EMC 16-400

A MULTICENTER RANDOMIZED CONTROLLED TRIAL TESTING HYALURONIC ACID SPACER INJECTION FOR SKIN TOXICITY REDUCTION OF PERMANENT BREAST SEED IMPLANT (PBSI)

CASE REPORT FORM (CRF)

A MULTICENTER RANDOMIZED CONTROLLED TRIAL TESTING HYALURONIC ACID SPACER INJECTION FOR SKIN TOXICITY REDUCTION OF PERMANENT BREAST SEED IMPLANT (PBSI)

Principal Investigator: Prof. dr. J.P. Pignol
Co-investigator: Drs. G. Struik
Protocol version: Mar 2018 (version 5)

Note: this CRF was built as an e-CRF in OpenClinica
Overview of events and CRF
The CRF’s are divided over the following events:

- Baseline
- Treatment
- Follow-up 2M, 6M, 1YR, 2YR, 3YR, 4YR, 5YR, 10YR
- Recurrence
- Off-study

Randomization Form will be built separately in ALEA (*)

This form will contain basic patient characteristics, and a selection of the eligibility criteria:

- Date of birth ➔ calculated age, ≥ 50 years (yes/no)
- Surgery: BCS + axillary lymph node dissection or BCS + sentinel lymph node biopsy, (yes/no)
- Histological diagnosis: IDC or DCIS, (yes/no)
- Conditional question:
  o if IDC: Surgical margins clear at ink or re-excision negative (yes/no)
  o if DCIS: Surgical margin ≥ 2mm or re-excision negative (yes/no)
- Tumor size (mm), ≤30mm (yes/no)
- Nodal status (positive/negative)
- Lymphovascular invasion (yes/no)
- Known allergy for hyaluronic acid (yes/no)
- Neo-adjuvant chemotherapy (yes/no)
- PBSI technically feasible (yes/no)
- Any other exclusion criterion (yes/no)
- Date of written informed consent
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- Date of randomization
- Randomization result
- Subject IDnr

(*) export of data any time in agreement with CTC

PROMs will be collected in ABC Zorgmonitor: QLQ-C30/BR23, EQ-5D, BCTOS

Additional questionnaires not yet in Zorgmonitor: BCTOS at BL, 2M, YR1 and YR2
### CRF: Patient Characteristics

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>[DOR]</td>
<td>Date of randomization</td>
<td>DD / MM/ YYYY</td>
</tr>
<tr>
<td>[AGE]</td>
<td>Age at registration</td>
<td>___</td>
</tr>
<tr>
<td>[ALLINCL]</td>
<td>Did patient meet all inclusion criteria?</td>
<td>___</td>
</tr>
<tr>
<td>[ALLEXCL]</td>
<td>Did patient meet any exclusion criteria?</td>
<td>___</td>
</tr>
<tr>
<td>[DDIAG]</td>
<td>Date of first histological diagnosis</td>
<td>DD/ MM/ YYYY</td>
</tr>
<tr>
<td>[HEIGHT]</td>
<td>Height</td>
<td>___</td>
</tr>
<tr>
<td>[WEIGHT]</td>
<td>Weight</td>
<td>___</td>
</tr>
<tr>
<td>[CUPSIZE]</td>
<td>Breast cup size</td>
<td>___ ___ ___ ___</td>
</tr>
<tr>
<td>[SMOKSTAT]</td>
<td>Smoking status</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = former smoker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = current smoker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 = unknown</td>
</tr>
<tr>
<td>[DM]</td>
<td>Diabetes Mellitus</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = insulin dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = not insulin dependent</td>
</tr>
<tr>
<td>[HT]</td>
<td>Hypertension</td>
<td>___</td>
</tr>
<tr>
<td>[CVRF]</td>
<td>History of MI, CVA, PAOD?</td>
<td>___</td>
</tr>
<tr>
<td>[ADJTX]</td>
<td>adjuvant therapy before/after PBSI</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = hormone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = chemo+ hormone</td>
</tr>
</tbody>
</table>
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If ADJTX>0:

- [STARTHTX] Start date hormone therapy
- [STARTCTX] Start date chemotherapy
- [STOPCTX] Date of last chemotherapy
- [SURGDATE] Date of surgery:
- [SURGTYPE] Type of surgery:
- [SSI] Surgical Site Infection (CDC)

CRF: Tumor Characteristics

- [T] T (NM)-classification 1997
- [N] (T)N(M)-classification 1997
- [M] (TN)M-classification 1997
- [STAGE] Clinical Stage

If ADJTX>0:

| __ | 0 = stage 0
| 1 = stage 1
| 11 = stage 1b
| 2 = stage 2a
| 22 = stage 2b
| 3 = stage 3a
| 33 = stage 3b
| 333 = stage 3c
| 4 = stage 4
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| [TUMLAT]  | Tumor laterality | 1 = left  
|  |  | 2 = right |
| [TUMSITE] | Tumor anatomical subsite | 1 = nipple  
|  |  | 2 = central  
|  |  | 3 = upper-inner quadrant  
|  |  | 4 = lower-inner quadrant  
|  |  | 5 = upper-outer quadrant  
|  |  | 6 = lower-outer quadrant  
|  |  | 7 = axillary tail |
| [TUMORSIZE] | Tumor size | __ | mm |
| [DISTSKIN] | Distance tumor to skin | __ | mm |
| [MARGIN] | Resection margin status | 1 = focal irradical or <2mm for DCIS |
|  |  | 2 = irradical |
|  |  | 3 = unknown |
| [HISTOL] | Histological Diagnosis | 1 = IDC  
|  |  | 2 = DCIS  
|  |  | 3 = IDC+DCIS  
|  |  | 4 = other, ...... |
| [HISTCOM] | IF HISTOL=4 please specify FREE TEXT |
| [TUMGRAD] | Modified Scarf-Bloom-Richardson grade |
| [PR] | PR-receptor status | 0 = negative  
|  |  | 1 = positive |
| [ER] | ER-receptor status | 0 = negative  
|  |  | 1 = positive |
| [HER2NEU] | Her-2neu-receptor status | 0 = negative  
|  |  | 1 = positive |
| [LVI] | Lymfovascular Invasion | 0 = no  
|  |  | 1 = yes |
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<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[MULTI]</td>
<td>multicentricity</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = yes</td>
</tr>
<tr>
<td>[EXTDCIS]</td>
<td>Extensive DCIS (beyond invasive tumor, or &gt;3cm)</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = yes</td>
</tr>
<tr>
<td>[BILAT]</td>
<td>Bilateral breast cancer?</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = yes</td>
</tr>
<tr>
<td>[RECUR]</td>
<td>Recurrent breast cancer?</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = yes</td>
</tr>
<tr>
<td>[ACTOTH]</td>
<td>Active other cancer (defined by malignancy in&lt;5 year?)</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = yes</td>
</tr>
</tbody>
</table>
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CRF: Baseline Adverse Events (as close as possible to start PBSI)

<table>
<thead>
<tr>
<th>[AEDATE]</th>
<th>Date of AE assessment</th>
<th>DD / MM/ YYYY</th>
</tr>
</thead>
</table>

| [BASPAIN] | Baseline pain in breast | 0 = none
1 = occasional and minimal, hypersensation, pruritus
2 = intermittent and tolerable
3 = persistent and intense
4 = refractory and excruciating |
|-----------|--------------------------|---------------|

| [BASSSI]  | Baseline Surgical Site Infection | 0 = none
1 = superficial SSI
2 = deep SSI |
|-----------|----------------------------------|---------------|

| [BASTELEANG] | Baseline Teleangiectasia (Bentzen scale) | 0 = none
1 = grade I – less than 1cm²
2 = grade II – 1 to 4 cm²
3 = grade III – over 4 cm² |
|-------------|------------------------------------------|---------------|

| [BASSUBINDUR] | Baseline Subcutaneous Induration | 0 = none
1 = slight induration and loss of subcutaneous fat
2 = moderate fibrosis but asymptomatic
3 = severe induration and loss of subcutaneous tissue; field contracture
4 = necrosis |
|--------------|---------------------------------|---------------|

| [BASPIGM] | Baseline pigmentation | 0 = none
1 = transitory, slight
2 = permanent, marked |
|-----------|----------------------|---------------|

| [OTHERAE] | Any other AE? in grid/table (multiple entries possible): | 0=no, 1=yes *If yes, enter
- System organ Class (conform CTCAE4/MEDRA)
- AE term (conform CTCAE4/MEDRA)
- CTC grade (1-4) |
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CRF: Pre-implant QA

Group: General

[PLANCT1] Date of planning CT scan DD / MM / YYYY

[PREECTV] CTV |__|__|.|__| cc

[PREETV] PTV |__|__|__|.|__| cc

[PRESEEDNUM] Total number of seeds |__|__|__|

[PRENEEDNUM] Total number of needles |__|__|__|

[TOTACT] Total activity of seeds |__|__|__|.|__|U

[PRESKINPTV] minimal distance skin to PTV |__|__|.|__| mm

[PRESKINISO] distance between CTV isocenter and skin |__|__|.|__| mm

Group: DVH parameters

[PREV100] Pre-implant V100 |__|__|__|.|__| %

[PREV200] Pre-implant V200 |__|__|__|.|__| %

[PRED90] Pre-implant D90 |__|__|__|.|__| cc

[PRESK90] Pre-implant skin isodose>90% over 1cm² |__| 0=no, 1=yes

[PRED0.2] Pre-implant D0.2cc skin dose |__|__|__|.|__| Gy

[PRED0.05] Pre-implant D0.05cc skin dose |__|__|__|.|__| Gy

CRF: PBSI +/- SPACER

[PBSIDATE] Date of PBSI procedure DD / MM / YYYY

[PBSIDUR] Duration of PBSI procedure |__|__|__|__| min

[PBSIDIFF] any difficulties in PBSI procedure, please specify........................................................................................................
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[SPACER] Spacer administered |__| 0=no; 1=yes
[SPACDUR] Duration of spacer injection procedure |__|__|__|__| min

[SPACMCR] Spacer administered in mediocranial quadrant of skin projection |__| 0=no, 1=yes
[SPACMCA] Spacer administered in mediocaudal quadrant of skin projection |__| 0=no, 1=yes
[SPACLCA] Spacer administered in laterocaudal quadrant of skin projection |__| 0=no, 1=yes
[SPACLCR] Spacer administered in laterocranial quadrant of skin projection |__| 0=no, 1=yes

If SPACER=1: [SPACVOL] Volume of spacer administered |__|__|__|__| cc
(enter 9999 if not recorded)

[SPACDIFF] any difficulties in spacer injection, please specify:.................................................................................................

[USSPATRANCEN] mid spacer thickness central transversal plane on ultrasound |__|__|__|__| mm
[USSPATRANCRA] mid spacer thickness cranial transversal plane on US |__|__|__|__| mm
[USSPATRANCAU] mid spacer thickness caudal transversal plane on US |__|__|__|__| mm
[USSPASAGCEN] mid spacer thickness central saggital plane on US |__|__|__|__| mm
[USSPASAGLAT] mid spacer thickness lateral saggital plane on US |__|__|__|__| mm
[USSPASAGMED] mid spacer thickness medial saggital planel on US |__|__|__|__| mm
[SPASUC] Spacer injection successful (>5mm in all injected quadrants) |__| 0=no, 1=yes
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CRF: treatment pain

<table>
<thead>
<tr>
<th>CRF Code</th>
<th>Description</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>[PAINBAS]</td>
<td>Pain before procedure (baseline, LENTSOMA)</td>
<td>0-4</td>
</tr>
<tr>
<td>[PAINPBSI]</td>
<td>Pain during procedure (baseline, LENTSOMA)</td>
<td>0-4</td>
</tr>
<tr>
<td>[PAINPOST]</td>
<td>Maximum pain after procedure (1-2 d post-implant, LENTSOMA)</td>
<td>0-4</td>
</tr>
</tbody>
</table>
# CRF: Adverse Events 2 months

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2MASSDATE]</td>
<td>Date of AE assessment</td>
<td>DD / MM / YYYY</td>
</tr>
<tr>
<td>[2MPAIN]</td>
<td>pain in breast</td>
<td>0 = none, 1 = occasional and minimal, hypersensation, pruritus, 2 = intermittent and tolerable, 3 = persistent and intense, 4 = refractory and excruciating</td>
</tr>
<tr>
<td>[2MPAINS]</td>
<td>If AEPAIN&gt;0: Was AE serious(SAE)?</td>
<td>0 = no, 1 = yes</td>
</tr>
<tr>
<td>[2MRED]</td>
<td>Redness</td>
<td>0 = none, 1 = yes but no effect on ADL, 2 = yes and effect on ADL</td>
</tr>
<tr>
<td>[2MREDS]</td>
<td>If AERED &gt;0: Was AE serious(SAE)?</td>
<td>0 = no, 1 = yes</td>
</tr>
<tr>
<td>[2MPIGM]</td>
<td>Pigmentation</td>
<td>0 = none, 1 = transitory, slight, 2 = permanent, marked</td>
</tr>
<tr>
<td>[2MPIGMS]</td>
<td>If AEPIGM &gt;0: Was AE serious(SAE)?</td>
<td>0 = no, 1 = yes</td>
</tr>
<tr>
<td>[2MSKININD]</td>
<td>Skin induration</td>
<td>0 = none, 1 = Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up), 2 = Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL, 3 = Severe induration, unable to slide or pinch skin; limiting self-care ADL, 4 = Generalized</td>
</tr>
<tr>
<td>[2MSKININDS]</td>
<td>If AESKININD &gt;0: Was AE serious(SAE)?</td>
<td>0 = no, 1 = yes</td>
</tr>
</tbody>
</table>
### A Multicenter Randomized Controlled Trial Testing Hyaluronic Acid Spacer Injection for Skin Toxicity Reduction of Permanent Breast Seed Implant (PBSI)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2MRADDERM]</td>
<td>Radiation dermatitis</td>
</tr>
<tr>
<td></td>
<td>0 = none</td>
</tr>
<tr>
<td></td>
<td>1 = Faint erythema or dry desquamation</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema</td>
</tr>
<tr>
<td></td>
<td>3 = Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion</td>
</tr>
<tr>
<td></td>
<td>4 = Skin necrosis/ulceration of full thickness dermis; spontaneous bleeding from involved site; (skin graft indicated)</td>
</tr>
</tbody>
</table>

**If AERADDERM >0:**

- Was AE serious (SAE)?  
  0 = no, 1 = yes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2MSKINTOXDIST]</td>
<td>Distance of clinical max skin toxicity from reference point (nipple lower inner)</td>
</tr>
<tr>
<td></td>
<td>0 = none</td>
</tr>
<tr>
<td></td>
<td>1 = Superficial SSI</td>
</tr>
<tr>
<td></td>
<td>2 = Deep SSI</td>
</tr>
</tbody>
</table>

**If AESSI >0:**

- Was AE serious (SAE)?  
  0 = no, 1 = yes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2MOTHERAE]</td>
<td>Any other RT (or spacer) induced AE?</td>
</tr>
<tr>
<td></td>
<td>0 = no; 1 = yes</td>
</tr>
</tbody>
</table>
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If OTHERAE=yes: Enter in grid/table (multiple entries possible):
- System organ Class (drop down list conform CTCAE4/MEDRA)
- AE term (drop down list conform CTCAE4/MEDRA)
- Worst grade observed since last AE evaluation (1-5)
- Serious: yes/no

CRF: Post-implant QA

Group: general postplanning CT variables

[PLANCT2] Date of post-implant CT scan DD/ MM/ YYYY

[POSTCTV] post-implant CTV |__|__|__|__| cc

[POSTVOL] post-implant treatment volume with Minimal peripheral dose (90Gy) |__|__|__|__|__| cc

[POSTSEEDNUM] Total number of seeds |__|__|__|

[SEEDDISPLACED] any seeds displaced>1 cm |__| 0=no, 1=yes

[DISPSPEC] If SEEDDISPLACED =1: Specify [FREE TEXT]

[POSTVOLSKIN] minimal distance skin to POSTVOL |__|__|__|__| mm

[POSTISOSKIN] distance between CTV isocenter and skin |__|__|__|__| mm

Group: DVH parameters on CT

[POSTV100] post-implant V100 |__|__|__|__| %

[POSTV200] post-implant V200 |__|__|__|__| %

[POSTD90VOL] post-implant D90 of skin |__|__|__|__| cc
A MULTICENTER RANDOMIZED CONTROLLED TRIAL TESTING HYALURONIC ACID SPACER INJECTION FOR SKIN TOXICITY REDUCTION OF PERMANENT BREAST SEED IMPLANT (PBSI)

| POSTSK90 | post-implant skin isodose >90% over 1cm² | __ | 0=no, 1=yes |
| POSTD02 | post-implant D0.2cc skin dose | __ |__|__|__| | Gy |
| POSTD005 | post-implant D0.05cc skin dose | __ |__|__|__| | Gy |

**Group: spacer measurements on CT at 2 months**

| CTSPACER | any spacer visible on CT | __ | 0=no, 1=yes |
| CTSPACMCR | spacer in mediocranial quadrant of skin projection | __ | 0=no, 1=yes |
| CTSPACMCA | spacer in mediocaudal quadrant of skin projection | __ | 0=no, 1=yes |
| CTSPACLCA | spacer in laterocaudal quadrant of skin projection | __ | 0=no, 1=yes |
| CTSPACLCR | spacer in laterocranial quadrant of skin projection | __ | 0=no, 1=yes |

IF SPACER=1:

| CTSPACVOL | Volume of spacer on CT | __ |__|__|__| cc |
| CTSPATRANCEN | mid spacer thickness central transversal plane on CT |__|__|__|__| mm |
| CTSPATRANCRA | mid spacer thickness cranial transversal plane on CT |__|__|__|__| mm |
| CTSPATRANCAU | mid spacer thickness caudal transversal plane on CT |__|__|__|__| mm |
| CTSPASAGCEN | mid spacer thickness central saggital plane on CT |__|__|__|__| mm |
| CTSPASAGLAT | mid spacer thickness lateral saggital plane on CT |__|__|__|__| mm |
| CTSPASAGMED | mid spacer thickness medial saggital plane on CT |__|__|__|__| mm |

**Group: gafchromic film skin dose measurement**

| FILMUSED | gafchromic film used? | __ | 0=no, 1=yes |

IF FILMUSED=1 then
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[FILMMAX]  
maximum point skin dose on film  
|_|_|_|_| | | Gy

[FILMMAX1CM]  
maximum skin dose on film over at least 1cm²  
|_|_|_|_| | | Gy

[FILMAUC]  
AUC skin dose on film  
|_|_|_|_| | | Gy*cm

[FILMLOCDIST]  
Distance of max point skin dose on film from reference point (projected isocenter)  
|_|_|_|_| | | mm

[FILMLOCANG]  
Angle of max point skin dose on film from reference point (projected isocenter)  
|_|_|_| | | 0-360°

**CRF: Survival and recurrence**

[FUDATE]  
Date last known to be alive / date of death  
DD/MM/YYYY

[SURVIVAL]  
Survival status  
| | 1 = alive  
2 = death  
8 = lost to follow-up

[RADDATE]  
Date last mammography or CT-scan  
DD/MM/YYYY  []not done

[RECURR]  
Any recurrent disease (not yet reported)  
| | 0=no; 1=yes

*If yes, please complete the recurrence form*
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**CRF: Recurrence**

*Please report/update all recurrences until start of a new anticancer treatment*

<table>
<thead>
<tr>
<th>LREC</th>
<th>Local recurrence <em>(ipsilateral breast/chestwall)</em></th>
<th>0=no; 1=yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If LREC=1:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LRECDATE</td>
<td>Date of local recurrence</td>
</tr>
</tbody>
</table>
|      | LRECLOC | Localization of local recurrence | 1 = ipsilateral breast same quadrant  
2 = ipsilateral breast other quadrant  
3 = ipsilateral chest wall same quadrant  
4 = ipsilateral chest wall other quadrant  
5 = ipsilateral, location not documented |
|      | LRECHIS | Cyt/hist proof of recurrence | 0 = no; 1=yes |
|      | LRECPATH | Local recurrence of disease under study confirmed by pathologist | 0 = no, (probably) a new primary tumor  
1 = yes, (probably) a local recurrence  
2 = uncertain, specify |
|      | SLRECDIA | Comments on diagnosis | [FREE TEXT] |

<table>
<thead>
<tr>
<th>RREC</th>
<th>Regional recurrence <em>(ipsilateral lymphnodes/axilla)</em></th>
<th>0=no; 1=yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If RREC=1:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RRECDATE</td>
<td>Date of regional recurrence</td>
</tr>
</tbody>
</table>
|      | RRECLOC | Localization of regional recurrence | 1 = internal mammary chain  
2 = supraclavicular area  
3 = axilla |
|      | RRECHIS | Cyt/hist proof of regional recurrence | 0 = no; 1=yes |
|      | RRECPATH | Regional recurrence of disease under study confirmed by pathologist | 0 = no, (probably) other tumor |
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A MULTICENTER RANDOMIZED CONTROLLED TRIAL TESTING HYALURONIC ACID SPACER INJECTION FOR SKIN TOXICITY REDUCTION OF PERMANENT BREAST SEED IMPLANT (PBSI)

1 = yes, (probably) regional recurrence
2 = uncertain, specify

[SRRECDIA]  [FREE TEXT]

[DMET] Distant metastases  |__| 0=no; 1=yes

If DMET=1:

[DMETDATE] Date of distant metastases  DD/MM/ YYYY

[DMETHIS] Cyt/hist proof of distant metastases  |__| 0 = no; 1=yes

[DMETPATH] Distant metastases from disease under study confirmed by pathologist  |__| 0 = no, (probably) (from) other primary tumor
1 = yes, (probably) from disease under study
2 = uncertain, specify

[DMETDIA] Comments on diagnosis  [FREE TEXT]

[PLANRTM] Planned further treatment  |__| 0= none
1= mastectomy
2= radiotherapy
3= chemotherapy
4= targeted therapy
5= combination

(only first anticancer treatment after PBSI)

[SPLANRTM] Specify: __________________________  [FREE TEXT]

If locoregional or distant recurrence, follow-up local recurrence
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A MULTICENTER RANDOMIZED CONTROLLED TRIAL TESTING HYALURONIC ACID SPACER INJECTION FOR SKIN TOXICITY REDUCTION OF PERMANENT BREAST SEED IMPLANT (PBSI)

**CRF: Adverse Events 6 months and year 1-5**

<table>
<thead>
<tr>
<th><strong>[AEDATE]</strong></th>
<th>Date of AE assessment</th>
<th>DD / MM / YYYY</th>
</tr>
</thead>
</table>
| **[AETELEANG]** | Telangiectasia (Bentzen scale) | 0 =none  
1 = grade I – less than 1 cm²  
2 = grade II – 1 to 4 cm²  
3 = grade III – over 4 cm² |
| **[AETELEANGS]** | If AETELEANG >0: Was AE serious (SAE)? | 0 =no, 1=yes |
| **[AEPAIN]** | pain in breast | 0 = none  
1 = occasional and minimal, hypersensation, pruritus  
2 = intermittent and tolerable  
3 = persistent and intense  
4 = refractory and excruciating |
| **[AEPAINS]** | If AEPAIN >0: Was AE serious (SAE)? | 0 =no, 1=yes |
| **[AERED]** | Redness | 0 =none  
1 = yes but no effect on ADL  
2 = yes and effect on ADL |
| **[AEREDS]** | If AERED >0: Was AE serious (SAE)? | 0 =no, 1=yes |
| **[AEPIGM]** | Pigmentation | 0 = none  
1 = transitory, slight  
2 = permanent, marked |
| **[AEPIGMS]** | If AEPIGM >0: Was AE serious (SAE)? | 0 =no, 1=yes |
| **[AESKININD]** | Skin induration | 0 = none  
1 = Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up) |
A MULTICENTER RANDOMIZED CONTROLLED TRIAL TESTING HYALURONIC ACID SPACER INJECTION FOR SKIN TOXICITY REDUCTION OF PERMANENT BREAST SEED IMPLANT (PBSI)

2 = Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL
3 = Severe induration, unable to slide or pinch skin; limiting self-care ADL
4 = Generalized

[AESKININDS] If AESKIND >0: Was AE serious(SAE)? | ___ | 0=no, 1=yes

[AESUBIND] Subcutaneous Induration | ___ | 0 = none
1 = slight induration and loss of subcutaneous fat
2 = moderate fibrosis but asymptomatic
3 = severe induration and loss of subcutaneous tissue; field contracture
4 = necrosis

[AESUBINDS] If AESUBIND >0: Was AE serious(SAE)? | ___ | 0=no, 1=yes

[OTHERAE] Any other RT (or spacer) induced AE? | ___ | 0=no; 1=yes

If OTHERAE=yes: Enter in grid/table (multiple entries possible):

- System organ Class (drop down list conform CTCAE4/MEDRA)
- AE term (drop down list conform CTCAE4/MEDRA)
- Worst grade observed since last AE evaluation (1-5)
- Serious: yes/no
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A MULTICENTER RANDOMIZED CONTROLLED TRIAL TESTING HYALURONIC ACID SPACER INJECTION FOR SKIN TOXICITY REDUCTION OF PERMANENT BREAST SEED IMPLANT (PBSI)

CRF: Off-study

[DOFF] Date off-study DD / MM / YYYY

[OFFREAS] Reason off-study | 1 = end of follow-up period, without recurrence
2 = recurrent disease
3 = start systemic/locoregional anti-cancer treatment/ breast surgery
4 = death
5 = patient withdrawal
6 = ineligibility
7 = other

[SPOFFREAS] Specify reason off-study [FREE TEXT]

If OFFREAS=3:

[CODEATH] Cause of death | 1 = Breast cancer
2 = Concurrent disease
3 = Treatment related toxicity
4 = Other

[SPCODEATH] Specify cause of death [FREE TEXT]

[SEEDMIGR] Any known seed migration? | 0=no; 1=yes

[MIGRSPEC] If SEEDMIGR=1: Specify [FREE TEXT]
CRF: Primary endpoint assessment (will initially be entered on paper CRF during clinical assessment, and entered in e-CRF later)

Date of assessment
DD / MM / YYYY

Physician who scored primary endpoint
_____________________________________

[TELEANG] Teleangiectasia (Bentzen)  |  [ ]  0 = none
|  [ ]  1 = grade I – less than 1cm2
|  [ ]  2 = grade II – 1 to 4 cm2
|  [ ]  3 = grade III – over 4 cm2

Evaluability of primary endpoint:  |  [ ]  0 = non-evaluable; 1 = evaluable

If non-evaluable, reason:  |  [ ]  Re-irradiation on ipsilateral breast/chestwall < 2 yrs post-treatment
|  [ ]  Re-surgery on ipsilateral breast/chestwall < 2 yrs post treatment
|  [ ]  Death < 2 yrs post treatment
|  [ ]  Lost to follow-up < 2 yrs post treatment
|  [ ]  other, specify

Specify  [FREE TEXT]