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Efficacy and safety of autologous adipose-derived stem cells in subjects with moderate to severe atopic dermatitis: a multicenter, randomized, single-blind, placebo-controlled, phase 2 trial

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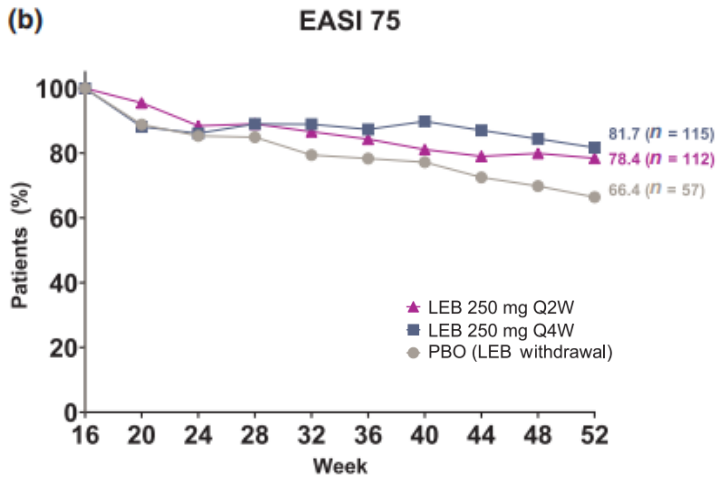
Objective: This study aimed to assess the efficacy and safety of adipose tissue-derived MSC (AdMSC) in moderate to severe AD refractory to conventional treatments.

Takeaway Message: AdMSC therapy improved moderate to severe AD, offering a promising treatment option with potential applications in chronic inflammatory diseases.

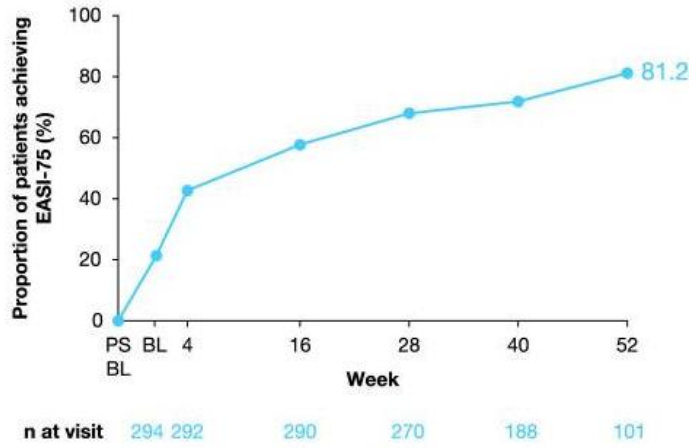
A declaration of Conflict of Interest for the authors: None declared.

Unmet needs - Atopic Dermatitis (AD)

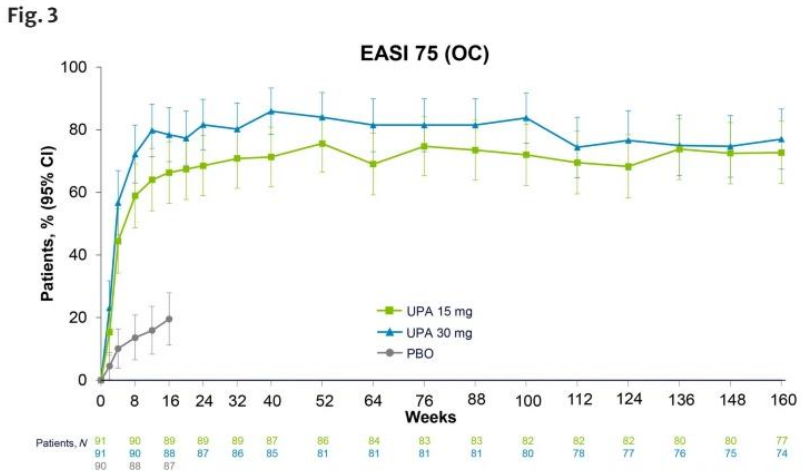
- Atopic dermatitis (AD) is a recurrent, chronic inflammatory skin condition characterized by intense itching and a spectrum of phenotypes.
- The severity of AD dictates the treatment approach, with severe cases often requiring biologics and systemic immunosuppressants such as steroids, and JAK inhibitors.
- However, many patients do not achieve complete or near-complete remission and experience side effects from the biologics and JAK inhibitors.



Lebrikizumab (anti-IL-13)



Dupliumab (anti-IL-4Rα)



Abrocitinib (JAK1 inhibitor)

There is a need for new therapeutic options for AD due to unmet needs.

Blauvelt A et al., *Br J Dermatol*, 2023; 188(6):740-748.
Blauvelt A et al., *Am J Clin Dermatol*, 2022; 23(3):365-383.
Katoh N et al., *Dermatol Ther (Heidelb)*, 2023; 13(1):221-234.

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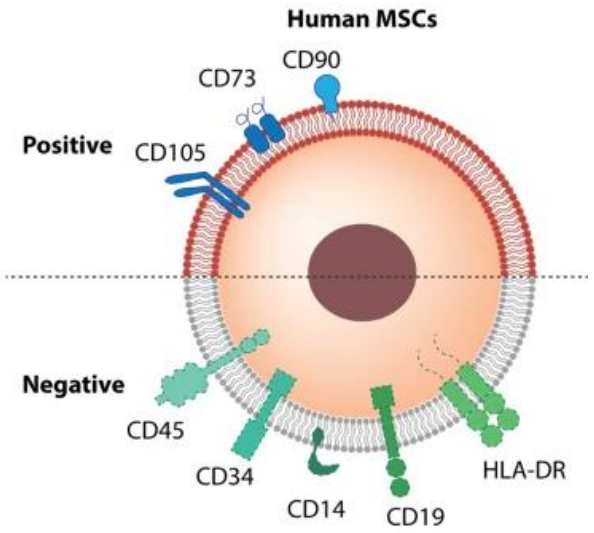
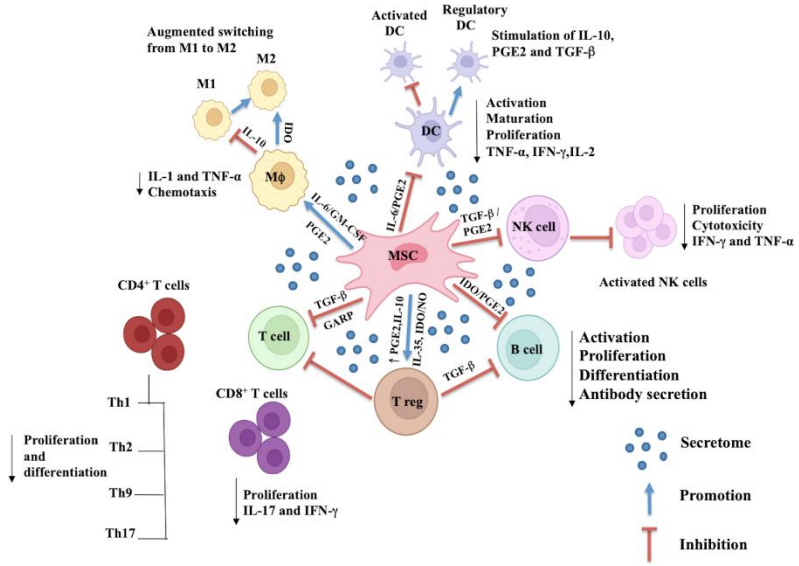
What is Mesenchymal stem cells (MSC)?

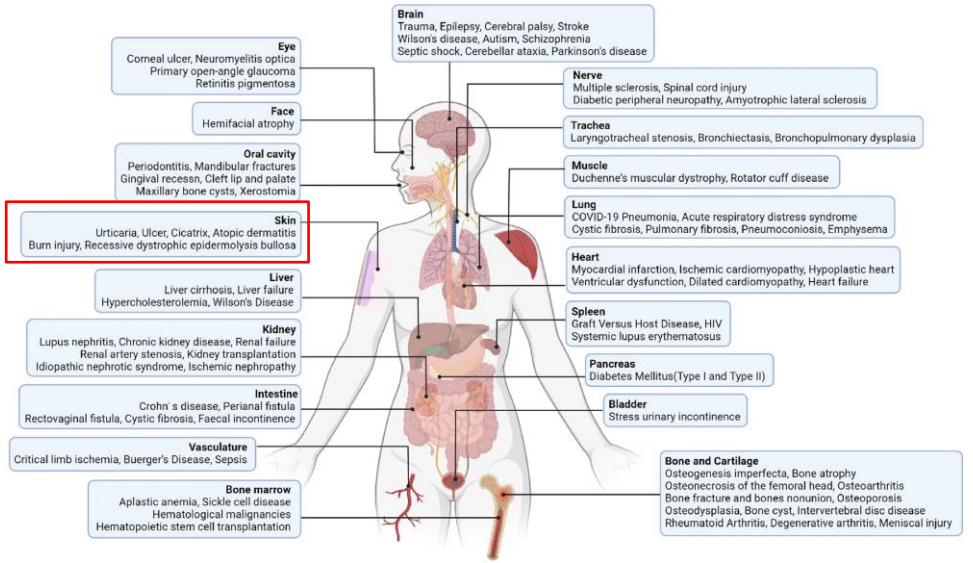
- Mesenchymal stem cells (MSCs), multipotent stem cells obtainable from various tissues including umbilical cord, bone marrow, and adipose tissue, are distinguished by cell-surface markers. (such as CD73, CD90, and CD105)
- MSCs exert a suppressive effect on the activation of immune cells such as T cells, B cells, dendritic cells, and natural killer cells, through interactions with the innate and adaptive immune systems.
- Their unique characteristics make MSCs an attractive option for treating chronic inflammatory disease such as AD.



Several markers of MSC



Immunomodulatory effects of MSC



MSC-based clinical trials

Qin L et al., *Acta Pharmacol Sin*, 2023; 44(2):268-287.
Devi A et al., *Cell Mol Immunol*, 2023; 20(6):600-612.
Han Y et al., *Signal Transduct Target Ther*, 2022; 21;7(1):92.

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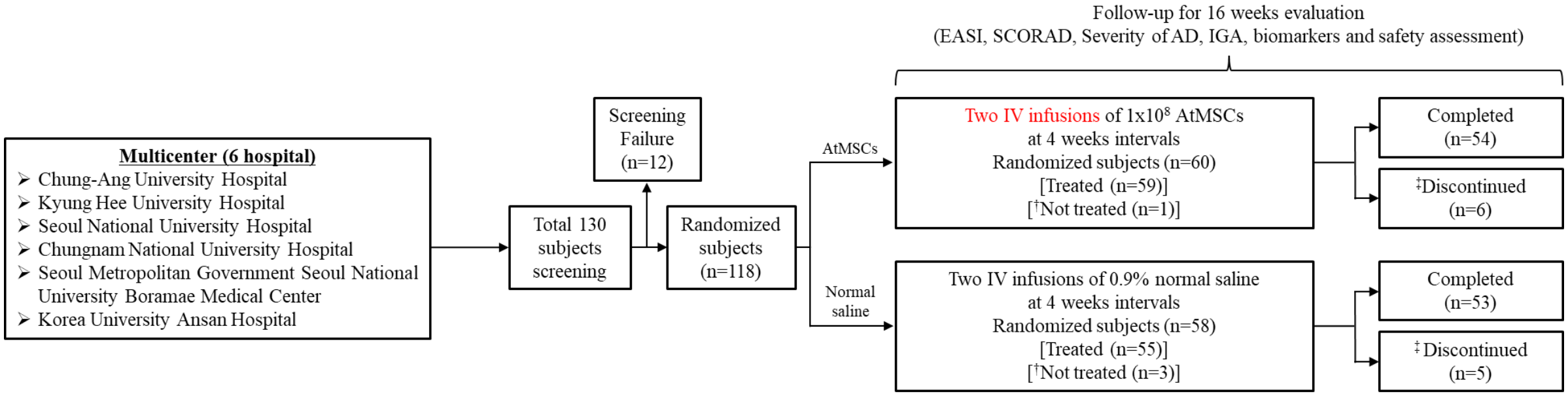
Summary of the disposition of study subjects in clinical trial.

AtMSC :autologous adipose tissue-derived MSC



†'Not treated' refers to the group that did not receive infusions of either AtMSC or normal saline.

‡'Discontinued' refers to the combined group consisting of those who were in the 'Not treated' group and those who discontinued AtMSC or normal saline infusions.

The effects of AtMSC treatment were observed over 16 weeks.

Unpublished Data

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Summary of the Key inclusion, exclusion criteria and demographics.

Key inclusion and exclusion criteria

Key Inclusion Criteria	
✓	Males and females aged 19 to 70 years.
✓	Patients with AD that meet the Hanifin and Rajka diagnostic criteria.
✓	Patients with subacute and chronic AD symptoms that have persisted for at least 6 months.
✓	Patients with moderate to severe AD. (SCORAD score > 20).
✓	Patients who have voluntarily given written consent to participate in this clinical trial.

Key Exclusion Criteria	
×	Patients with systemic infections or carriers of HIV, HBV, or HCV.
×	Patients with uncontrolled asthma or serious adverse reactions to stem cell therapies.
×	Women who are pregnant, breastfeeding, or not using contraception during the trial.
×	Patients unable to stop medications that may affect the trial, including steroids, antibiotics, phototherapy, and immunosuppressants, one month before the trial drug administration.
×	Significant renal or liver dysfunction, as indicated by screening tests.

Baseline of age, sex, EASI and IGA score

	Treatment group (N = 59)	Placebo group (N = 55)
Age (years)		
N	59	55
Mean (SD)	30.61(9.93)	31.85(11.61)
Median	28.00	28.00
Min, Max	19.00, 68.00	19.00, 69.00
P-value [1]	0.74[d]	
Sex, n (%)		
Male	41(69.5)	41(74.6)
Female	18(30.5)	14(25.5)
P-value [1]	0.55[a]	
EASI score (Baseline)		
N	59	55
Mean (SD)	19.4(7.9)	19.7(9.0)
Median	18.8	18.3
Min, Max	5.1, 41.1	6.4, 51.8
P-value [1]	.90[d]	
IGA score (Baseline)		
N	59	55
Mean (SD)	3.3(0.8)	3.3(0.7)
Median	3.00	3.0
Min, Max	2.00, 5.00	2.00, 4.00
P-value [1]	.96[d]	

SD = Standard Deviation, Min = Minimum, Max = Maximum

1] P-value for comparisons between Placebo group and Treatment group: [a] Chi-square test [b] Fisher's exact test [c] Two-sample t-test [d] Wilcoxon's rank sum test.

Unpublished Data

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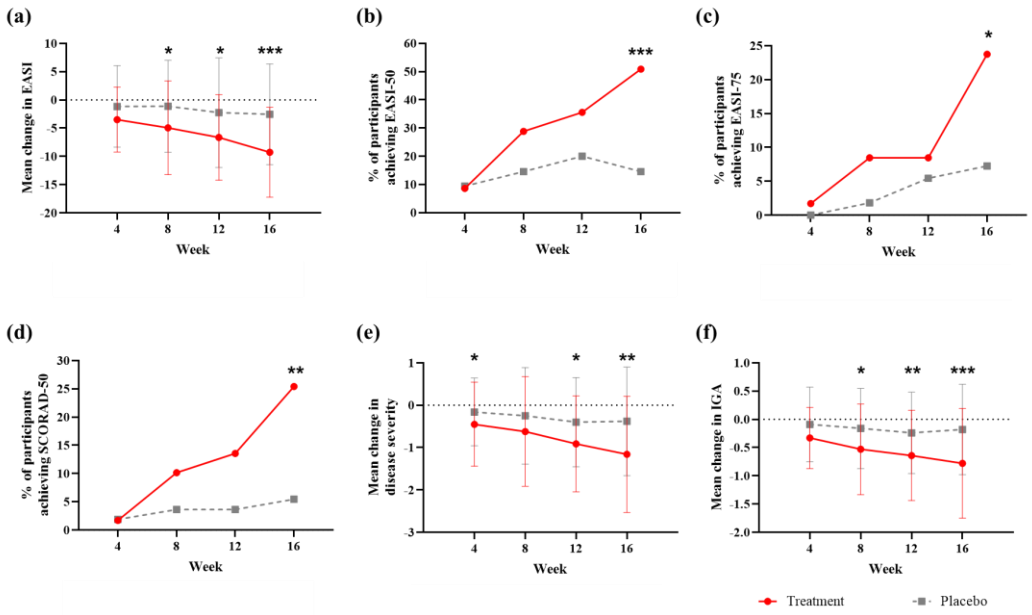
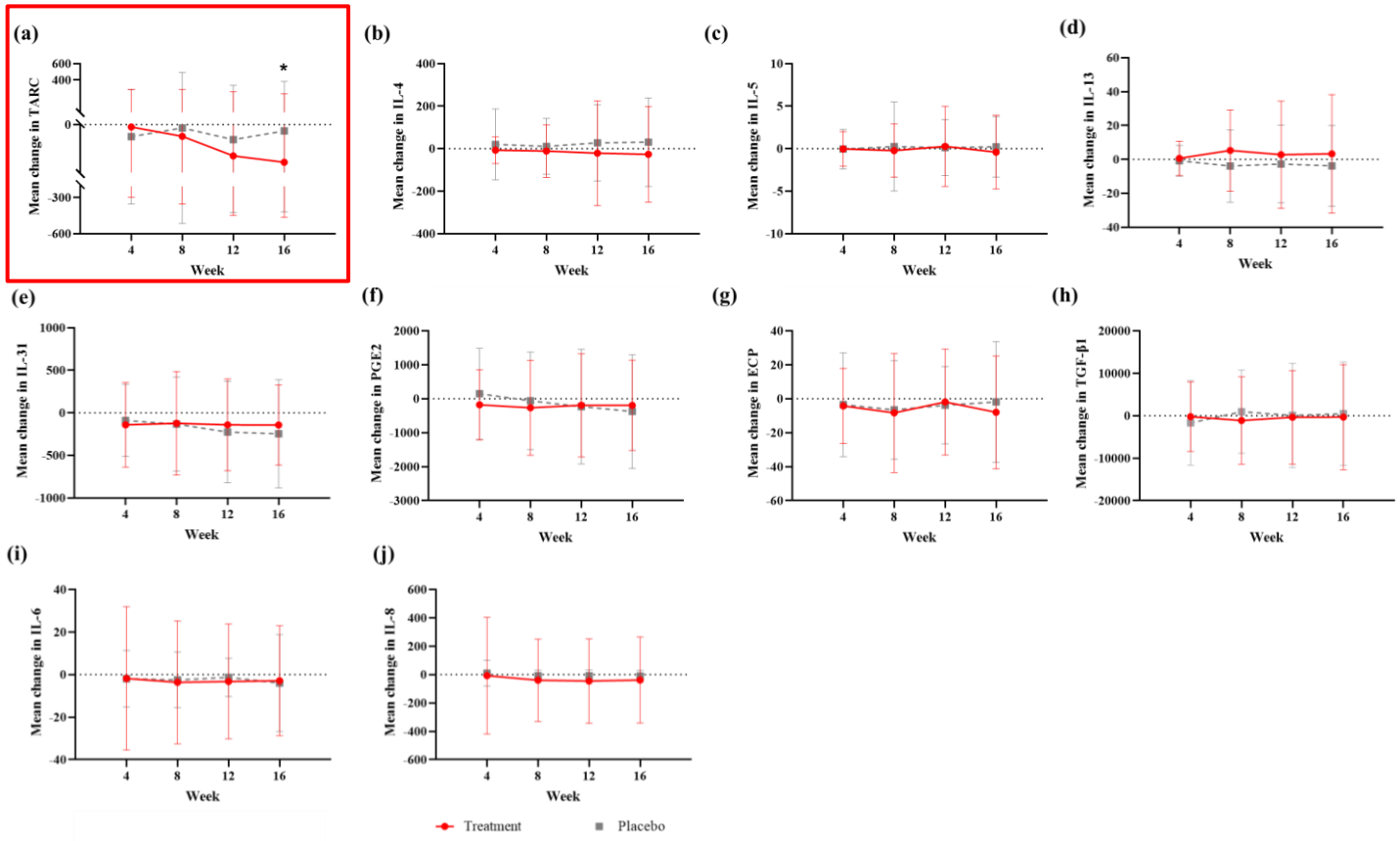
Changes in clinical outcomes and serum biomarker levels in patients with AD.

➢ **Changes in clinical symptoms of AD.**



➢ **Changes in serum biomarker levels.**

AtMSC :autologous adipose tissue-derived MSC
* $P < .05$, ** $P < .01$, *** $P < .001$



AtMSC therapy improved AD clinical symptoms.

AtMSC reduced TARC level in AD patient serum.

Unpublished Data

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No safety issue of AtMSC therapy in this clinical trial.

Summary of TEAE

MedDRA System Organ Class Preferred Term	Treatment group (N=59)	Placebo group (N=55)
Any TEAEs, n(%)[event]	17(28.8)[26]	12(21.8)[17]
Infections and infestations	6(10.2)[7]	7(12.7)[7]
Skin and subcutaneous tissue disorders	4(6.8)[4]	2(3.6)[2]
Nervous system disorders	3(5.1)[6]	0(0.0)[0]
Investigations	1(1.7)[2]	2(3.6)[3]
Gastrointestinal disorders	2(3.4)[2]	1(1.8)[1]
Vascular disorders	2(3.4)[2]	1(1.8)[1]
Eye disorders	1(1.7)[1]	0(0.0)[0]
Injury, poisoning and procedural complications	1(1.7)[1]	0(0.0)[0]
Metabolism and nutrition disorders	0(0.0)[0]	1(1.8)[1]
Musculoskeletal and connective tissue disorders	1(1.7)[1]	0(0.0)[0]
Respiratory, thoracic and mediastinal disorders	0(0.0)[0]	1(1.8)[1]
Life-threatening TEAE	0(0.0)[0]	0(0.0)[0]
Serious ADR	0(0.0)[0]	0(0.0)[0]

Adverse events are coded according to MedDRA 25.1.

Percentages are based on the number of subjects in the treatment group.

AtMSC therapy poses no safety issues.

Unpublished Data

Image: flaticon.com

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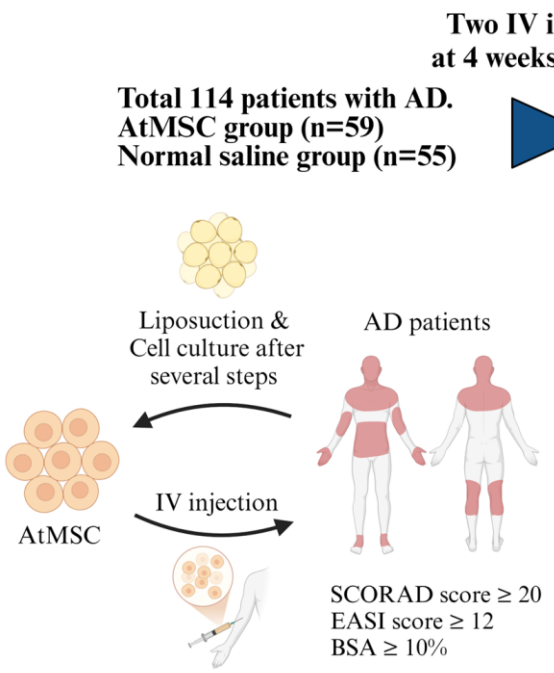
Summary

Unpublished Data

AD and AtMSC treatment

- This study the first large scale phase 2 investigation, to our knowledge.
- AtMSCs administered to patients with moderate to severe AD are markedly effective in diminishing EASI, SCORAD, disease severity, and IGA scores compared with a placebo, all without significant complications.
- Also, among blood cytokines, TARC recognized as pivotal AD clinical biomarkers, exhibited substantial differences in the study group relative to the placebo cohort at the 16-week mark following administration of the investigational drug.
- Overall, The immunomodulatory properties of AtMSCs render them a promising therapeutic strategy, which might be applicable to chronic inflammatory diseases, including AD.
- Limitations of this study include its single-blind design, with plans for future phase 3 trials to be double-blind. Additionally, the levels of IFN-γ and IL-17 were not examined, which may be influenced by MSCs.

<Graphical summary>



Efficacy of AtMSC group compared to normal saline group.

Parameter		Week 4	Week 8	Week 12	Week 16
EASI	Mean change		*	*	***
	EASI-50				***
	EASI-75				*
SCORAD	SCORAD-50				**
Disease severity	Mean change	*		*	**
IGA	Mean change		*	**	***
Serum	TARC (CCL17)				*

* $P < .05$, ** $P < .01$, *** $P < .001$

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