

**Fact check comments form  
for manufacturers**

Company name: Celsius				
Page number	Line or section number	Description of factual inaccuracy and proposed amendment <i>(Please insert each new comment in a new row.)</i>	Character of comment 1= 'major' 2= 'minor' 3= 'linguistic'	Authors' reply
		No specific comments		
Company name: Oncotherm				
Page number	Line or section number	Description of factual inaccuracy and proposed amendment <i>(Please insert each new comment in a new row.)</i>	Character of comment 1= 'major' 2= 'minor' 3= 'linguistic'	Authors' reply

32	3.2 Results/Regional Hyperthermia	<p>Deep hyperthermia is achievable with 13.56MHz too. For example, Oncotherm Kft. has various phase III and phase II. studies on uterus cervix, phase II. trials on glioblastoma, phase II. trials on lung and pancreas. In all the above cases, deep hyperthermia is needed for treatment, which can be achieved on 13.56MHz, with Oncothermia as well. Please check the previously submitted publication list (<a href="https://oncotherm.com/en/clinical-publications">https://oncotherm.com/en/clinical-publications</a>) For theoretical approaches, we have two publications (which are also included in the previously submitted publication list):</p> <p>Szasz O, Szasz A (2016) Heating, efficacy and dose of local hyperthermia. Open Journal of Biophysics, 6:10-18, <a href="http://www.scirp.org/journal/PaperInformation.aspx?paperID=62874">http://www.scirp.org/journal/PaperInformation.aspx?paperID=62874</a></p> <p>Szasz O, Szigeti GyP, Vancsik T, Szasz A. (2018) Hyperthermia dosing and depth of effect, Open Journal of Biophysics, 2018, 8, 31-48, <a href="http://www.scirp.org/journal/PaperInformation.aspx?PaperID=81896">http://www.scirp.org/journal/PaperInformation.aspx?PaperID=81896</a></p>	1	The value in MHz has been removed; the first paper cited is related to local Hyperthermia and therefore excluded from the publication list, while the second one has been included.
32	3.2 Results/Regional Hyperthermia	In the paragraph where deep hyperthermia is discussed, it is stated that "With deep hyperthermia, the patients lie in a ring applicator", which is not entirely correct. In the case of deep hyperthermia, the patient is in a capacitive applicator arrangement, which is not necessarily a ring applicator.	1	Thank you. The sentence has been rephrased
33	3.2 Results/Side effects of regional hyperthermia	<p>"Because the patient's ability to detect pain is an essential safety mechanism, hyperthermia is contraindicated in patients whose pain response has been significantly decreased by any means (previous surgery or ionizing radiation therapy, regional or general anaesthetic, or other condition)."</p> <p>This sentence is contradictory to the statement on page 51 since local anaesthesia changes the patients' heat sensation which is a safety issue according to the participants' users' manual; therefore, hyperthermia cannot be applied in these cases. As it has been stated on page 33, patients must be in a condition in which they are able to feel pain in order to reduce the risk of burns and other heat-related injuries. We recommend changing the statement on page 51.</p>	1	Thank you. We changed the statement on page 51 as requested
35	Figure 2 Oncotherm	"The principle of operation is based on the usage of a single applicator (available in different sizes) that has to be positioned on the target area." Please add that in capacitive treatments the patient is between two electrodes, and opposite to the applicator, a counter electrode is fixed in the treatment	1	Corrected, thank you

35	Figure 2 Oncotherm	<p>"In EHY-2030, a new mechanical arm is introduced, and its arm is designed to have a better reach more conveniently.". The text before this sentence is a general introduction; however, this sentence is only about the EHY-2030. It should be in the next paragraph.</p>	1	See comment below
35	Figure 2 Oncotherm	<p>Please change the structure of the paragraph that discusses the electrodes. It is meant to be a general description; however, the information that is shared in that paragraph is not entirely correct for all Oncothermia devices. Recommendation (with the previous sentence we have mentioned):</p> <p>"In EHY2000, the changeable applicator has conventional bolus cooling, which keeps the surface temperature in the homeostatic range. In EHY2030 and EHY3010ML, the radiating elements (electrode types) are composed of a metallised textile with a temperature-controlled bolus where circulates distilled water for thermoregulation.</p> <p>In EHY-2030, a new mechanical arm has been introduced, that was designed to provide a better reach more conveniently. The diameters of the two possible electrode variants are of 20 cm (max of 150 W) and 30 cm (max of 250 W). <del>Systems for monitoring patient temperature are not described.</del>Temperature measurements are available by the TM200 and TM300 devices developed by Oncotherm, for sensing temperature under RF-power. It is widely used in experiential applications, but its approval for clinical use is in progress."</p>	1	Thank you. We modified the paragraph as suggested
43	Table 3-2/Range of application or indications	<p>The same formatting should be used on every participants' texts. In the case of BSD and Alba, there are words and paragraphs highlighted in bold and bigger letters. Each item on their lists is in separate rows in the "application range" row, while in case of Oncotherm, the very same list is crammed into one paragraph. Also, in case of the contraindications row, the whole text has been copy-pasted into the table for Oncotherm, while in case of other participants, the contraindications are just listed. Because of this, it seems like Oncotherm has much more contraindications than other participants, while in numbers, it has the same or less amount as others. Also, since the list of contraindications seems long, while the range of application seems short, Oncotherm Kft. appears in a disadvantageous light.</p>	3	The table has been compiled using data obtained from your user manuals. Specific information related to the other devices was more difficult to retrieve, but contents are substantially the same.

51	Line 1	<p>"In case the hyperthermia treatment requires patient anaesthesia or the introduction 1 inside the patients of thermometric monitors, these procedures must be performed by specialised professionals, each with their own specific skills (doctor, nurse)."</p> <p>This sentence is contradictory to the statement on page 33. We recommend stating here that hyperthermia treatments are not applicable in case any kind of anaesthesia is applied to the treated area since patients must be able to feel pain for safety measures.</p>	1	Thank you, we changed the statement (see previous comment)
51	Line 29	It is stated that Alba and Oncothermia devices work at 434 MHz. Oncothermia devices, however, work on 13.56 MHz. Please specify this in the case of each company; this cannot be generalised!	1	Corrected, thank you
510	Line 14-23	As we understand, in line 15, the two categories listed – 29 and 30- include Oncothermia as well; however, this paragraph is not entirely correct in the case of Oncothermia. None of our devices needs anything else than a treatment room (no operator or technical room, no shielding needed). Our devices only need around 12-16m <sup>2</sup> free space where they can be placed in the middle of the room, at least 1,5m away from any walls. Please specify the requirements of each device separately; this cannot be generalised!	1	Thank you, we changed that statement
57	Line 14	Tumour-related mortality is not the same as overall mortality, which involves the possibility of treatment-related mortality as well. If the patient was killed by the treatment, and not by the tumour, it is still not an admirable achievement. The admirable achievement would be if the patient lived – tumour-free or not.	1	Agree. However, that paragraph is just descriptive, not weighing the relevance of different outcomes
99	10. References	<p>We were surprised to find that three of Oncothermia and sarcoma-related publications were not included in the reference list. Please find the mentioned publications here:</p> <p>Volovat C, Volovat SR, Scripcaru V et al. (2014) The results of combination of ifosfamide and locoregional hyperthermia (EHY 2000) in patients with advanced abdominal soft-tissue sarcoma after relapse of first line chemotherapy. Romanian Reports in Physics, 66(1):175-181, <a href="http://www.rrp.infim.ro/2014_66_1/A19.pdf">http://www.rrp.infim.ro/2014_66_1/A19.pdf</a></p> <p>Jeung T-S, Ma S-Y, Choi J et al. (2015) Results of oncothermia combined with operation, chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma. Case Reports in Clinical Medicine 4:157-168, <a href="http://www.scirp.org/journal/PaperInformation.aspx?PaperID=56280">http://www.scirp.org/journal/PaperInformation.aspx?PaperID=56280</a></p> <p>Lee SY, Lee N-R. (2016) Positive response of a primary leiomyosarcoma of the breast following salvage hyperthermia and pazopanib, Korean J Intern Med, DOI: 10.3904/kjim.2015.242, <a href="http://www.ncbi.nlm.nih.gov/pubmed/27079325">http://www.ncbi.nlm.nih.gov/pubmed/27079325</a></p> <p>Please find our previously sent publication list here: <a href="https://oncotherm.com/en/clinical-publications">https://oncotherm.com/en/clinical-publications</a></p>	1	Those references have been added following your suggestion.

107-117	Appendix 1	We were disappointed to see that Oncotherm, EHY-2000 (2030,3010), Oncothermia, and mEHT were not searched at all, while all other participants and their devices were. We have found the following search words in the assessment document: Alba 4d, Celsius tcs, Synchrotherm, bsd-2000, bsd-500, bsd medical. This is an extremely crucial problem with this assessment since a vast number of authors and users use the name Oncothermia or mEHT (modulated electro-hyperthermia). For the assessment to be fair and square, the search words should include all participants. We would like to	1	We have updated the search in accordance with your comment.
8-27.	All	From page 8 to page 27, the text is aligned left. From that point, it is aligned justified.	3	This will be adjusted before publication
<b>Company name: Medlogix</b>				
Page number	Line or section number	Description of factual inaccuracy and proposed amendment (Please insert each new comment in a new row.)	Character of comment 1= 'major' 2= 'minor' 3= 'linguistic'	Authors' reply
31	3.2 Hyperthermia	Authors state: "Hyperthermia (HT) usually is taken to mean a body temperature that is higher than normal (15,16). This definition is not complete. It should be added that, as hyperthermia, it is intended when the temperature of the target is increased in the range 40-44 °C. Indeed, European Society for Hyperthermic Oncology (ESHO) quality assurance guidelines for regional hyperthermia (J. W. Lagendijk, J & Rhooon, Gerard & Hornsleth, Sten & Wust, Peter & Leeuw, Astrid & J Schneider, C & Van Dijk, J.D.P. & van der Zee, Julie & Van Heek-Romanowski, R & Rahman, Sultan & Gromoll, C. (1998). Esho Quality Assurance Guidelines for Regional Hyperthermia. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 14. 125-33. 10.3109/02656739809018219.) define 40 °C as the minimum temperature where the hyperthermia treatment starts, while the temperature in the target tissue should not exceed 44 °C." Guidelines also state that : " <b><i>The proven effectiveness of hyperthermia in clinical studies relies exclusively on its thermal effect on tumours.</i></b> " and " <b><i>Measuring temperature is of great significance, in order to verify therapeutically necessary temperatures in the target volume and to avoid unwanted hot spots in the surrounding normal tissue.</i></b> These aspects should be underlined by the authors.	1	Thank you, we rephrased this.
32	3.2(regional hyperthermia)	Authors state " Here, the tumour region is heated to the desired temperature using targeted electromagnetic energy radiating at around 100 MHz."This is partially correct, frequency should be: 70-120 MHz	1	Thank you. We simplified in order to avoid
32	3.2(regional hyperthermia)	Authors state "A water bolus and antennas that radiate high-frequency electromagnetic waves are integrated into this applicator."This is partially correct, water bolus is not always integrated in the applicator. In ALBA 4D for example 2 water bolus are positioned between antennas and patient, but not integrated into the applicators.	1	Thank you, we rephrased this.

33	3.2(regional hyperthermia technologies)	<p>Authors state “. Among the commercially available capacitive systems operating at 13.56 MHz, a frequency that allows the highest penetration into biological tissues without overheating lipidic tissues, there are all EHY models (OncoTherms), Celsius TCS (Celsius42), and RF 1200 S (SynchroTherm). “ This is not correct. The paper <i>Kok HP, Navarro F, Strigari L, Cavagnaro M, Crezee J. Locoregional hyperthermia of deep-seated tumours applied with capacitive and radiative systems: a simulation study. Int J Hyperthermia. 2018 Sep;34(6):714-730. doi: 10.1080/02656736.2018.1448119. Epub 2018 Apr 18. PubMed PMID: 29509043</i> shows differences between the radiative and capacitive hyperthermia technologies for deep hyperthermia and their impact on the clinical performances, both on phantom and patients. As it is possible to read from this paper, radiative phased array systems, as BSD-2000 and the 4 waveguides phased array working at 70 MHz, as ALBA 4D, can properly heat tumors at any depth in the abdominal and pelvic area. On the other hand, capacitive systems reach lower temperature at depth and this limitation is due to the fat layer. In particular authors of the paper state that:</p> <p>- “<b>adequate temperatures can only be obtained with capacitive heating when accepting very high temperatures in the superficial fat and muscle layers</b>”....”“Precooling is often applied clinically in order to reduce the incidence of treatment limiting hot spots with capacitive heating, even though clinical experience shows that this is not always effective in avoiding preferential heating at fat–muscle interfaces.”....”Precooling in combination with switching the active electrodes from top and bottom to the sides can improve patient comfort since hot spot complaints are resolved temporarily. <b>However, the target temperature is not expected to improve sufficiently to realize a substantial improvement in treatment outcome.</b>”</p> <p>- “<b>The fundamental problem that causes the treatment limiting hot spots is the E-field direction that is perpendicular to the fat–muscle interface in combination with the lack of steering possibilities.</b> Switching electrode positions does not overcome these fundamental problems, but continuously changes the location of the treatment limiting hot spot which does improve the target temperature, but again not sufficiently to meet the clinical requirements. “</p> <p>For this reason also ESHO guidelines (<i>J. W. Lagendijk, J &amp; Rhoon, Gerard &amp; Hornsleth, Sten &amp; Wust, Peter &amp; Leeuw, Astrid &amp; J Schneider, C &amp; Van Dijk, J.D.P. &amp; van der Zee, Julie &amp; Van Heek-Romanowski, R &amp; Rahman, Sultan &amp; Gromoll, C. (1998). Esho Quality Assurance Guidelines for Regional Hyperthermia. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 14. 125-33. 10.3109/02656739809018219.</i>) state that “<b>patients in the western world are more adequately treated with “phased array” systems because the surface fat layer thickness in the relevant body region is often more than 2 cm</b>”.</p>		We eliminated the controversial phrase
33	3.2(regional hyperthermia technologies)	The description of radiative superficial technologies is missed. Please add it.	1	Thank you, we added it
38	ALBA ON 4000	Linguistic error: The temperature is “measured”.	3	Corrected
38	ALBA ON 4000	Authors state: the temperature is measured during the entire duration of the treatment by means of a probe placed on the skin or interstitially (is wanted).” This is partially correct. It should be “ by means of multiple probes”.	1	Corrected
39	ALBA 4D	Linguistic error: The temperature is “measured”.	3	Corrected

39	ALBA 4D	Please add: " An innovative element of ALBA 4D is the RF signal measuring device (DET, "detector") integrated in the signal generator (DDS / DET) that measures power and phase of the forward and reflected signals allowing, together with specifically designed tracking algorithms, a feedback control to counter-react and correct, in real time during treatment, any eventual phase or power drift."		Added
45	Table 3.2, Intended use	Please add: - ALBA ON4000 is indicated to be used in conjunction with standard therapies, such as chemotherapy and radiotherapy, in the management of solid tumors up to about 4 cm of depth. - ALBA 4D is indicated to be used in conjunction with standard therapies, such as chemotherapy and radiotherapy, in the management of deep seated solid tumors.	1	Added