

# **Outline of the Non-Interventional Prospective Study:**

## **Title: Punctal Occlusion for the treatment of severe dry eyes in patients after allogeneic stem cell transplantation; a multicenter EBMT Non-Interventional Prospective Study of the CLWP and LEWP**

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### **Introduction**

After allogeneic stem cell transplantation patients may develop severe dry eyes, most of the times associated with chronic graft-versus-host-disease. Hypotheses for the etiology of dry eyes are lacrimal gland inflammation and destruction, and ocular surface inflammation. Standard therapies for dry eyes are topical lubricants that will relieve symptoms in some patients. However, in many patients, normal daily activities are impaired by the dry eye symptoms. Application of autologous serum eye drops or topical cyclosporine may relieve symptoms in some patients.<sup>1,2</sup>

For patients insufficiently responding to these treatments installation of punctal plugs may be helpful. These plugs, usually placed in the inferior nasolacrimal canaliculi only, occlude these canaliculi and thereby reduce the outlet of the few tear drops and increases the moistness of the outer eye. Two major types of plugs are on the market: Silicone Punctal Plugs and SmartPlugs. Silicone Punctal Plugs can be easily removed but have a disadvantageous high spontaneous loss rate. SmartPlugs, when correctly positioned, are wholly intracannicular. At room temperature SmartPlugs are solid, but become soft gel at body temperature and thereby fixated in the canniculus. The chance of dislocation is therefore lower but not absent.

Although common practice in some stem cell transplantation centers, no prospective study on the short- and long-term feasibility and efficacy of punctal occlusion has been performed in patients with dry eyes after allogeneic stem cell transplantation. We therefore propose a non interventional prospective study to provide the evidence and increase the awareness of this potentially beneficial therapy among physicians in the haematopoietic stem cell transplantation field.

### **Study Objective:**

To study in time the short- and long-term efficacy and feasibility of punctal plugs for severe dry eyes after allogeneic stem cell transplantation

### **Inclusion criteria:**

1. Diagnosis of dry eyes (with onset of > 3 months?) after alloSCT<sup>3\*</sup> and
2. eye symptom score  $\geq 2$  for at least two months since last adjustment in topical lubricants prescription\*\*
3. Availability of an ophthalmologist with experience in punctal occlusion
4. Patient age at transplant  $\geq 18$  year.

**Exclusion:**

1. active ocular infection or other past or present eye disease
2. prior punctal plug insertion
3. dry eyes before SCT
4. Sjögren's disease prior to SCT
5. use of contact lenses

**Data to collect:**

Data at entry, and at one, three, six and twelve months (when plugs are in situ for >1 month in case of silicone plugs):

1. days after alloSCT
2. concomitant use of systemic immunosuppressive therapy (from last assessment on)
3. *Subjective parameters*
  - a. 0-10 patient reported intensity scale of worst eye symptom (visual analogue scale symptoms score (VAS), according to NIH Consensus)\*\*\*<sup>4</sup>
  - b. type and average number of daily topical lubricant(s) medication (diminished use should not have resulted in worsening of symptoms)
    - i. not on a daily basis
    - ii. thrice daily or less
    - iii. 4-6 times/day
    - iv. >6 times/day
4. *Objective teardynamic parameters*
  - a. mean Schirmer's test of both eyes (according to NIH Consensus)<sup>4</sup>
  - b. tear film break-up time (TBUT; <5 sec. is abnormal)
5. *Objective corneal damage parameter*
  - a. standard fluorescein punctate staining (measuring ocular surface disease)\*\*\*\*<sup>5</sup>
6. complications of punctal plug insertion; of notice:
  - a. loss will not be judged as complication or failure in case of prompt replacement;
  - b. need for placement in upper nasolacrimal canaliculi is also not judged as complication or failure)
7. documentation of alternative treatment after punctal plug installation and reason:
  - a. repeated loss,
  - b. complication(s),
  - c. no effect,
  - d. other reason

Analysis at each evaluation time point:

1. Mean values of each parameter of whole group
2. Mean change of each parameter of whole group from start of treatment
3. Percentage of patients with clinically relevant (i.e. normalisation, >50% or 25-50%) improvement in
  - a. subjective parameters
    - i. VAS
    - ii. daily lubricants use
  - b. objective parameters
    - i. Schirmer's test } analysed as no, <25%, 25-50%
    - ii. TBUT } or >50% improvement
    - iii. standard fluorescein punctate staining (scale form 0 till 5)

**Number of patients: 50**

An interim analysis six months after inclusion of the last patient will be performed and published. The evaluation at twelve months may be submitted as a brief report, as we feel, but don't know, that six months follow-up will be enough to assess long-term efficacy.

Asterisks:

\* One or more of the following distinctive symptoms are needed:

distinctive: new onset of dry, gritty or painful eyes, cicatricial conjunctivitis, keratoconjunctivitis sicca or confluent areas of punctate keratopathy  
other features: photophobia, periorbital hyperpigmentation, blepharitis (erythema of the eyelids with erythema)

AND (obligatory) low Schirmer's test without anesthesia

- mean of both eyes  $\leq 5$  mm at 5 minutes, or
- mean values of 6-10 mm at 5 minutes in patients with sicca symptoms or new keratitis detected by slit lamp examination

Scoring of dry eyes according to NIH Consensus:<sup>3</sup>

Mean Schirmer's tear test (mm at 5 minutes)

- $> 10$
- 6-10
- $\leq 5$

\*\*Eye symptom score<sup>3</sup>

Score 0 no symptoms

Score 1 mild dry eye symptoms not affecting ADL (requiring eye drops  $\leq 3$  x per day) **OR** asymptomatic signs of sicca keratitis

Score 2 Moderate dry eye symptoms partially affecting ADL (requiring drops  $> 3$  x per day or punctal plugs, **WITHOUT** vision impairment)

Score 3 Severe dry eyes symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because ocular symptoms **OR** loss of vision caused by pseudomembranes or corneal ulceration

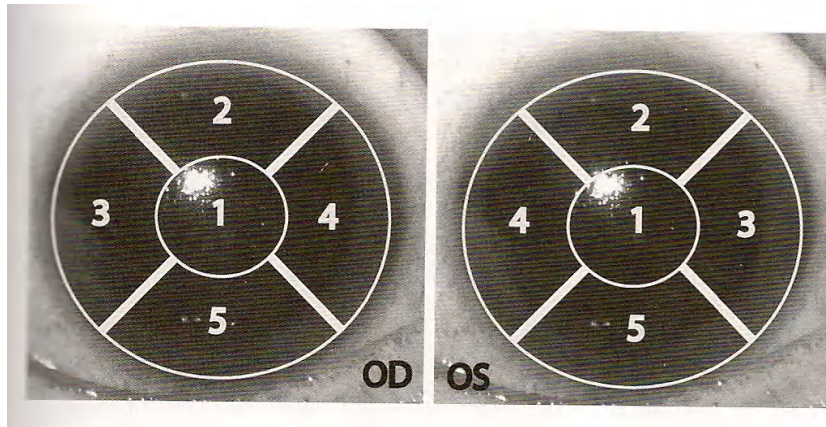
\*\*\* 0-10 patient reported intensity scale (VAS): chief ocular complaint at the time of the visit (10-cm lines are prepared, the patients write down his worst eye symptom and then checks a point on the line corresponding to the degree of this worst symptom)

chief ocular symptom:

symptom score:

0	1	2	3	4	5	6	7	8	9	10
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\*\*\*\* standard fluorescein punctate staining, scored according to "The National Eye Institute Corneal Grading System":



Each cornea is divided in five areas. Each area is scored for fluorescent staining (0 = absent, 1 = present; >3 is abnormal).

Fluorescent score OD:

Fluorescent Score OS:

## Literature

1. Ogawa Y, Okamoto S, Mori T, et al. Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. *Bone Marrow Transplant.* 2003;31:579-583.
2. Wang Y, Ogawa Y, Dogru M, et al. Ocular surface and tear functions after topical cyclosporine treatment in dry eye patients with chronic graft-versus-host disease. *Bone Marrow Transplant.* 2008;41:293-302.
3. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant.* 2005;11:945-956.
4. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant.* 2006;12:252-266.
5. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. *Clao J.* 1995;21:221-232.