SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name:
Amplitude-Modulated Radiofrequency Electromagnetic Fields (AM RF EMF) device

Device Trade Name: TheraBionic P1

Device Procode: QOM

Applicant's Name and Address:
Boris Pasche, MD, PhD
TheraBionic Inc.
4108 Ryan Way
Winston-Salem, NC 27106-3567

Date(s) of Panel Recommendation: N/A

Humanitarian Device Exemption (HDE) Number: H220001

Humanitarian Use Device (HUD) Designation Number: HUD # 20-1473

Date of HUD Designation: June 23, 2022

Date of Notice of Approval to Applicant: September 26, 2023

II. INDICATIONS FOR USE

The TheraBionic P1 medical device is indicated for the treatment of persons ≥18 years of age with advanced hepatocellular carcinoma (HCC) who fail first and second line therapy.

The indication for use statement is identical to that which was granted for the HUD designation.

III. CONTRAINDICATIONS

- The TheraBionic P1 may not be used by patients younger than 18 years as it has not yet been tested in such patients.
- The Therabionic P1 should not be described for patients receiving calcium channel blockers and any agent blocking L-type of T-type Voltage Gated Calcium Channels, e.g., amlodipine, nifedipine, ethosuximide, ascorbic acid (vitamin C), etc. unless their medical treatment is modified to exclude calcium channel blockers prior to treatment.

- The materials from which the spoon is made of are all designed for use in medical products and tested for biocompatibility. If intolerance or allergic reactions to the patient‘s spoon occur, the treatment should only be continued after consultation with the treating physician.
- If the oral mucosa is not intact, do not use the therapeutic device: for example, in case of mucositis, thrush, bleeding mucosal lesions, oral herpes (also known as aphthous stomatitis, mouth ulcers, canker sores or gingivostomatitis), herpangina, aphthae.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TheraBionic Instructions for Use and Operation Manual.

Warnings
All uses and modes of operation that are not included in the descriptions of the intended use and are not described in the regulation-compliant accompanying documentation or contradict this documentation must be considered to be improper.
In particular, the following is prohibited:

- The patient‘s spoon is only intended for use in the oral cavity.
- It is absolutely prohibited to tamper with the equipment.
- Modification of the medical device is prohibited.
- Opening the product casing is prohibited.
- Do no use the therapeutic device in the shower or in the bathtub, or whenever part of the body is immersed in water.

Precautions

- Pay attention to the warnings on the product and check the product and accessories for completeness and damage.
- Do not modify or alter any product or accessory.
- Do not use any damaged products or parts.
- The TheraBionic P1 and its components do not belong in children’s hands because improper use of the equipment, cables, patient spoon and plug-in power supply can lead to injuries caused by electric shock, strangulation and swallowing.
- Never leave packing material in proximity to children as this could result in cuts. Additionally, the packing material is a potential swallowing and inhaling hazard.
- During treatment the patient spoon is placed on the tongue, between the tongue and the palate, with the therapeutic device switched on and the mouth closed. Before each application, check that the patient spoon is not damaged and is connected to the therapeutic device as intended, to an ensure contact between the therapeutic device and the tongue.
- The patient spoon is intended to be used repeatedly by only one and always the same patient.
- A complete uninterrupted treatment session lasts 60 minutes. The treatment can be interrupted by any number of breaks. Any treatment session interruption should be no longer than 20 minutes. However, it is recommended not to interrupt any 60 minute treatment session.

V. DEVICE DESCRIPTION

The TheraBionic P1 System consists of a battery-driven radiofrequency (RF) electromagnetic field (EMF) generator that is coupled with an antenna (Patient Spoon) that is placed in the patient's mouth. The system includes a charging Docking Station with a power supply unit, and an activation card that allows a defined number of therapeutic sessions as prescribed by the physician. The system emits EMF at a carrier frequency of 21.12 MHz and amplitude modulated to tumor-specific frequencies. The device is intended for multiple uses by the same patient.

The generator of amplitude-modulated electromagnetic fields consists of a battery-driven radiofrequency (RF) electromagnetic field (EMF) generator connected to a 1.2 m long 50 Ohm coaxial cable with a medical grade 316 stainless steel spoon-shaped mouthpiece connected via an impedance transformer.

The RF source of the device corresponds to a linear amplifier operating at 27.12 MHz. The carrier frequency is amplitude-modulated with a modulation depth of 85%. The resolution of the modulation frequencies is $16MHz/2^{32}$ (3.725mHz in decimal). The output signal is in its entirety synthesized by a Field-Programmable Gate Array (FPGA).

An HDE activation card allows a defined number of therapeutic sessions, as prescribed by the physician. The docking station has a chip card reader for the activation card as well as a RS-232 interface for monitoring treatment for use by the physician's office. The power supply for the docking station is an external wall-cube type power supply.

The P1 device has one two-color LED lamp as an indicator, an LCD and two buttons. The functions are: Switch the device on and off, start and pause the treatment, initiate charging of activation time. It is charged by inductive wireless charging when placed on the Docking Station. The device shows a start/pause button which allows to start or interrupt the treatment.

Principles of Operation

Whole body administration of low-level radiofrequency electromagnetic fields, which are derived from the generation of an amplitude-modulation of a specific carrier frequency at specific frequencies ranging from 0.01 Hz to 150 kHz have shown efficacy in the treatment of certain types of cancer. The technology used by TheraBionic P1 is using low-level radiofrequency electromagnetic fields, derived from an amplitude modulation of the carrier frequency of 27.12 MHz (AM RF EMF). These electromagnetic fields have been shown to have probable efficacy in advanced hepatocellular carcinoma (HCC).

The patient holds the spoon-shaped antenna in his/her mouth during treatment, which is the only point of contact between the device and the oral mucosa. Treatment is administered three hours per day. Treatment is split in three separate one-hour sessions. Treatment starts

only after the spoon-shaped mouthpiece antenna is placed in contact with the anterior part of the tongue. If the mouthpiece loses contact with the tongue, treatment pauses and a beep sounds until proper repositioning of mouthpiece. Treatment resumes automatically once the spoon-shaped antenna is placed back on the patient's tongue. This also enables treatment compliance monitoring. Patient receives low levels of RF EMF that are minimally absorbed and distributed with the body acting as an antenna.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no commercially available devices for the systemic treatment of advanced HCC who have failed 1st and 2nd line systemic therapy. Radiofrequency ablation devices are used for the treatment of early-stage HCC. Also, radioactive beads are approved for the treatment of early and advanced HCC prior to failure to systemic therapy. However, these two modalities are not indicated in patients who have failed first and second-line systemic therapy.

VII. MARKETING HISTORY

The TheraBionic P1 received CE approval as a Class IIa device in July 2018. Four (4) devices were distributed to patients with advanced HCC in France (1), Switzerland (3).

The TheraBionic P1 has not been withdrawn from marketing for any reason relating to the safety and probable benefit of the device.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

- Mild Fatigue
- Mucositis

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

Animal Studies

The in vivo effects of amplitude-modulated radiofrequency electromagnetic fields are discussed in the Jimenez publication provided.(Jimenez, Wang et al. 2019)

Mice carrying human HCC xenografts were exposed to AM RF EMF using a small animal AM RF EMF exposure system replicating human dosimetry and exposure time. This exposure system was specifically designed and built to study the effects of TheraBionic amplitude-modulated radiofrequency electromagnetic fields in rodents (Capstick, Gong et al. 2016). Histological analysis of tumors was performed following exposure to AM RF EMF. The tumor-specific anti-proliferative effects of TheraBionic HCC frequencies were assessed using two separate types of human HCC xenografts. These experiments demonstrated that HCC-specific frequencies are significantly more effective at blocking the growth of two separate human HCC xenografts when compared with either randomly chosen frequencies or sham. Additional experiments showed that the onset of HCC-specific anti-proliferative effects on HCC xenografts occurs within one week of exposure. Immunohistochemistry analysis of the tumors exposed to HCC specific frequencies demonstrated a significant decrease in cell proliferation markers when compared with tumors exposed to randomly chosen frequencies (Jimenez, Wang et al. 2019).

These findings provide strong support for the novel notion that delivery of radiofrequency electromagnetic fields, amplitude modulated at HCC-specific frequencies, is a targeted systemic therapy that selectively block the growth of HCC cells but does not affect non-tumor cells.

Dosimetry Simulation

Simulated testing is performed to measure and estimate the total power delivered, SAR distribution, and organ specific SAR. These results are compared with experimental results to characterize the levels of AM RF EMF exposure in humans. Intrabuccal delivery with the TheraBionic P1 device results in systemic absorption of AM RF EMF. The amount of EMF delivered to the body is estimated to be 100 to 1000 times lower than the amount of electromagnetic fields delivered by cellular phones and does not result in any thermal heating in the brain or other specific body organs.

Biocompatibility Assessment.

Biocompatibility tests were conducted on the patient-contacting materials of the device and included: cytotoxicity, sensitization, irritation, and acute systemic toxicity. The results showed that the patient contacting materials are safe for the intended use.

Electrical Safety and Electromagnetic Compatibility Testing

The TheraBionic P1 system passed testing in accordance with of applicable electrical safety standards IEC 60601-1 and IEC 60601-1-11. Additionally the system was tested for EMC in accordance with applicable standard IEC 60601-1-2. The rechargeable Li-Ion battery has been tested to compliance with IEC 62133.

Test results show that the device passed acceptance criteria and is in compliance with the requirements of that standard.

Software Verification Test.
The applicant submits documentation of the software design, verification and validation testing. The software documentation and testing are found to be adequate.

X. SUMMARY OF CLINICAL INFORMATION

Clinical Study: TheraBionic phase I/II study. The following clinical study has been completed for the TheraBionic P1, findings for which have been published in a peer-reviewed journal.(Costa, de Oliveira et al. 2011) The trial was approved by the local IRB and conducted in accordance with the Declarations of Helsinki.

Table 1. Study Protocol Synopsis

Single arm open label study of the treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electrical fields	
Purpose	Assess the safety and effectiveness of the intrabuccal administration of very low levels of electromagnetic fields amplitude modulated at HCC-specific frequencies
Clinicaltrial.gov identifier	NCT00534664
Study Design	• Investigator-initiated single center single arm study in patients with advanced HCC. • Self-administered AM RF EMF treatments three time daily ○ Treatment administered until tumor progression objectively documented according to RECIST criteria • Follow up every 8 weeks
Study Population	Patients age 18 years or older with hepatocellular carcinoma with or without metastases, diagnosed by imaging or biopsy, with an ECOG performance of 0 to 2 who have exhausted all curative treatment options with at least one liver lesion measurable by RECIST and permanently impaired liver function defined as: MELD score up to 29, BCLC Stage B and C, or Child Pugh Class A or B.

Sample Size	41 subjects (6 females, 35 males; median age: 64 years; range: 18 – 85; Child-Pugh A: n = 20, Child-Pugh B: n = 21; BCLC status B: n=6, BCLC status C: n=35).
Inclusion Criteria	• Patients age 18 years or older with hepatocellular carcinoma with or without metastases • diagnosed by imaging or biopsy • ECOG performance of 0 to 2 • have exhausted all curative treatment options and with at least one liver lesion measurable by RECIST and permanently impaired liver function defined as:
Exclusion Criteria	• Confirmed or suspected brain metastases • Child Pugh Class C • Previous liver transplant • Pregnancy
Safety Endpoints	Incidence and occurrence of treatment related toxicities (Grade 1 – 4)
Effectiveness Endpoints	Primary endpoint: Proportion of patients progression-free at 6 months Secondary endpoints: Progression free survival (PFS) and overall survival (OS)
Follow-up Schedule	Every 8 weeks

From October 2005 to July 2007, patients in Brazil with advanced hepatocellular carcinoma and Child-Pugh A or B were enrolled in this study and were exposed to amplitude-modulated electromagnetic fields three times a day for 60 minutes at each session, until disease progression or death. The primary endpoint was progression-free survival ≥ 6 months. Secondary endpoints were progression-free survival and overall survival. Adverse events were documented at each follow up visit using NCI-CTCAE v.3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Patients with advanced HCC with or without metastases, diagnosed by imaging or biopsy, age 18 years or older with an ECOG performance status of 0 to 2 with permanently impaired liver function were eligible for enrollment. Previous local or systemic treatments were allowed as long as they were discontinued at least 4 weeks before enrollment. Out of 267 assessed patients, 43 were allocated (exclusion criteria: other standard treatment options available, patient too sick to undergo experimental therapy, patient not willing to participate). Two of these were excluded for screening failure, thus 41 patients with advanced HCC and Child Pugh A or B disease and limited therapeutic options received intervention (6 females, 35 males; median age: 64 years; range: 18 – 85; Child-Pugh A: n = 20, Child-Pugh B: n = 21; BCLC status B: n=6, BCLC status C: n=35). Thirty-one patients (75.6%) had radiological evidence of disease progression at the time of enrollment as

defined by comparison of baseline imaging studies with imaging studies obtained within the previous six months. Thirty-four (82.9%) patients had received therapy prior to enrollment, 25 of them chemoembolization. Seven (17.1%) patients had not received therapy prior to enrollment because of (1) severely impaired liver function in five cases, or (2) refusal to receive chemotherapy for metastatic disease.

Battery-operated devices were used for all patients enrolled in this study. The HCC treatment program consisted of sequential emission of repeated cycles of 194 tumor-specific modulation frequencies for 60 min.

Three daily 60-minute outpatient treatments were administered until disease progression or death. Imaging studies were performed every 8 weeks. Patients were treated in two subsequent cohorts. After the first cohort (n=23) showed encouraging results (Progression-free survival at 6 months: n=6), the second cohort (n=18) was enrolled. The primary endpoint was the proportion of patients progression-free at 6 months. Secondary endpoints were progression-free survival (PFS) (first day of treatment until progression of disease or death) and overall survival (OS) (first day of receiving treatment to death).

All eligible patients who began treatment were considered assessable for the primary and secondary endpoints. A Simon two-stage phase II minimax design was used to evaluate the rate of progression-free survival at 6 months. The interim analysis was performed once enrollment into the first stage was completed. In the first stage, 23 patients were evaluated. If two or fewer patients had progression-free survival greater than 6 months, the trial would be terminated early for lack of efficacy. If the progression-free survival of 3 or more of the first 23 patients was equal or greater than 6 months, then an additional 18 patients would be enrolled to a maximum of 41 patients. If eight or more of the 41 had PFS of at least 6 months, we would conclude that the treatment was efficacious. This design had a Type I error rate of 5% and a Type II error rate of 10% for the null hypothesis of a 6-month PFS rate of 10% vs. the alternative of 27.5%. Kaplan–Meier estimates of survival, PFS, and duration of response were calculated with standard errors based on Greenwood's formula. If eight or more of the 41 had progression-free survival of at least 6 months, the treatment would be considered efficacious. Overall tumor response was scored as a complete response (CR), partial response (PR), or stable disease (SD) (Stable disease was defined as no change in tumor size at 8 weeks, confirmed with another imaging study done at least 4 weeks later). Adverse event and pain were assessed according to the NCI-CTCAE v.3.0.

Treatment efficacy: Six of the first 23 patients (26.1%) had progression-free survival greater than 6 months, which led the researchers to continue enrolling patients up to the preplanned total of 41 patients. Out of these 41 patients, 14 patients (34.1%) had stable disease (SD) for more than 6 months, which met the preplanned primary efficacy criterion of 8 patients with progression-free survival of at least 6 months. Median progression-free survival was 4.4 months (95% CI 2.1–5.3) and median OS was 6.7 months (95% CI 3.0–10.2). Estimated survival at 12, 24 and 36 months is 27.9% (s.e. = 7.1%), 15.2% (s.e. = 5.7%), and 10.1% (s.e. = 4.8%), respectively. Overall, there were six long-term survivors with an OS greater than 24 months and four long-term survivors with an OS greater than 3 years. Importantly, five of the six (83%) long-term survivors had radiological evidence of

disease progression at the time of study enrolment. Two of three patients with the longest survival (44.6 and 62 months) had radiological evidence of disease progression at the time of enrolment, and BLCL stage C disease. The latter patient remained on therapy with a near complete response for 62 months prior to expiring of causes unrelated to her malignancy.

Tumor shrinkage as assessed by radiological imaging as well as changes in AFP levels were documented in patients with advanced HCC receiving RF EMF modulated at HCC-specific frequencies administered by an intrabuccal probe. Antitumor activity in patients with advanced HCC was exemplified by partial responses observed in four patients (9.8%) and decreases in AFP levels greater than 20% in four patients. A total of 18 patients (43.9%) either had objective response or SD for greater than 6 months. Importantly, clinical benefit also was observed in patients with Child Pugh B disease, i.e., patients with severely impaired liver function who are not eligible for most antitumor treatment. Specifically, one patient with Child-Pugh B9 liver function had a partial response lasting 11.7 months.

In all, 11 patients reported pain before treatment initiation, 3 patients reported grade 3, 5 patients reported grade 2, and 3 patients grade 1 pain. After initiation of treatment, five (45.5%) patients reported complete disappearance of pain and two (18.2%) patients reported decreased pain. Two patients reported no changes and two patients reported increased pain. Hence, 63.6% of patients with cancer-related pain experienced symptomatic benefit.
All responses were confirmed by an independent reviewer. There was no NCI grade 2, 3 or 4 toxicities. One patient developed grade 1 mucositis and one patient grade 1 fatigue. The authors concluded that in patients with advanced hepatocellular carcinoma and impaired hepatic function, treatment with amplitude-modulated electromagnetic fields is safe, well tolerated, and shows evidence of anti-tumor effects, which are long-lasting in some patients.

Compassionate and post CE approval Use and pooled analyses.

TheraBionic has received numerous requests for compassionate use of the TheraBionic P1 device for patients with advanced hepatocellular carcinoma who have either failed or are intolerant to standard therapies. The patients received the same treatment regimen as described in the TheraBionic P1 IFU. Three institutions received authorization for compassionate use treatment for patients with HCC. Furthermore, each patient fulfilled the criteria outlined in the TheraBionic P1 IFU. All patients treated after 2011 received treatment with the 194 HCC specific frequencies supplemented with additional HCC specific frequencies identified until 2018. There are a total of 18 patients with advanced HCC, one from TheraBionic feasibility study, those treated under FDA compassionate use authorization, and post CE approval patients treated in Europe and Brazil. The studies described in this section include analyses of these 18 patients and pooled analysis of these 18 patients combined with the 41 patients from the previously summarized Therabionic Phase I/II trial (total n=59).

Methods

This study was approved by the Wake Forest Baptist Comprehensive Cancer Center Investigational Review Board (IRB). All patients who received treatment with the

TheraBionic device programmed with HCC specific frequencies were included in this analysis.

Survival data and patient-rated symptoms according to NCI CTCAE were extracted from the TheraBionic phase I/ II study(Costa, de Oliveira et al. 2011) case report forms (CRFs) and from the TheraBionic Device Registry Forms (TDRFs) for patients who received treatment with the TheraBionic device in the feasibility study,(Barbault, Costa et al. 2009) on compassionate use or post CE approval. The TDRFs capture the same information as that captured by the phase I/II study, including demographics, prior treatment history, liver function laboratory results, ascites, encephalopathy, target lesions per RECIST 1.1 and mRECIST criteria, performance status, history of hepatitis, symptoms prior to treatment, symptoms while receiving treatment using NCI CTCAE criteria, and adverse device events. The design of the TDRFs was reviewed and approved by two experts in the field of HCC. Patient-rated symptoms were assessed prior to TheraBionic treatment initiation and at each follow up visit during treatment using the NCI CTCAE version 3 for the phase I/II study and version 5 for the real-world patients. The obtained pain score was either the average score while receiving treatment for patients who had more than one follow up visit or the final measurement for patients with one follow up visit.

We summarized patient AE data across real-world patients (n=18) and the previously conducted Phase I/II study (n=41). For each study, both separately and pooled, we summarize the incidence of each AE grade individually, any grade AE, and grade 3 and 4 AE. For each summary table, we present the incidence of patient experienced AEs by maximum grade post-baseline and baseline adjusted approach proposed by Basch et al.. (Basch, Rogak et al. 2016) Following the latter approach, baseline adjusted AEs are calculated for each AE such that if a patient's maximum grade AE post-baseline is less than or equal to their baseline AE, their adjusted AE grade is 0. Otherwise, if a patient's max-grade AE is greater than their baseline AE, their adjusted AE grade is equal to their max-grade AE. Additionally, we compare the AEs experienced by patients in the Phase I/II study (n=41) to AEs reported in two Sorafenib trials. Specifically, for each overlapping AE experienced in both the TheraBionic phase I/II trial and the Sorafenib trials, we compare statistically using a Fisher's Exact Test.

Primary data was reviewed independently by several authors and tabulated in an excel spreadsheet. Data analysis examining time to event data (i.e., survival or progression) was conducted using SAS ProcSAS version 9.4 Lifetest Procedure.

Results

Real-world data

The median age was 71. Fifteen (83.3%) patients were male. ECOG performance status ranged from 1 to 3. Twelve patients had Child-Pugh A, four patients Child-Pugh B, and two patients had Child-Pugh C liver function. Half of the patients had AFP levels greater than 400 ng/mL. Fifteen (83.3%) patients had evidence of disease progression and all patients except for one had received at least one systemic therapy prior to initiation of treatment with the TheraBionic device. Sorafenib was the most used anticancer therapy by 14 (77.8%) patients. In addition to 17 patients who had received 1 systemic therapy, three had received

2 systemic therapies, one 4 systemic therapies, and one 6 systemic therapies prior to treatment initiation with the TheraBionic device.

With a cutoff date of June 7, 2021, one patient was alive and receiving single modality treatment with the TheraBionic device, which is reported in Blackstock et al. 2021(Blackstock, Benson et al. 2021). This patient passed away on August 3, 2021 without any treatment-related AEs. The other patients have expired. The median overall survival of these patients is 6.67 (95% CI 4.44-9.50) months, which is identical to the 6.7 (95% CI 3.0-10.2) months median OS of patients enrolled in previously published phase I/II study. (Costa, de Oliveira et al. 2011) Two (11.1%) of the 18 patients had a partial response (PR) as assessed by RECIST criteria, a PR rate similar to the 9.8% observed in the phase I/II study.

Pooled Overall survival: The median overall survival in the pooled analysis (n=59) was 6.72 (95% CI 4.53-9.53) months. The median overall survival in the Child-Pugh A group (n=32) was 10.36 (95% CI 5.42-14.07) months. The median overall survival in the Child-Pugh B group (n=25)) was 4.44 (95% CI 1.64-7.13) months. The median OS in the Child-Pugh C group (n=2) was 1.99 (95% CI 0.76-3.22) months.

Overall safety and efficacy in patients who have failed first line and second line therapy

From our existing series of patients receiving TheraBionic therapy, we identified six patients (three from the phase I/II study: # 16, 17, 38, three from the real-world data study: # 101, 106, 107) who had received both 1st line and 2nd line systemic therapy prior to receiving treatment with the TheraBionic device:

Patient #	Child-Pugh	First-Line Therapy	Second-line therapy
16	B9	Doxorubicin	Octreotide LAR
17	A5	Doxorubicin + Cisplatin	Oxaliplatin + Capecitabine
38	A5	Oxaliplatin + Capecitabine	gemcitabine + oxaliplatin
101	A5	sorafenib	sunitinib
106	A6	nivolumab	lenvatinib
107	A6	nivolumab	Regorafenib + sorafenib + atezolizumab

The median OS of these six patients was 9.15 (95% CI 1.6-34.8) months and the median OS of the five Child-Pugh A patients was 9.5 months, which are comparatively longer than the 7.74 months pooled estimated medians of the placebo arms of 11 randomized first line and second line placebo-controlled studies assessing the safety and efficacy of new agents for the treatment of Child-Pugh A advanced HCC (Table 1).(Llovet, Montal et al. 2019, Blackstock, Benson et al. 2021) Importantly, the patients enrolled in these 11 studies were either treatment naïve (first line) or had only received one line of therapy (2nd line). These patients would therefore have a better prognosis than patients who have failed first line and second line therapy. There are no published studies providing data to evaluate the median

OS of patients who have failed first line and second line systemic therapy, i.e., the TheraBionic intended HDE population. However, the median OS of such a population is expected to be lower than 7.74 months.

We also analyzed the survival of patients who had received two lines of systemic therapy (TheraBionic HDE population) and did not receive any additional anticancer treatment while and after receiving treatment with the TheraBionic device (patients # 16, 17, 38, 106). The median OS of these patients was 9.8 months and the median OS of the three Child-Pugh A patients was 17.2 months, which are comparatively longer than the 7.74 months pooled estimated medians of the placebo arms of the above cited 11 randomized studies.

These data provide evidence of probable benefit in the HDE intended population, i.e., patients who have failed 1st line and 2nd line therapy.

To further assess unknown device-related adverse events, we assessed patient reported symptoms using the same scale (Costa, de Oliveira et al. 2011, Blackstock, Benson et al. 2021) as that used in the SHARP (Llovet, Ricci et al. 2008) and Asian-Pacific sorafenib (Cheng, Kang et al. 2009) studies. Here we report that the incidence of any grade AEs among the 20 Child-Pugh A patients who received treatment with the TheraBionic device in the phase I/II study (Costa, de Oliveira et al. 2011) was not different from the Placebo groups of the SHARP (Llovet, Ricci et al. 2008) and Asian Pacific (Cheng, Kang et al. 2009) Sorafenib studies.

	Table: Incidence of Any Grade AEs				
	TheraBionic (N=20)	**Placebo[a] (N=302)**		**Placebo[b] (N=75)**	
AE	**n (%)**	**n (%)**	**P-Value***	**n (%)**	**P-Value**
Abdominal Pain	1 (5%)	9 (3%)	0.478	--	--
Anorexia	0 (0%)	9 (3%)	1	2 (3%)	1
Diarrhea	1 (5%)	33 (11%)	0.707	4 (5%)	1
Fatigue	4 (20%)	48 (16%)	0.544	6 (8%)	0.21
Hand foot syndrome	0 (0%)	9 (3%)	1	2 (3%)	1
Nausea	0 (0%)	24 (8%)	0.381	8 (11%)	0.197
Note:					
P-Values based on Fisher's Exact Test comparing TheraBionic and each Sorafenib Trial's Placebo arms					
[a] Llovet, Josep M., et al. 'Sorafenib in advanced hepatocellular carcinoma.' New England journal of medicine 359.4 (2008): 378-390.					
[b] Cheng, Ann-Lii, et al. 'Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial.' The lancet oncology 10.1 (2009): 25-34.					

In summary, the data provides evidence that the potential benefit of treatment with the TheraBionic device in the intended HDE population outweighs the risk of adverse events.

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one investigator of which none were full-time or part-time employees of the sponsor and one had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None.
- Significant payment of other sorts: None.
- Proprietary interest in the product tested held by the investigator: One (1).
- Significant equity interest held by investigator in sponsor of covered study: None.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

A. Probable Benefit Conclusions

The information to support a probable benefit for the TheraBionic P1 device treatment in patients meet the HDE criteria (who fail first- and second-line therapy and did not receive additional anticancer treatments) includes data for the TheraBionic treatment of four (4) patients including data collected in published OUS clinical evidence (Blackstock, 2021.) The reported median OS of these 4 patients was 12.3 months and 2 of the patients may have experienced a survival benefit (compared to the survival reported for placebo in randomized controlled trials for which FDA has approved effective products for the treatment of patients with advanced HCC).

B. Safety Conclusions

The risks of the device are based on data collected in published OUS clinical evidence (Blackstock, 2021) to support HDE approval as described above. Published

clinical data reports a 5.8% incidence of Grade 1 somnolence/fatigue and a 1.4% incidence of Grade 1 Mucositis. These are considered to be device-related non-serious adverse events.

C. Probable Benefit-Risk Conclusions

The information to support a probable benefit for the TheraBionic P1 device treatment in patients meet the HDE criteria (who fail first- and second-line therapy and did not receive additional anticancer treatments) includes data for the TheraBionic treatment of four (4) patients. The reported median OS of these 4 patients was 12.3 months and 2 of the patients may have experienced a survival benefit (compared to the survival reported for placebo in randomized controlled trials for which FDA has approved effective products for the treatment of patients with advanced HCC).

The probable risks of the device are also based on data collected in a clinical study conducted to support HDE approval as described above. There were no NCI Grade 2, 3 or 4 toxicities. One patient developed grade 1 mucositis and one patient reported grade 1 fatigue.

Additional factors considered in the determination of probable benefit and risks for the TheraBionic P1 device includes the totality of all the data provided, the natural history of the underlying disease, that there are no alternative forms of treatment, and known or postulated mechanism(s) of action of the device in relation to the disease process. the review concludes a possible benefit for TheraBionic P1 device treatment for patients with advanced HCC who fail first- and second-line therapy.

It is in the best interest of these patients to grant HDE approval on the condition of a post approval study for the purpose of assessing the safety, overall survival and patient reported outcomes for the TheraBionic device treatment for the HDE indication (i.e., treatment for patients with advanced HCC who fail first- and second-line therapy). This pathway would provide for the knowledge base needed to support a determination of reasonable assurance of safety and effectiveness.

Finally, this submission did not include specific information on patient perspectives and therefore patient perspectives did not serve as part of the basis of the decision to approve or deny the HDE for this device.

In conclusion, based upon the totality of all the data provided and taking into account the natural history of the underlying disease, that there are no alternative forms of treatment, and known or postulated mechanism(s) of action of the device in relation to the disease process the review concludes a possible benefit for TheraBionic P1 device treatment for patients with advanced HCC who fail first- and second-line therapy.

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D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. Based upon the totality of all the data provided and taking into account the natural history of the underlying disease, that there are no alternative forms of treatment, and known or postulated mechanism(s) of action of the device in relation to the disease process the review concludes a possible benefit for TheraBionic P1 device treatment for patients with advanced HCC who fail first- and second-line therapy.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the General and Plastic Surgery Device Panel because the submission does not raise any anticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIV. CDRH DECISION

It is in the best interest of these patients to grant HDE approval on the condition of a post approval study for the purpose of assessing the safety, overall survival and patient reported outcomes for the TheraBionic device treatment for the HDE indication (i.e., treatment for patients with advanced HCC who fail first- and second-line therapy). This pathway would provide for the knowledge base needed to support a determination of reasonable assurance of safety and effectiveness.

CDRH has determined that, based on the data submitted in the HDE, the TheraBionic P1 will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on September 26, 2023.

The final clinical conditions of approval cited in the approval order are described below.

The impact of the TheraBionic P1 should be evaluated in the intended patient population of adults with Advanced HCC having failed first and second-line systemic therapies in a prospective study structured and statistically powered to demonstrate i) overall survival representing the period starting at the date of treatment initiation until death; and ii) Quality of Life (QoL) and/or other Patient Reported Outcomes (PPO). It is recommend that validated patient reported outcomes and/or patient preference information tools be used, or provide a validation method/protocol for QoL assessment.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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