



Sjögren
Abend

**2. Sjögren-
Abend**
Für Betroffene,
Angehörige &
Interessierte

Herzlich willkommen! Bienvenue ! Benvenuti! Bainvegni!

Klinik für Rheumatologie, Universitätsspital Zürich, 06.11.2023

Menü

1. Sjögren & Forschung – was sind die bisherigen Stolpersteine & wie ist der Zukunftsausblick?

Dr. med. Marco Sprecher

2. Trockener Mund – was hilft, wenn der Speichel wegbleibt?

Patricia Huber (Fachexpertin Pflege)

3. Sjögren & Zahngesundheit – was muss ich beachten, was bezahlt die Krankenkasse?

Dr. med. dent. Philipp Körner (Oberarzt, Klinik für Zahnerhaltung und Präventivzahnmedizin)



Sjögren & Forschung: Stolpersteine & Zukunftsausblick?

Dr. med. Marco Sprecher, Oberarzt Rheumatologie

Klinik für Rheumatologie, Universitätsspital Zürich, 06.11.2023

Disclosures

AbbVie (Forschungsförderpreis 2023)

Wie viele Medikamente, welche das Immunsystem beeinflussen, sind für Sjögren zugelassen?



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Bildquelle: Böack Eyed Peas © 2022



Dilemma



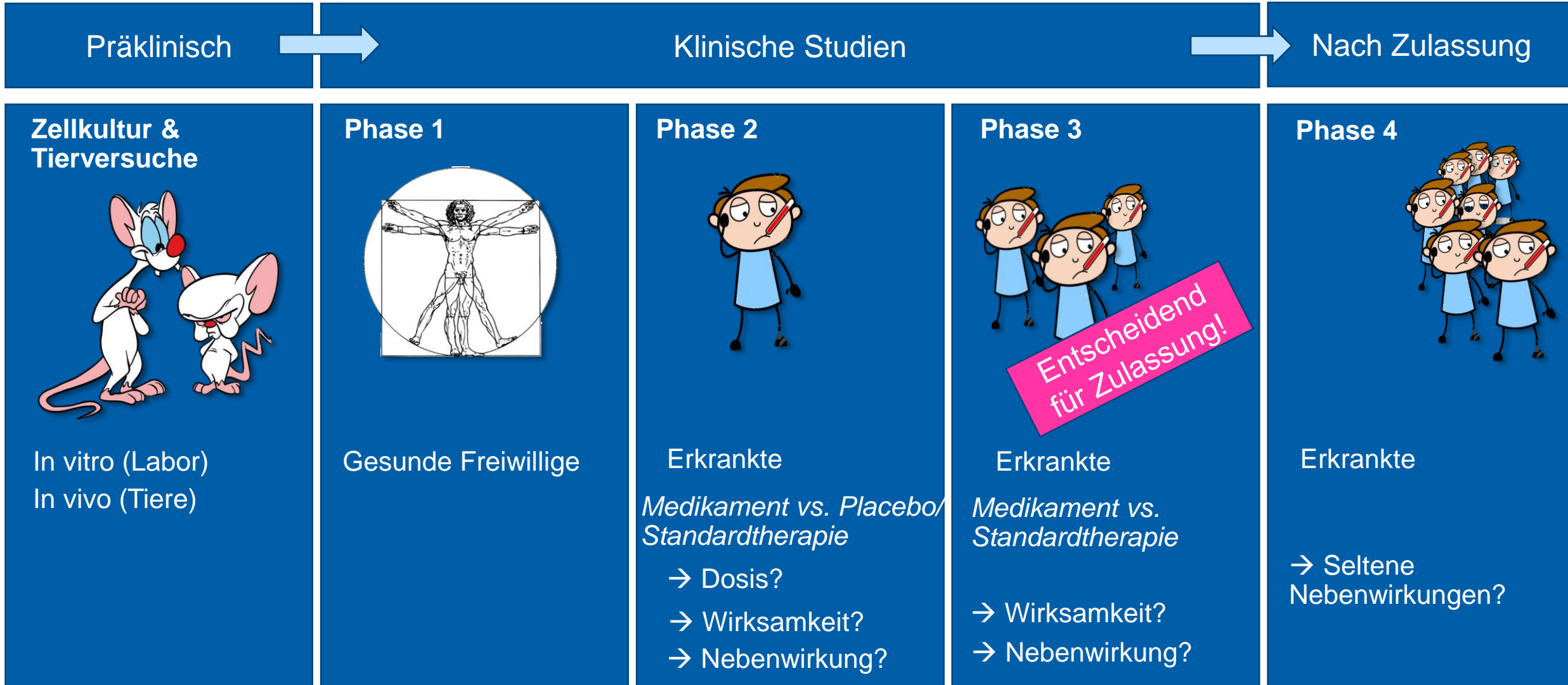
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Dilemma 1: Der lange Weg bis zur Zulassung



Bildquelle: Böack Eyed Peas © 2022

Dilemma 1: Der lange Weg zur Zulassung



Dilemma 1: Der lange Weg zur Zulassung

- «**Off-Label**»-Gebrauch von Medikamenten
 - Anwendung **ohne** Zulassung
 - Strenge Kriterien gemäss Artikel 71a-d KVV:
 - Krankheit mit tödlichem Verlauf oder schweren und chronischen gesundheitlichen Beeinträchtigungen
 - Hoher therapeutischer Nutzen
 - Keine andere wirksame zugelassene Behandlungsmethode

Dilemma 2: Wer?

Bildquelle: Böack Eyed Peas © 2022



Dilemma 1: Wer?

- **Schwierige** Rekrutierung
- Sehr viele haben eine **niedrige** Krankheitsaktivität
- Krankheit hat sehr viele **unterschiedliche** Gesichter



Dilemma 3: Was messen?



Bildquelle: Böack Eyed Peas © 2022

Dilemma 2: Was messen?

- Früher: Fokus auf **Sicca** und **patientenbezogene** Ergebnisse
 - Hohes Plazeboansprechen
 - Drüsenschäden irreversibel? Diagnose zu spät? Antikörper häufig Jahre vor Krankheit nachweisbar
- **Aktivitätsparameter** ESSDAI und ESSPRI:
 - ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index)
 - ESSPRI (EULAR Sjögren's Syndrome Patient Reported Index)

Dilemma 2: Was messen?

– ESSPRI (EULAR Sjögren's Syndrome Patient Reported Index)

1) How severe has your **dryness** been during the last 2 weeks ?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10	

2) How severe has your **fatigue** been during the last 2 weeks ?

No fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable fatigue
	0	1	2	3	4	5	6	7	8	9	10	

3) How severe has your **pain** (joint or muscular pains in your arms or legs) been during the last 2 weeks ?

No pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable pain
	0	1	2	3	4	5	6	7	8	9	10	

Quelle Bild: Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T, Bootsma H, Tzioufas A, Solans-Laqué R, Mandl T, Gottenberg JE, Hachulla E, Sivils KL, Ng WF, Fauchais AL, Bombardieri S, Valesini G, Bartoloni E, Saraux A, Tomsic M, Sumida T, Nishiyama S, Caporali R, Kruize AA, Vollenweider C, Ravaut P, Vitali C, Mariette X, Bowman SJ; EULAR Sjögren's Task Force. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis. 2015 May;74(5):859-66. doi: 10.1136/annrheumdis-2013-204615. Epub 2014 Jan 17. PMID: 24442883.

Dilemma 2: Was messen?

– ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index)

Domain	Proportion of patients with disease activity
Skin	4.2%
Pulmonary	14.4%
Renal	2.8%
Articular	18.6%
Muscular	3.3%
Peripheral neuropathy	9.6%
Central nervous system	2.0%
Glandular	12.1%
Constitutional	4.1%
Haematological	15.6%
Lymphadenopathy	2.4%
Biological	37.4%

Clinical involvement corresponding to each of these twelve domains is defined according to the ESSDAI (ref 6).
doi:10.1371/journal.pone.0059868.t002

- **Niedrige Aktivität:** <5 Punkte
- **Mittlere Aktivität:** 5-13 Punkte
- **Hohe Aktivität:** ≥14 Punkte

Dilemma 2: Was messen?

- **clinESSDAI** (EULAR Sjögren's Syndrome Disease Activity Index)

Domain	Proportion of patients with disease activity
Skin	4.2%
Pulmonary	14.4%
Renal	2.8%
Articular	18.6%
Muscular	3.3%
Peripheral neuropathy	9.6%
Central nervous system	2.0%
Glandular	12.1%
Constitutional	4.1%
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Lymphadenopathy	2.4%
Biological	37.4%

Clinical involvement corresponding to each of these twelve domains is defined according to the ESSDAI (ref 6).
doi:10.1371/journal.pone.0059868.t002

Dilemma 2: Was messen?

– STAR («Sjögren's Tool for Assessing Response»)

Candidate STAR

Domain	Point	Definition of response
Systemic activity	3	Decrease of ≥ 3 in clinESSDAI.
Patient-reported outcome	3	Decrease of ≥ 1 point or $\geq 15\%$ in ESSPRI.
Lachrymal gland function (assessed by Schirmer's test or ocular staining score)	1	Schirmer's test: If abnormal score at baseline: increase ≥ 5 mm from baseline. If normal score at baseline: no change to abnormal. <i>Or</i> Ocular staining score: If abnormal score at baseline: decrease of ≥ 2 points from baseline. If normal score at baseline: no change to abnormal.
Salivary gland function (assessed by unstimulated whole salivary flow or ultrasound)	1	Unstimulated whole salivary flow: If score is >0 at baseline: increase of $\geq 25\%$ from baseline. If score is 0 at baseline: any increase from baseline. <i>Or</i> Ultrasound: Decrease of $\geq 25\%$ in total Hocevar score from baseline.
Biological (assessed by serum IgG or RF level)	1	Serum IgG level: decrease of $\geq 10\%$. <i>Or</i> RF level: decrease of $\geq 25\%$.
Candidate STAR responder	≥ 5 points	

- For ocular tests, Schirmer's test should be performed without anaesthesia and is considered abnormal if <5 mm. Ocular staining score is considered abnormal if score is ≥ 3 . The mean of both eyes was used for calculation.
- Total RF or RF-IgM was measured in IU/mL.
- For unstimulated whole salivary flow, we recommend establishing an SOP for each future trial using STAR. The SOP should specify if the collection should be done over 5 or 15 min (both are possible but one option should be selected for each trial and applied to all patients), and should specify that patients should not eat, drink or smoke for 60 min before the collection, should not take secretagogue morning dose, and should perform the collection in the morning and at a fixed time.
- ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index ; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; RF, rheumatoid factor; SOP, standard operating procedures; STAR, Sjögren's Tool for Assessing Response.

- clinESSDAI
- ESSPRI
- Schirmertest
- Speicheltest
- Rheumafaktor/ Immunglobulin G

≥ 5 Punkte?

Beispiele aus der Forschung:

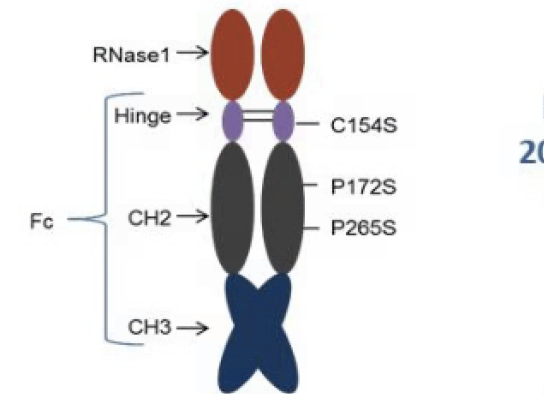
- RSLV-132
- Inalumab
- Stammzellen aus Fettgewebe

RSLV-132

Bildquelle: Böack Eyed Peas © 2022

RSLV-132 (Posada J et al.: Arthritis Rheumatol 2021; 73: 143-50)

- RSLV-132: RNase-Fc-Fusionsprotein
- Bei Sjögren zirkulierten Auto-Antikörper, welche RNA-Autoantigene (statt Viruspartikel) präsentieren & dadurch eine Entzündung provozieren
- RSLV-132 eliminiert die RNA-Autoantigene



RSLV-132 is a first-in-class biologic targeting the initiation of type I interferon – a fusion protein of RNase I and IgG1 Fc

RSLV-132

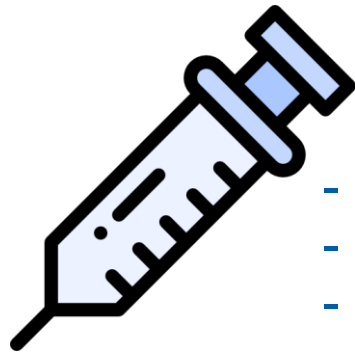
- Posada J, Valadkhan S, Burge D, Davies K, Tarn J, Casement J, Jobling K, Gallagher P, Wilson D, Barone F, Fisher BA, Ng WF. **Improvement of Severe Fatigue Following Nuclease Therapy in Patients With Primary Sjögren's Syndrome: A Randomized Clinical Trial.** *Arthritis Rheumatol.* 2021 Jan;73(1):143-150. doi: 10.1002/art.41489. Epub 2020 Nov 22. PMID: 32798283; PMCID: PMC7839752.
 - Randomisierte, doppelblinde, placebokontrollierte Studie
 - Primärer Endpunkt: Messung der Genexpression durch Interferon

RSLV-132



30 x Sjögren

SSA/SSB +



- **Woche 0**
- **Woche 1**
- **Dann alle 2
Wochen für 12
Wochen**

Placebo

Bildquelle:
Menschen: TSP/ freepik, abgerufen am 01.11.23 auf <https://www.tagesspiegel.de/wissen/bald-800000000-bewohner-fur-wie-viele-menschen-reicht-die-erde-noch-8859097.html>
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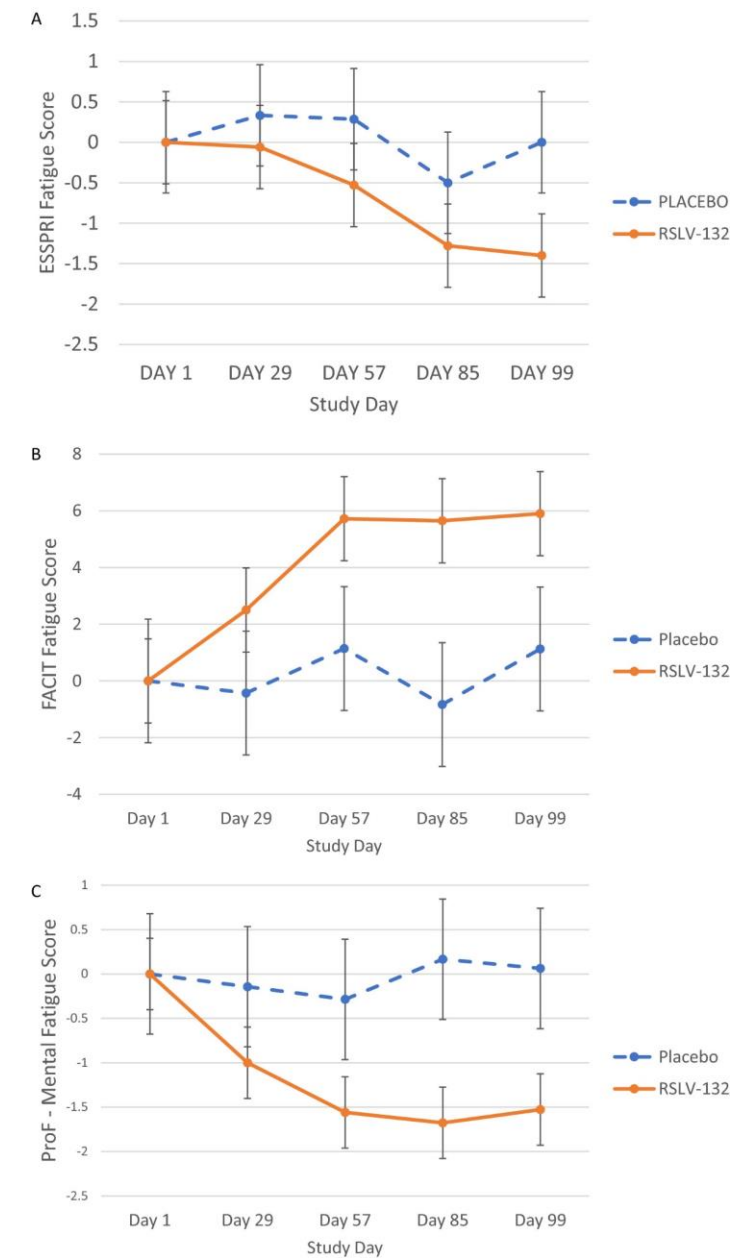
RSLV-132 (Posada J et al.: Arthritis Rheumatol 2021; 73: 143-50)

- Resultate:
 - RSLV-132-Gruppe mit einer **erhöhten Aufregulierung** ausgewählter Interferon-induzierbarer Gene (im Vgl. zu Placebo) nach 99 Tagen
 - ESSDAI blieb bei RSLV-132 stabil, während bei Placebo von 5 auf 2.9 sank (2 Placebo-Ausstiege)
 - ESSPRI -1.2 Punkte bei RSLV-132, bei Placebo -0.54

RSLV-132 (Posada J et al.: Arthritis Rheumatol 2021; 73: 143-50)

– Resultate:

- ESSPRI-Fatigue-Score: -1.4 Punkte (RSLV-132) vs. 0 Punkte (Placebo)
- Ähnlicher Effekt in 2 anderen subjektiven Fatigue-Scores
- Nebenwirkungsprofil in beiden Gruppen gleich (keine schweren Infektionen oder Infusionsreaktionen)



RSLV-132

Quintessenz, die

Wortart: **Substantiv, feminin**

Gebrauch: **bildungssprachlich**

Häufigkeit: ■■■■■

DUDEN

Quint·es·senz

Substantiv [die] geh.

das, was sich als das Wesentliche einer Sache herausstellt.
"die Quintessenz des Buches/der Diskussion"

RSLV-132



- Quintessenz der Studie:
 - Unerwartete Erhöhung der Expression von Interferon-induzierbaren Genen
 - Wirkung auf Müdigkeit (ähnlich wie frühere Studien, welche umgekehrten Zusammenhang zwischen Zytokinen (Entzündungsstoffe) & Müdigkeit aufzeigten)

→ Grösse Studien zur Bestätigung notwendig

Ianalumab

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Ianalumab

- Monoklonaler Antikörper gegen BAFF-Rezeptor (BAFF = «B-Zell-aktivierender Faktor»)
→ B-Zellen werden abgebaut

Ianalumab

- Bowman SJ, Fox R, Dörner T, Mariette X, Papas A, Grader-Beck T, Fisher BA, Barcelos F, De Vita S, Schulze-Koops H, Moots RJ, Junge G, Woznicki JN, Sopala MA, Luo WL, Hueber W. **Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial.** Lancet. 2022 Jan 8;399(10320):161-171. doi: 10.1016/S0140-6736(21)02251-0. Epub 2021 Nov 30. PMID: 34861168.

THE LANCET

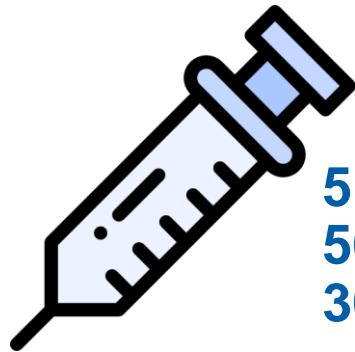
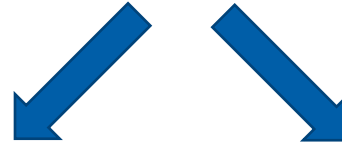
Ianalumab



190 x Sjögren

18-75 J.

Mittel bis stark aktiv



**5 mg
50 mg
300 mg s.c.**

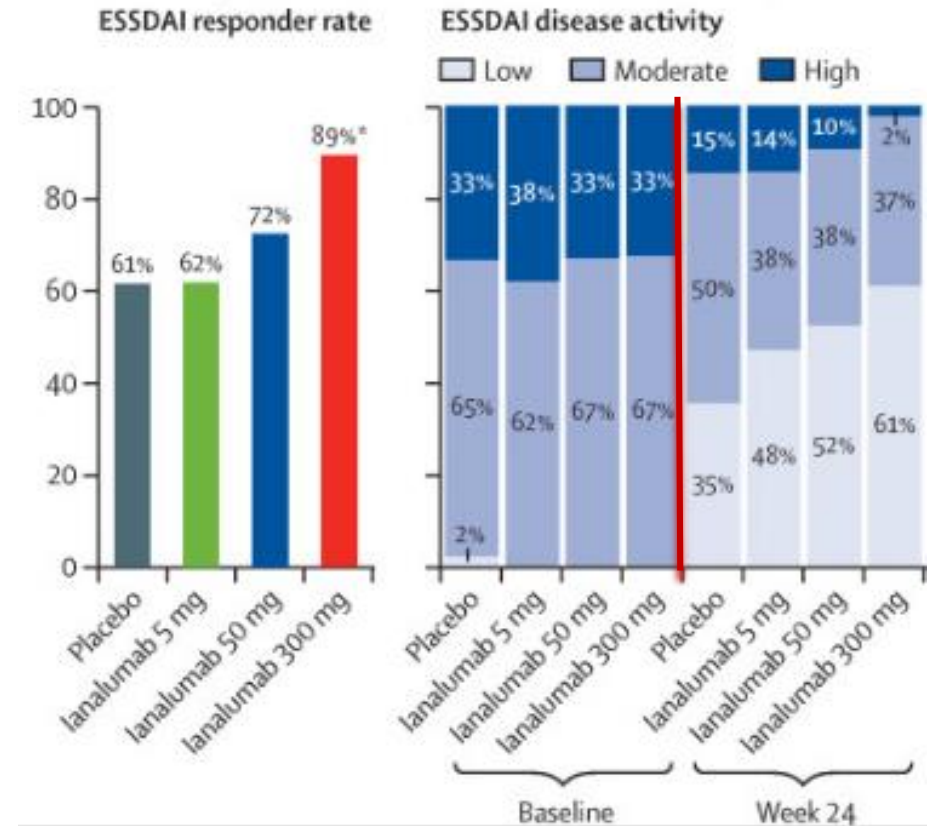
Placebo

Bildquelle:
Menschen: TSP/ freepik, abgerufen am 01.11.23 auf <https://www.tagesspiegel.de/wissen/bald-800000000-bewohner-fur-wie-viele-menschen-reicht-die-erde-noch-8859097.html>
Spritze: Flaticon, abgerufen am 01.11.23 auf https://www.flaticon.com/de/kostenloses-icon/spritze_898626

Ianalumab

- Primärer Endpunkt:
 - Unterschied in der Krankheitsaktivität (ESSDAI) nach 24 Wochen
- Sekundärer Endpunkt:
 - Speichelflussrate nach 24 Wochen
→ + 0.2 ml/Min. (300 mg)

F ESSDAI responder rate and distribution of disease activity at week 24



Ianalumab

- Nebenwirkungen

	Placebo (n=49)	Ianalumab 5 mg (n=47)	Ianalumab 50 mg (n=47)	Ianalumab 300 mg (n=47)
Patients with any adverse events	41 (84%)	40 (85%)	39 (83%)	44 (94%)
Patients with any serious adverse events	4 (8%)	0	1 (2%)	2 (4%)
Patients discontinued for any adverse events	0	2 (4%)	2 (4%)	0

Entzündung Blinddarmfortsatz & Eierstöcke

(Gallensteinentzündung)
(Taubheit)

lanalumab

Quintessenz, die

Wortart: **Substantiv, feminin**

Gebrauch: **bildungssprachlich**

Häufigkeit: ■■■■■

DUDEN

Quint·es·senz

Substantiv [die] geh.

das, was sich als das Wesentliche einer Sache herausstellt.
"die Quintessenz des Buches/der Diskussion"

Ianalumab



- Quintessenz der Studie:
 - Dosisabhängige Wirkung auf die **Krankheitsaktivität** nach 24 Wochen
 - Insgesamt **gut toleriert & sicher** (keine erhöhte Infektgefahr)
 - **Erste** grosse, randomisierte, kontrollierte Sjögren-Studie, welche den primären Endpunkt erreicht hat

→ Grösse Studien zur Bestätigung notwendig (Phase-3-Studie in Rekrutierung)

Stammzellen aus Fettgewebe

Stammzellen aus Fettgewebe

- Li F, Lu J, Shi X, Li D, Zhou T, Jiang T, Wang S. **Effect of adipose tissue-derived stem cells therapy on clinical response in patients with primary Sjogren's syndrome.** Sci Rep. 2023 Aug 19;13(1):13521. doi: 10.1038/s41598-023-40802-5. PMID: 37598237; PMCID: PMC10439962.

scientific reports

OPEN **Effect of adipose tissue-derived stem cells therapy on clinical response in patients with primary Sjogren's syndrome**

Fangfang Li¹, Junhui Lu², Xinlian Shi³, Dongya Li³, Tingting Zhou³, Tianqi Jiang³ & Shengming Wang³✉

The purpose of this trial was to clinically assess the effect and safety of Adipose Tissue-derived Stem Cells (ADSCs) treatment on primary Sjogren's Syndrome (pSS). In this 6-month randomized, triple-blind, placebo-controlled clinical trial, pSS patients were randomly assigned to two groups. After demographic characteristics and clinical examination were achieved, local injection of ADSCs into bilateral glands was performed with patients in ADSCs group (n = 35) and placebo solution was used for another group (n = 39) at three time points. Patients were followed up at 1-, 3- and 6-month. At each visit, studies of clinical and laboratory outcomes, as well as subjective symptoms, were conducted. A total of 74 subjects who met the including criteria were allocated in two groups and eventually 64 subjects (86.5%) completed the treatments and the follow-up assessments. Secretion of salivary and lacrimal glands were significantly improved in 3-month ($P < 0.05$). A great improvement of European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) was found after ADSCs treatment with intergroup comparison from baseline to follow-up ($P < 0.05$). There is also a significant difference of European Alliance of Associations for Rheumatology SS Patient Reported Index (ESSPRI) between the two groups in the follow-up ($P < 0.05$). A significant abatement of IgG, IgM, C3, C4 and ESR between two groups was observed in part of follow-up time points ($P < 0.05$). The ADSCs therapy can provide relief of oral and eye's dryness in our trial in a short time and has potential improvement of subjective and systemic syndromes of pSS.

Sjogren's syndrome (SS) is a systemic autoimmune chronic disease characterized by marked exocrine glandular dysfunction such as salivary and lacrimal glands, presenting a persistent dryness of mouth and eyes¹. In some areas like China, the prevalence can reach as high as 5.6%, with a female-to-male ratio of 9:1 due to an association with hormonal changes². SS process can also extend to several other organs and tissues including lungs, kidneys, blood vessels, skin, and nervous system, which may impair patients' quality of life. pSS occurs in the absence of an associated systemic autoimmune disease, whereas secondary SS (sSS) occurs secondary to other autoimmune disorder, such as systemic lupus erythematosus, rheumatoid arthritis, interstitial lung disease or interstitial nephritis³. As a rule, sSS is an accompanying disease while the main autoimmune disease is the determinant of treatment decision. Consequently, this trial focuses on treatment outcomes in pSS.

pSS has a very heterogeneous clinical presentations and the etiology has not been fully elucidated. Infiltration of a large number of lymphocytes and expression of various cytokines in the exocrine glands were detected in animal models⁴. Therefore, the primary of therapy are limited to palliation of symptoms and prevention of complications. Systemic treatment is often ineffective and can result in major side effects. At present, local treatments such as artificial tears or oral sprays rely on patients' compliance. The secretagogues including pilocarpine and cevimeline have been specifically approved for the treatment of xerostomia⁵. In recent reports, the properties of different monoclonal antibodies against B and T cells have been investigated widely⁶. However, these marketed medicines were reported to potentially induce lymphoma-gastrointestinal symptoms or cardiovascular and

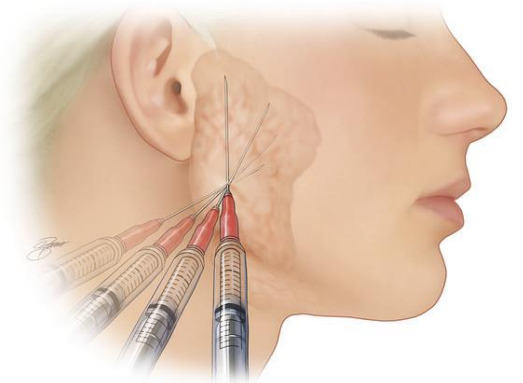
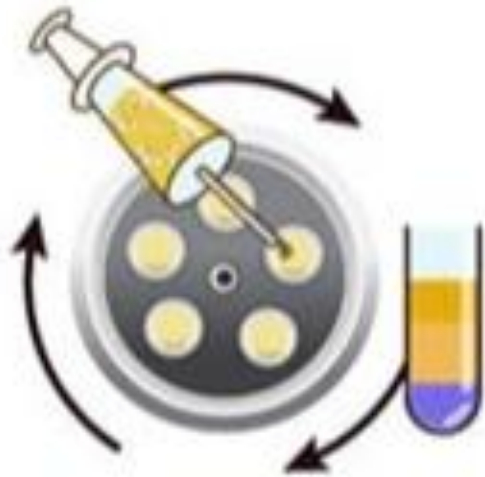
¹Department of Ophthalmology, The Affiliated Hua'an Hospital of Xuzhou Medical University, Hua'an City, China. ²Department of Rheumatology, The Affiliated Hua'an Hospital of Xuzhou Medical University, Hua'an City, China. ³Department of Stomatology, The Affiliated Hua'an Hospital of Xuzhou Medical University, Hua'an City, China. [✉]email: 365646113@qq.com

Scientific Reports | (2023) 13:13521 | <https://doi.org/10.1038/s41598-023-40802-5> nature portfolio 1

Stammzellen aus Fettgewebe

– Prinzip:

- Stammzellen aus dem Fettgewebe (differenzierte mesenchymale Stammzellen) haben die Fähigkeit zur multilinearen **Reifung**, **Entzündungshemmung**, Veränderung des **Immunsystems** und **Selbsterneuerung**



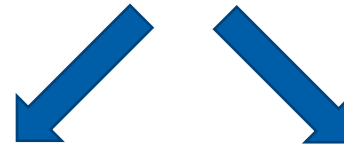
Stammzellen



74 x Sjögren

Neudiagnose

Keine Therapie



Woche 0
Woche 2
Woche 4

Placebo

6 Monate

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Spritze: Flaticon, abgerufen am 01.11.23 auf https://www.flaticon.com/de/kostenloses-icon/spritze_898626

Stammzellen aus Fettgewebe

– Resultate

- Effekt nach 3 Monaten (nicht nach 1 Monat)
- Speichel nimmt nach 6 Monaten ab
- Effekt auf Tränen länger

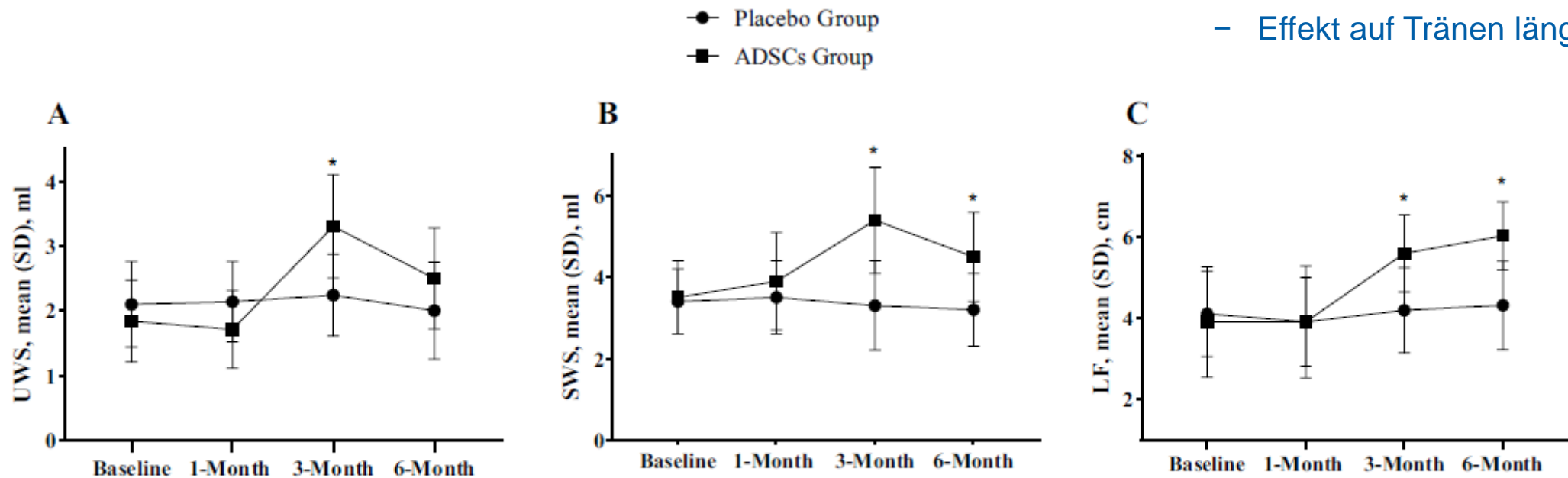


Figure 3. Clinical examination at baseline and each follow-ups in the two groups. *Significantly enhanced ADSCs group compared to placebo group. UWS: unstimulated whole saliva; SWS: Stimulated whole saliva; LF: lacrimal flow.

Stammzellen aus Fettgewebe

– Resultate

– Effekt bereits nach 1 Monat und anhaltend bis Monat 6

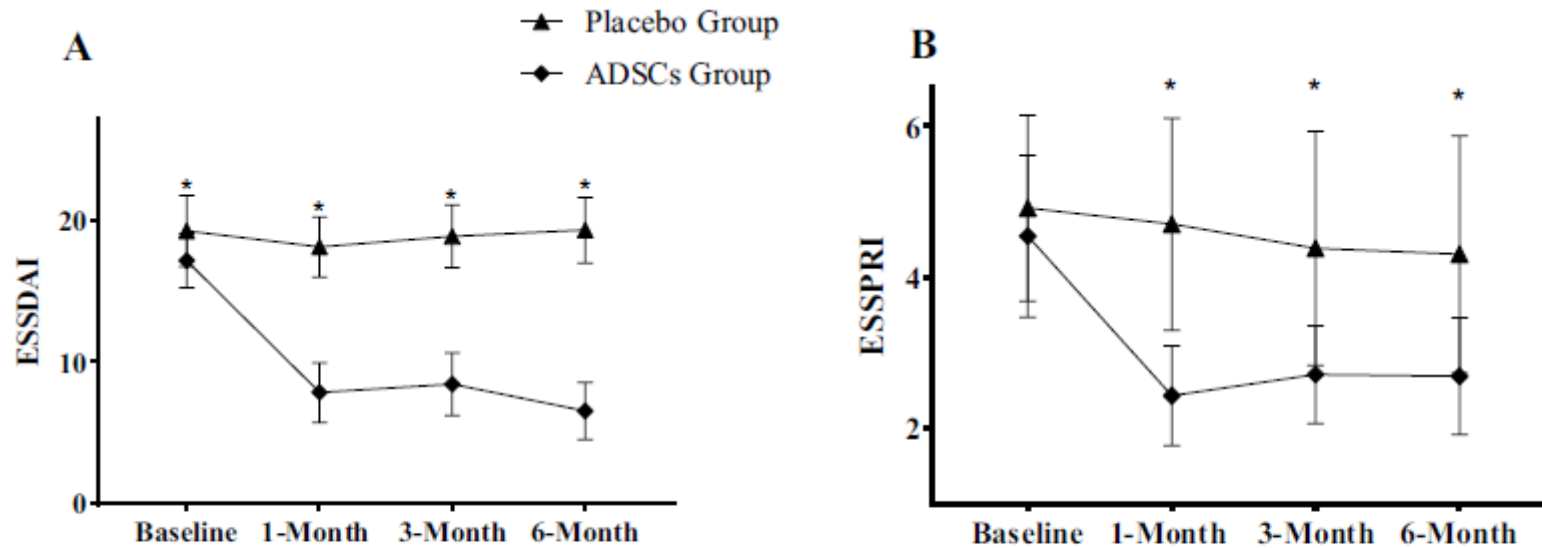


Figure 4. (A, B) Disease activity assessment at baseline and each follow-ups in the two groups. * Significantly reduction in ADSCs Groups compared to Placebo Group; ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI: European Alliance of Associations for Rheumatology SS patient Reported Index.

Stammzellen aus Fettgewebe

- Kommentar:
 - Studie aus 1 einzigen Klinik
 - Sehr hohe Krankheitsaktivität
 - Han-Chines*innen, 20.7 % Männer

	Placebo	ADSCs	t/χ^2	P
Current systemic involvement, No. (%)	8 (27.6)	11 (31.4)	$\chi^2=0.11$	0.79
Disease activity indexes				
ESSDAI, No. (%)	19.2 (2.5)	17.1 (4.9)	$t=3.82$	0.00
ESSPRI, No. (%)	4.9 (1.2)	4.5 (1.1)	$t=1.74$	0.15



ESSDAI:

- **Niedrige Aktivität:** <5 Punkte
- **Mittlere Aktivität:** 5-13 Punkte
- **Hohe Aktivität:** ≥14 Punkte

Stammzellen aus Fettgewebe

Quintessenz, die

Wortart: **Substantiv, feminin**

Gebrauch: **bildungssprachlich**

Häufigkeit: ■■■■■

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"die Quintessenz des Buches/der Diskussion"

Stammzellen aus Fettgewebe



- Quintessenz der Studie:
 - Positives Signal für neue Behandlungsstrategie
 - Keine Nebenwirkungen (ausser 2x Juckreiz an Injektionsstelle)

→ Internationale grössere Studien zur Wirksamkeit & Sicherheit notwendig



Danke! Merci! Grazie! Grazia!

- **Feedback-Formular ausfüllen!**
- **Newsletter: sjogren@usz.ch**
- **Nächster Sjögren-Abend: 11.03.24, 18 Uhr, USZ**