÏVE COMPARISON

Table 12 Patient baseline demographic characteristics in QuiremSpheres and comparator studies included in the EAG naïve comparison

Trial	N	SIRT Intervention	Age, years	Male: n (%)	Cirrhosis present: n (%)	ECOG PS: n (%)	PVT / PVI present: n (%)
Reinders 2022 (HEPAR Primary)[11]	31	QuiremSpheres	Median: 73 Range: 44-85	28 (90)	20 (65)	0: 18 (58) 1: 13 (42)	PVT: 6 (19)
RECORD[14]	HCC: 55[a] Total: 146	QuiremSpheres	Median: 66.2 SD: 10.9	99 (67.8)	NR	0: 59 (41) 1: 46 (32); ≥2: 8 (5.5) Unknown: 33 (22.6)	PVT: 6 (10.9)
Drescher 2023 (Jena Clinical Experience)[13]	14	QuiremSpheres	Median: 73 Range: 58-82	13 (93)	12 (86)	NR	NR
Vilgrain 2017 (SARAH)[21]	174[b]	SIR-Spheres	Mean: 66.3 SD: 9.4	158 (90.8)	154 (88.5)	0: 1.09 1:65 (37.4)	PVI: 100 (57.5)
Chow 2018 (SIRveNIB)[22]	130[b]	SIR-Spheres	Mean: 60.9 SD: 11.5	107 (82.3)	NR	0: 106 (81.5) 1: 24 (18.5)	PVT: 30 (23.1)
Frantz 2021 (RESiN)[36]	448[c]	SIR-Spheres	Median: 66 IQR: 61-72	349 (78)	NR	0: 205 (51) 1: 155 (39); ≥2: 41 (10)	PVI: 60 (15)
Van Thai 2021[35]	97	SIR-Spheres	Mean: 64 ± 12.3	90 (92.8)	94 (96.9)	0: 14 (14.4) 1: 71 (73.2); 2: 12 (12.4)	61 (62.9)
Helmberger 2021 (CIRT)[37]	442	SIR-Spheres	NR for HCC	NR for HCC	300 (71.1)	0: 252 (59.7) 1: 136 (32.2); ≥2: 34 (8.1)	PVT: 140 (33.2)
Casáns-Tormo 2023[30]	53	SIR-Spheres (94%) TheraSphere (6%)	Mean: 68 SD: 10	41 (77.4)	NR	NR	NR
Hur 2023[31]	124[d]	SIR-Spheres (% NR) TheraSphere (% NR)	Median: 59.4 IQR: 51.8-68	103 (83.1)	24 (83)	0: 68 (54.8) 1: 54 (43.6); 2: 2 (1.6)	124 (100)
Garin 2020 (DOSISPHERE-01)[38]	28[e]	TheraSphere[d]	Mean: 62.5 SD: 13.1	26 (93)	24 (86)	0: 13 (46) 1: 15 (54)	PVI: 21 (75)
Lam 2022 (TARGET)[34]	209	TheraSphere	Median: 66 Range: 27-87	166 (79.4)	185 (88.5)	0: 135 (64.6) 1: 67 (32.1); ≥2: 7 (3.4)	PVT: 69 (33.0)

[a] Characteristics are presented for the entire study cohort of 146 patients; presence of PVT only presented for 55 patients with HCC, [b] per protocol/treated population, [c] ECOG PS percentages were calculated using a denominator of 401, and a denominator of 397 for PVI, [d] Unmatched cohort [e] characteristics presented for the modified ITT population of the standard dosimetry group
Abbreviations: EAG: evidence assessment group; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HCC: hepatocellular carcinoma; IQR: interquartile range; ITT: intention to treat, NR: not reported; PVI: portal vein invasion; PVT: portal vein thrombosis; SD: standard deviation; SIRT: selective internal radiation therapy

Table 13 Patient baseline disease characteristics in QuiremSpheres and comparator studies included in the EAG naïve comparison

Trial	N	SIRT Intervention	Child-Pugh Classification: n (%)	BCLC stage: n (%)	Prior Treatments: n (%)	Tumour involvement: n (%)	Number of Tumours: n (%)
Reinders 2022 (HEPAR Primary)[11]	31	QuiremSpheres	A (5-6): 28 (90) B7: 3 (10) C: 0 (excluded)	0: 0 (0) A: 0 (0) B: 22 (71) C: 9 (29)	None: 26 (84) Resection: 4 (13) Ablation: 4 (13) TACE: 1 (3)	Unilobar: 14 (45) Bilobar: 17 (55)	1: 4 (13) 2-3: 4 (13) >3: 23 (74)
RECORD[14]	55	QuiremSpheres	A (5-6): 36 (65.5) B7: 17 (30.9) C: 2 (3.6)	0: 2 (3.6) A: 3 (5.5) B: 32 (58.2) C: 11 (20) Unknown: 7 (12.7)	NR	Unilobar: 13 (23.6) Bilobar: 35 (63.6)	NR
Drescher 2023 (Jena Clinical Experience)[13]	14	QuiremSpheres	A (5-6): 13 (93) B7: 1 (7)	A: 2 (14) B: 9[a] (64) C: 3[a] (21)	None: 8 (57) Resection: 4 (29) TACE: 1 (7) Percutaneous Radiation: 1 (7)	NR	NR
Vilgrain 2017 (SARAH)[21]	174[b]	SIR-Spheres	A (5 - 6): 153 (87.9) B7: 20 (11.5) C: 0 (excluded) Unknown: 1 (0.6)	A: 7 (4) B: 53 (30.5) C: 114 (65.5)[c]	NR	Unilobar: 136 (78.2) Bilobar: 38 (21.8)	1: 81 (46.6) ≥2: 93 (53.4)
Chow 2018 (SIRveNIB)[22]	130[d]	SIR-Spheres	A: 117 (90.0) B: 10 (7.7)	A: 0 (excluded) B: 79 (60.8) C: 50 (38.5)	NR	NR	NR
Frantz 2021 (RESiN)[36]	448[e]	SIR-Spheres	A: 70% B: 29% C: <1%	A: 19% B: 59% C: 15% D: 7%	Systemic: 16% TACE: 26% Ablation: 13% Resection: 8% Radiotherapy: 2%	Unilobar: 58% Bilobar: 42%	1: 36% 2-5: 40% 6-10: 3% >10: 21%
Van Thai 2021[35]	97	SIR-Spheres	A: 91 (93.8) B: 6 (6.2) C: 0 (excluded)	A: 0 B: 38 (39.2) C: 59 (60.8) D: 0	None: 78 (80.4) Resection: 5 (5.2) RFA: 3 (3.1) TACE: 9 (9.3) PEI: 2 (2.1)	Unilobar: 81 (83.5) Bilobar: 16 (16.5)	NR
Helmberger 2021 (CIRT)[37]	442	SIR-Spheres	(N= 162) A: 131 (80.9) B: 30 (18.5) C: 1 (0.6)	NR	Systemic: 45 (10) Surgical: 72 (17.1) Ablation: 62 (14.7) TACE: 97 (23.0) Vascular: 15 (3.6) Abdominal radiotherapy: 7 (1.7)	Unilobar: 263 (62.3) Bilobar: 159 (37.7)	1: 110 (26.1) 2-5: 154 (36.5) >10: 55 (13) Uncountable: 80 (19)

Casáns-Tormo 2023[30]	53	SIR-Spheres (94%) TheraSphere (6%)	All Child-Pugh A5 or A6.	B or C: 49 (92.4)	Embolization, TACE or RFA: 27 (51)	Unilobar: 23 (43.3) Bilobar: 30 (56.6)	NR
Hur 2023[31]	124[f]	SIR-Spheres (NR) TheraSphere (NR)	A (5-6): 105 (97.6) B7: 3 (2.4)	NR	NR	Unilobar: 88 (54.0) Bilobar: 36 (29.0)	1: 69 (55.7) 2: 21 (16.9) ≥ 3: 34 (27.4)
Garin 2020 (DOSISPHERE-01)[38]	28[g]	TheraSphere[g]	A5: 22 (79) A6 or B7: 6 (21)	A: 0 (0) B: 3 (10) C: 26 (90)	None: 25 (89) Previous SIRT: 3 (11)	Unilobar: 12 (43) Bilobar: 16 (57)	NR
Lam 2022 (TARGET)[34]	209[d]	TheraSphere	A (5-6): 187 (89.5) B7: 22 (10.5)	A: 27 (12.9) B: 68 (32.5) C: 114 (54.5)	Sorafenib: 21 (10)	Unilobar: 148 (70.8) Bilobar: 61 (29.2)	1: 145 (69.4) 2: 45 (21.5) 3: 14 (6.7) 4-10: 5 (2.4)

[a] Conservative assessment as 5 patients are characterised tumour Stage II that can also imply vascular invasion which would make patients BCLC C (CS, Table 9), [b] Per protocol population. [c] 36 patients in the SIRT group had both BCLC C and TACE failure, [d] Treated population, [e] percentages only reported as different denominators are used for each characteristic, [f] Unmatched cohort. [g] characteristics are presented for the modified ITT population of the standard dosimetry group

Abbreviations: EAG: evidence assessment group; ITT: intention to treat; NR: not reported; PEI: Percutaneous ethanol injection therapy, RFA: radiofrequency ablation, SIRT: selective internal radiation therapy, TACE: transarterial chemoembolization,

Table 14 Clinical effectiveness results in studies in QuiremSpheres and comparator studies included in the EAG naïve comparison

Trial	N	SIRT interventions	Follow-up (months)	OS (Median, months)	PFS (Median, months)	Response: n (%) ORR: % and (95% CI[a])
Reinders 2022 (HEPAR Primary) [11]	31	QuiremSpheres	≥6 months: 21 (68%) ≥12 months: 18 (58%) ≥24 months: 11 (35%)	14.9 (95% CI: 10.4-24.9)	NR	mRECIST at 3 months (n=26): CR: 5 (19.2); PR: 9 (34.6) ORR: 53.8 (33.4 -76.6) mRECIST at 6 months (n=19): CR: 7 (36.8); PR: 9 (47.4) ORR 84.2 (60.4 - 96.6)
RECORD [14]	55	QuiremSpheres	Median 7.1 (95% CI 7.4 to 9.3)	14.7 (95% CI: 13.8 – NE)	9.1 (95% CI: 7.1- 14.0)	Mixed mRECIST and RECIST 1.1 at >3 months (n=37): CR+PR=26 ORR: 70.3 (53.0 - 84.1)[b]
Drescher 2023 (Jena Clinical Experience)[13]	14	QuiremSpheres	Median 17.7 (range 0.8 – 58)	22.1 (95% CI: 13.6 – 29.8)	7.3 (95% CI: 5.5-15.7)	mRECIST at 3 months (n=12): CR: 1 (8); PR: 7 (58) ORR: 66.7 (34.9-90.1)
Vilgrain 2017 (SARAH)[21]	174[c]	SIR-Spheres	Median: 27.9 IQR: 21.9-33.6	9.9 (95% CI: 8.0 – 10.7)	4.1 (95% CI: 3.8 – 4.6)	Best response, RECIST 1.1 (n=164): CR: 4 (2.4); PR: 28 (17.1) ORR: 19.5 (13.7 – 26.4)
Chow 2018 (SIRveNIB)[22]	130[d]	SIR-Spheres	≥6 months: 65 (50%) ≥12 months: 22 (17%) ≥24 months: 6 (5%)	11.3 (95% CI: 9.2 - 13.6)	6.3 (95% CI: 5.9-8.3)	Best response, RECIST 1.1 (n=103): CR: 0 (0); PR: 30 (29.1) ORR: 29.1 (20.6 – 38.9)
Frantz 2021 (RESiN)[36]	Child-Pugh A: 151[e]	SIR-Spheres	Up to 48 months	BCLC B (n=132): 21.5 (95% CI: 16.5-25.2) BCLC C (n=19): 21.8 (6.2-N/R)	BCLC B (n=132): 10.6 (95% CI: 9.0 – 15.4) BCLC C (n=19): N/R (3.5-N/R)	NR
Van Thai 2021[35]	97	SIR-Spheres	Median 16.4 (range: 1.8 -62)	Median: 23.9 (95% CI NR)	NR	mRECIST at 3 months (n=87): CR: 10 (11.5); PR: 42 (48.3) ORR: 59.8 (48.7-70.1) mRECIST at 6 months (n=64): CR: 12 (18.8); PR: 23 (35.9) ORR: 54.7 (41.7 – 67.2)
Helmberger 2021 (CIRT)[37]	422	SIR-Spheres	26 (2.5%) with less than 2 years follow-up	16.5 (95% CI: 14.2 – 19.3)	NR	NR

Casáns-Tormo 2023[30]	53	SIR-Spheres (94%) TheraSphere (6%)	Follow-up period was at least 1 year	Mean: 17.7 SD: 12.8	Mean: 9.6[f] SD: 8.9	mRECIST after mean of 3.7 months: CR and PR: NR ORR: 69.2 (95% CI NR)
Hur 2023[31]	124[g]	SIR-Spheres (NR) TheraSphere (NR)	≥12 months: 70 (56%) ≥24 months: 42 (34%)	28.2 IQR: 7.6-91.1	5.3 IQR: 2.4 – 23.3	Best response, mRECIST (n=124): CR: 28 (22.6), PR: 48 (38.7) ORR: 61.3 (52.1 -69.9)
Garin 2020 (DOSISPHERE-01)[38]	29[h]	TheraSphere[h]	27.2 IQR: 33.9-18.7	10.7 (95% CI: 6.0- 16.8)	3.4 (95% CI: 2.9-8.5)	RECIST 1.1 at 3 months (n=28): Investigator Evaluated: CR: 3(11); PR: 7 (25) ORR: 36 (19-56) Centralised Evaluation: CR: 6 (21); PR: 6 (21) ORR: 43 (24-63)
Lam 2022 (TARGET)[34]	209	TheraSphere	Median 13.3 range: 0.6 - 98.0	20.3 (95% CI: 16.7 – 26.4)	NR	mRECIST, ≤ day 180 post SIRT (n=209): CR + PR: 129 (61.7) ORR 61.7 (55.0-68.0) RECIST 1.1, ≤ day 180 post SIRT (n=209): CR + PR: 72 ORR 34.4 (28.3-41.1)

[a] Binomial confidence interval, ORR and 95% CI extracted from study reports or calculated by the EAG based on number of evaluable patients [b] Not used in company in their naïve comparisons as the tumour response was evaluated using a mixture of mRECIST and RECIST 1.1, [c] Per protocol population, [d] Treated population, [e]The results presented here are the stratified results presented for the patients who had a Child-Pugh grade A, and either BCLC B (n=132, 14% treated aiming to downstage to transplant) or C (n=19), [f]PFS was defined as the time until tumour recurrence or disease progression. [g] Unmatched cohort. [h] results are presented for the modified ITT population of the standard dosimetry group

Abbreviations: CR: complete response; EAG: evidence review group, HCC: hepatocellular carcinoma, IQR: Interquartile range; ITT: intention to treat. mRECIST: modified Response Evaluation Criteria in Solid Tumours for HCC, NR: not reported, N/R: not reached, ORR: objective response rate; OS: overall survival; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours, SD: standard deviation, SIRT: selective internal radiation therapy

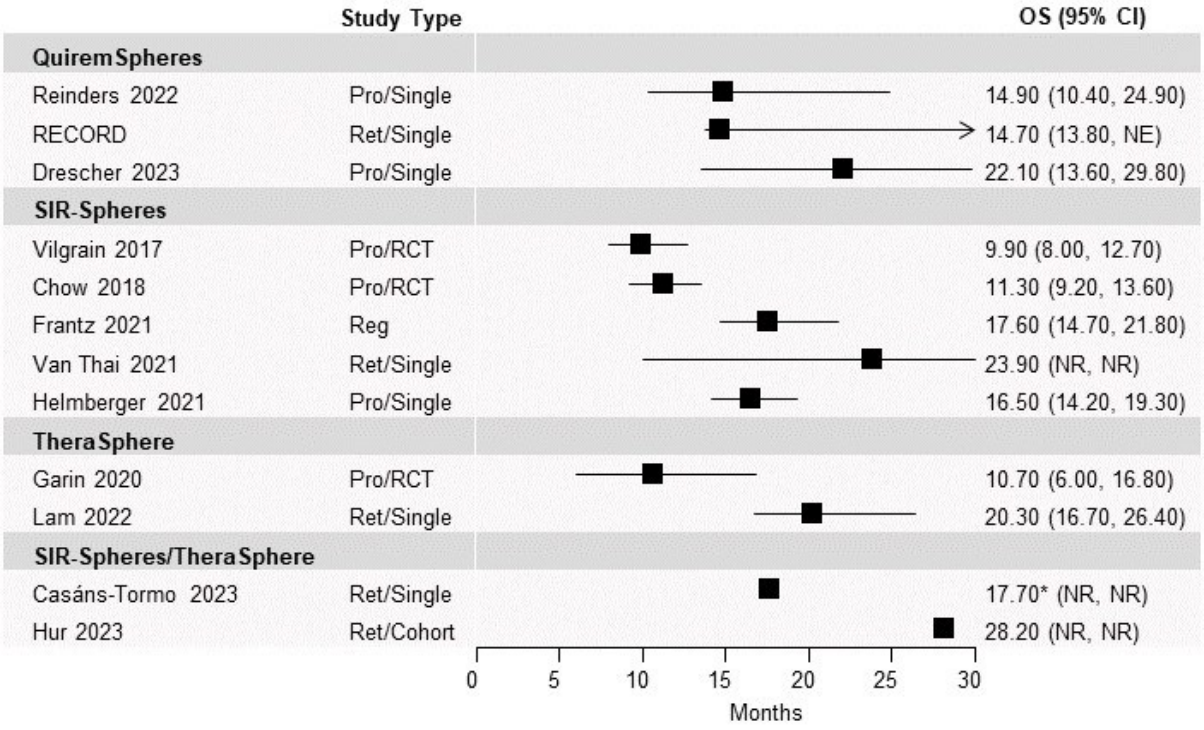

Figure 1 EAG naïve comparison of median OS in QuiremSpheres and comparator studies

Studies report median OS with the exception of Casáns-Tormo 2023[30] which reported mean OS (indicated with an asterisk*)
Abbreviations: CI: confidence interval; OS: overall survival; NE: not evaluable, NR: not reported; Pro: prospective; RCT: randomised controlled trial; Reg: registry data Ret: retrospective; Single: single-arm.

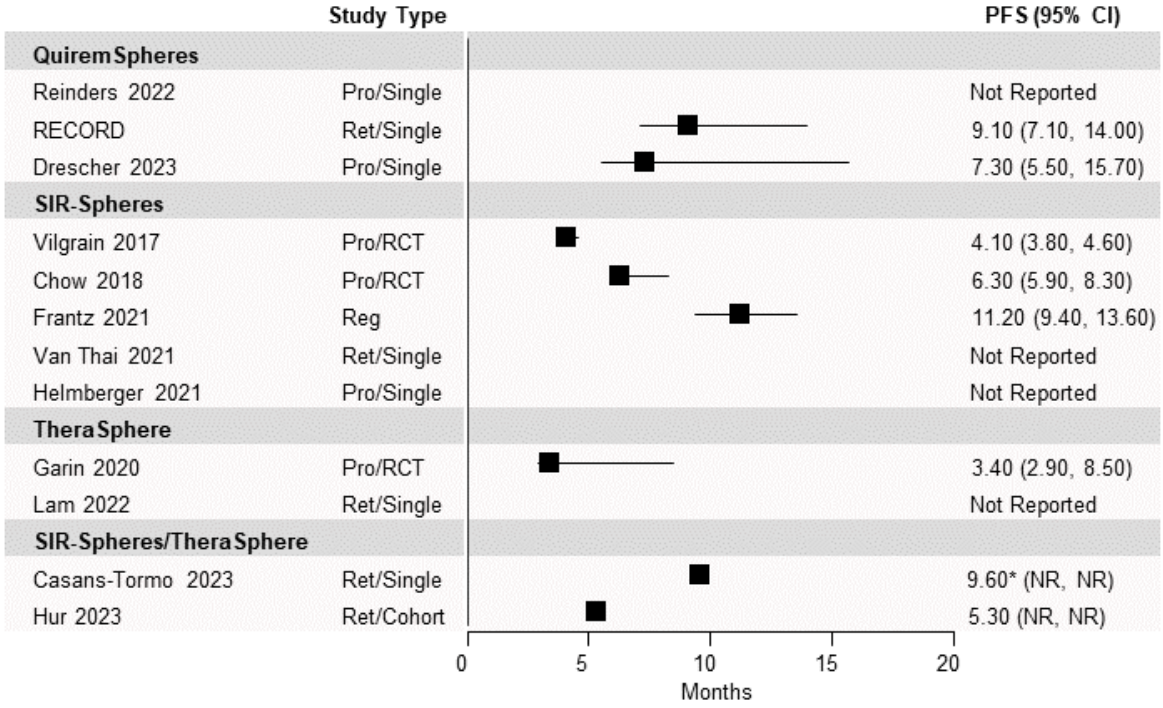

Figure 2 EAG naïve comparison of median PFS in QuiremSpheres and comparator studies

Studies report median OS with the exception of Casáns-Tormo 2023[30] which reported mean OS (indicated with an asterisk*)
Abbreviations: CI: confidence interval; NR: not reported; PFS: progression-free survival; Pro: prospective; RCT: randomised controlled trial; Reg: registry data. Ret: retrospective; Single: single-arm.

Cost Comparison Appraisal

Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm** on **Friday 22 March 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Inaccuracy in the number of treated patients in RETOUCH

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Inaccuracy in the number of treated patients in RETOUCH *1.2 Summary of the clinical evidence (page 7) RETOUCH, **14** treated patients*	RETOUCH 15 patients treated	In RETOUCH 15 patients have been treated, but only 14 patients had a 3-month evaluation. It will not have any impact as RETOUCH was not considered in the EAG report.	This has been changed.

Issue 2 Inaccuracy in one paragraph of the EAG report regarding amount of comparator studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Inaccuracy in the number of comparator studies used in the company submission. *2.1 Introduction (4th paragraph) at page 10.*	Six comparator studies	In our CS, six comparator studies have been used (in accordance with other paragraphs in EAG report stating six comparator studies have been used in the CS)	This has been changed.

Seven *comparator studies (two of which were included in TA688).*		No impact as the evidence of the six comparator studies was considered and EAG added additional 3 studies.	

Issue 3 No evidence of QuiremScout visualization under MRI

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
In Table 2, it is stated that work-up imaging technology SPECT/CT or MRI (if QuiremScout is used) could be used. (p.14) Currently no evidence is available that MRI is capable of visualizing QuiremScout	Work-up imaging technology: SPECT/CT	Currently there is no evidence available that MRI is capable of visualizing QuiremScout. It will have no impact as QuiremScout was not part of the cost-comparison assessment.	This has been changed.

Issue 4 Inaccuracy in the range of ORR for comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
In paragraph 3 from 4.3.3 Objective response rate It is stated that: ORR rates ranged from 53% to 84% for QuiremSpheres and from **59.5%** to 69.2% for comparators. We believe the value of 59.5% is inaccurate and should be 54.7% as per table 14 (Van Thai et al).	ORR rates ranged from 53% to 84% for QuiremSpheres and from **54.7%** to 69.2% for comparators.	In line with the results stated in Table 14. Will have no impact on the assessment as the numerical change is minor and makes the overlap between the ORR between QuiremSpheres and Y90 SIRT even higher.	This has been changed.

Issue 5 Inaccuracy in median PFS value used of Drescher publication

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
In table 14 – Clinical effectiveness results (page 47) Drescher 2023 (Jena Clinical Experience) is stated. In the column of PFS the value **8.8 months (95% CI: 6.6-15.2)** is mentioned. This is however the hepatic (untreated liver) PFS. We have used in our company submission the overall PFS of 7.3 months. This should also be adapted in Figure 2	Drescher 2023 (Jena Clinical Experience): PFS 7.3 months (95% CI: 5.5-15.7)	In the publication of Drescher 2023 median whole body PFS is 7.3 months (95% CI: 5.5-15.7) Will have no impact as the value remains within the range on naïve visual comparison between QuiremSpheres and Y90 SIRT.	Table 14 and Figure 2 updated.

Issue 6 Inaccuracy in number of patients in Garin 2020

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
In table 14 – Clinical effectiveness results (page 47) Garin 2020 (DOSISPHERE-01) it is stated that **28**[h] patients were included based on the modified ITT population of the standard dosimetry group We believe that for the results presented in the table the ITT population was used.	Garin 2020 (DOSISPHERE-01) it is stated that **29** patients were included based on the ITT population of the standard dosimetry group	We believe the data used in the table for the publication of Garin 2020 consist of the ITT population instead of modified ITT. Will have no impact as it does not change the clinical effectiveness results used for the cost-comparison evaluation.	This has been changed.