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Open Access Article

Safety Profile and Issues of Subcutaneous Immunotherapy in the Treatment of Children with Allergic Rhinitis

by Anang Endaryanto [1,*] and Ricardo Adrian Nugraha [2]

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(This article belongs to the Section **Stem Cells**)

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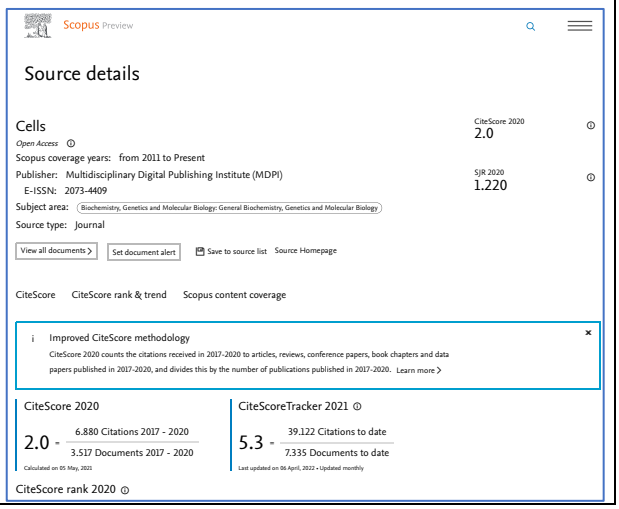

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Cover Letter

28 Maret 2022

March 28th, 2022

Editor-in-Chief, Cells

Dear Professor / Doctor,

We wish to submit the manuscript entitled **"Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis"** for consideration of publication in the **Cells**.

In the field of child allergic diseases, the private sector's role in the Indonesian health care system has grown dramatically over the past decade. There is an overall wide acceptance among Indonesian parents, even among the poorest socio-economic groups, to use private sector providers for specific treatment such as subcutaneous immunotherapy which isn't covered by national health insurance.

In our 6-year analysis looking back in time of children newly diagnosed as having rhinitis allergies, we compared safety and efficacy incurred during the 18 months before starting immunotherapy to the adverse effects and efficacy for these same children that were incurred during the 18 months after completion. If the results are safe and effective to improve quality of life, we would like to advocate our government to implement immunotherapy in the national health-care insurance, so the poorest socio-economic groups could also get the benefit of this treatment.

We believe this study may fulfil scientific holes in the field and hopefully fit the scope of your journal. This study has not been published in part or whole or is not under consideration for publication elsewhere. All authors involved in this study have agreed to be listed and approved the manuscript.

We thank you for considering our work for publication in the **Cells**.

Yours sincerely,

Anang Endaryanto, M.D., Ph.D.
Corresponding author
Department of Child Health, Soetomo General Hospital, Faculty of Medicine, Universitas Airlangga
Mayjen Prof. Dr. Moestopo Street No.6-8
Surabaya 60286, Indonesia
Email: anang.endaryanto@fk.unair.ac.id
Phone: +62-31-5020251, 5030252, 5030253. Fax. +62-31-5022472.

Submission Received

29 Maret 2022

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ANANG ENDARYANTO <anang.endaryanto@fk.unair.ac.id>

[Cells] Manuscript ID: cells-1680618 - Submission Received

1 pesan

Editorial Office <cells@mdpi.com> 29 Maret 2022 21.41
Balas Ke: cells@mdpi.com
Kepada: Anang Endaryanto <anang.endaryanto@fk.unair.ac.id>
Cc: Ricardo Adrian Nugraha <ricardo.adrian.nugraha-2019@fk.unair.ac.id>

Dear Dr. Endaryanto,

Thank you very much for uploading the following manuscript to the MDPI submission system. One of our editors will be in touch with you soon.

Journal name: Cells
Manuscript ID: cells-1680618
Type of manuscript: Article
Title: Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis
Authors: Anang Endaryanto *, Ricardo Adrian Nugraha
Received: 29 March 2022
E-mails: anang.endaryanto@fk.unair.ac.id, ricardo.adrian.nugraha-2019@fk.unair.ac.id
Submitted to section: Stem Cells, https://www.mdpi.com/journal/cells/sections/stem_cells
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Assistant Editor Assigned 30 Maret 2022	ANANG ENDARYANTO <anang.endaryanto@fk.unair.ac.id> **[Cells] Manuscript ID: cells-1680618 - Assistant Editor Assigned** 1 pesan **Anna Zhao** <anna.zhao@mdpi.com> 30 Maret 2022 10.29 Balas Ke: anna.zhao@mdpi.com Kepada: Anang Endaryanto <anang.endaryanto@fk.unair.ac.id> Cc: Anna Zhao <anna.zhao@mdpi.com>, Ricardo Adrian Nugraha <ricardo.adrian.nugraha-2019@fk.unair.ac.id>, Cells Editorial Office <cells@mdpi.com> Dear Dr. Endaryanto, Your paper has been assigned to Anna Zhao, who will be your main point of contact as your paper is processed further. Journal: Cells Manuscript ID: cells-1680618 Title: Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis Authors: Anang Endaryanto *, Ricardo Adrian Nugraha Received: 29 March 2022 E-mails: anang.endaryanto@fk.unair.ac.id, ricardo.adrian.nugraha-2019@fk.unair.ac.id You can find it here: https://susy.mdpi.com/user/manuscripts/review_info/d5e07303fa0f4d3a20c1493390226b05 Best regards, Anna Zhao Assistant Editor Email: anna.zhao@mdpi.com Skype: live:.cid.74552a3f7df2b942
Major Revisions 28 April 2022	ANANG ENDARYANTO <anang.endaryanto@fk.unair.ac.id> **[Cells] Manuscript ID: cells-1680618 - Major Revisions** 1 pesan **Cells Editorial Office** <cells@mdpi.com> 28 April 2022 16.16 Balas Ke: anna.zhao@mdpi.com Kepada: Anang Endaryanto <anang.endaryanto@fk.unair.ac.id> Cc: Ricardo Adrian Nugraha <ricardo.adrian.nugraha-2019@fk.unair.ac.id>, Cells Editorial Office <cells@mdpi.com> Dear Dr. Endaryanto, Thank you again for your manuscript submission: Manuscript ID: cells-1680618 Type of manuscript: Article Title: Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis Authors: Anang Endaryanto *, Ricardo Adrian Nugraha Received: 29 March 2022 E-mails: anang.endaryanto@fk.unair.ac.id, ricardo.adrian.nugraha-2019@fk.unair.ac.id Submitted to section: Stem Cells, https://www.mdpi.com/journal/cells/sections/stem_cells New Insights into Cellular Transplantation and Immunotherapy https://www.mdpi.com/journal/cells/special_issues/cell_transplant Your manuscript has now been reviewed by experts in the field. Please find your manuscript with the referee reports at this link: https://susy.mdpi.com/user/manuscripts/resubmit/d5e07303fa0f4d3a20c1493390226b05 Please revise the manuscript according to the referees' comments and upload the revised file within 10 days. Please use the version of your manuscript found at the above link for your revisions. (I) Any revisions to the manuscript should be marked up using the "Track Changes" function if you are using MS Word/LaTeX, such that any changes can be easily viewed by the editors and reviewers. (II) Please provide a cover letter to explain, point by point, the details of the revisions to the manuscript and your responses to the referees' comments. (III) If you found it impossible to address certain comments in the review reports, please include an explanation in your rebuttal. (IV) The revised version will be sent to the editors and reviewers. If one of the referees has suggested that your manuscript should undergo extensive English revisions, please address this issue during revision. We propose that you use one of the editing services listed at https://www.mdpi.com/authors/english or have your manuscript checked by a native English-speaking colleague. Do not hesitate to contact us if you have any questions regarding the revision of your manuscript. We look forward to hearing from you soon. https://mail.google.com/mail/u/1/?ik=89490e8b4a&view=pt&sear...ad-f%3A1731343075324360681&simpl=msg-f%3A1731343075324360681 Page 1 of 2

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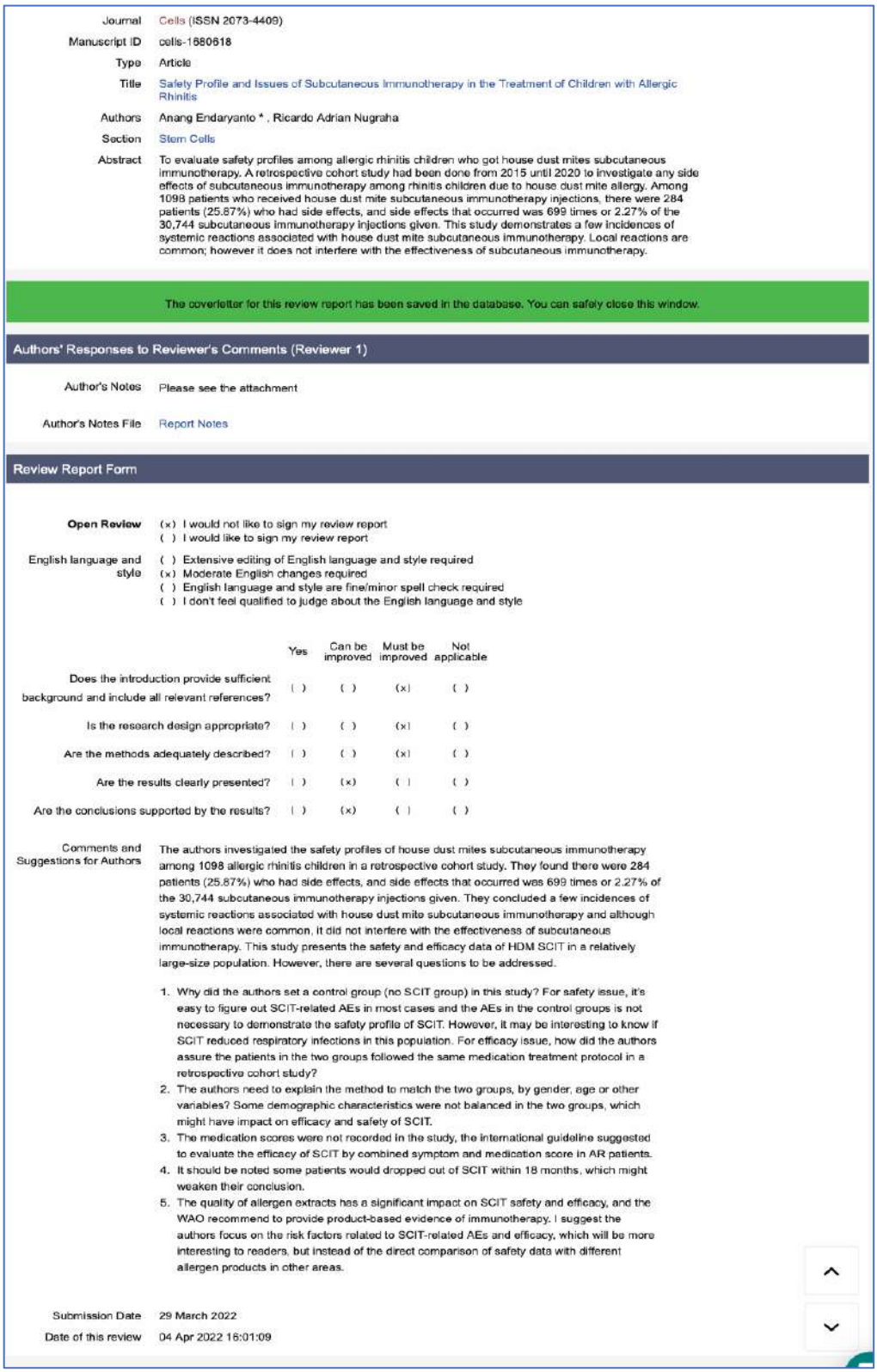

Journal: Cells (ISSN 2073-4409)

Manuscript ID: cells-1680618

Type: Article

Title: Safety Profile and Issues of Subcutaneous Immunotherapy in the Treatment of Children with Allergic Rhinitis

Authors: Anang Endaryanto * , Ricardo Adrian Nugraha

Section: Stem Cells

Abstract: To evaluate safety profiles among allergic rhinitis children who got house dust mites subcutaneous immunotherapy. A retrospective cohort study had been done from 2015 until 2020 to investigate any side effects of subcutaneous immunotherapy among rhinitis children due to house dust mite allergy. Among 1098 patients who received house dust mite subcutaneous immunotherapy injections, there were 284 patients (25.87%) who had side effects, and side effects that occurred was 699 times or 2.27% of the 30,744 subcutaneous immunotherapy injections given. This study demonstrates a few incidences of systemic reactions associated with house dust mite subcutaneous immunotherapy. Local reactions are common; however it does not interfere with the effectiveness of subcutaneous immunotherapy.

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Authors' Responses to Reviewer's Comments (Reviewer 1)

Author's Notes: Please see the attachment

Author's Notes File: Report Notes

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English language and style
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(x) Moderate English changes required
( ) English language and style are fine/minor spell check required
( ) I don't feel qualified to judge about the English language and style

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	( )	( )	(x)	( )
Is the research design appropriate?	( )	( )	(x)	( )
Are the methods adequately described?	( )	( )	(x)	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors: The authors investigated the safety profiles of house dust mites subcutaneous immunotherapy among 1098 allergic rhinitis children in a retrospective cohort study. They found there were 284 patients (25.87%) who had side effects, and side effects that occurred was 699 times or 2.27% of the 30,744 subcutaneous immunotherapy injections given. They concluded a few incidences of systemic reactions associated with house dust mite subcutaneous immunotherapy and although local reactions were common, it did not interfere with the effectiveness of subcutaneous immunotherapy. This study presents the safety and efficacy data of HDM SCIT in a relatively large-size population. However, there are several questions to be addressed.

1. Why did the authors set a control group (no SCIT group) in this study? For safety issue, it's easy to figure out SCIT-related AEs in most cases and the AEs in the control groups is not necessary to demonstrate the safety profile of SCIT. However, it may be interesting to know if SCIT reduced respiratory infections in this population. For efficacy issue, how did the authors assure the patients in the two groups followed the same medication treatment protocol in a retrospective cohort study?
2. The authors need to explain the method to match the two groups, by gender, age or other variables? Some demographic characteristics were not balanced in the two groups, which might have impact on efficacy and safety of SCIT.
3. The medication scores were not recorded in the study, the international guideline suggested to evaluate the efficacy of SCIT by combined symptom and medication score in AR patients.
4. It should be noted some patients would dropped out of SCIT within 18 months, which might weaken their conclusion.
5. The quality of allergen extracts has a significant impact on SCIT safety and efficacy, and the WAO recommend to provide product-based evidence of immunotherapy. I suggest the authors focus on the risk factors related to SCIT-related AEs and efficacy, which will be more interesting to readers, but instead of the direct comparison of safety data with different allergen products in other areas.

Submission Date: 29 March 2022

Date of this review: 04 Apr 2022 16:01:09

Author Responses to Reviewer's Comments (Reviewer 1)

(Page 1)

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Reviewer 1

<table>
<tr>
<td>Why did the authors set a control group (no SCIT group) in this study?</td>
<td>The main reason we set a control group is because we aimed to obtain the estimated incidence of the side effects from SCIT groups compared to the no SCIT group. Adverse events (AE) following SCIT are often reported as SCIT Side Effects (SE), even though it could be a coincidence that does not originate from SCIT. Urticaria, angioedema, asthma, and rhinoconjunctivitis occurring after SCIT may also occur in children with allergic rhinitis who do not receive SCIT. By comparing these symptoms in the SCIT group with the non-SCIT group in a large population, we can estimate how significant the side effect (SE) is due to SCIT purely.
(we have added this statement to the manuscript)

<table>
<tr><th rowspan="2">Side effects (SE)/ Adverse Events (AE)</th><th colspan="2">SE occurred in SCIT group</th><th colspan="2">AE occurred in non-SCIT group</th><th colspan="2">Pure effect of SE in SCIT group</th></tr>
<tr><th>n</th><th>%</th><th>n</th><th>%</th><th>n</th><th>%</th></tr>
<tr><td>1. Local</td><td>530</td><td>1,72</td><td>0</td><td>0</td><td>530</td><td>1,72</td></tr>
<tr><td>2. Urticaria</td><td>54</td><td>0,18</td><td>2</td><td>0,01</td><td>52</td><td>0,17</td></tr>
<tr><td>3. Angioedema</td><td>2</td><td>0,01</td><td>0</td><td>0</td><td>2</td><td>0,01</td></tr>
<tr><td>4. Asthma</td><td>32</td><td>0,10</td><td>13</td><td>0,04</td><td>19</td><td>0,06</td></tr>
<tr><td>5. Rhinoconjungtivitis</td><td>30</td><td>0,10</td><td>40</td><td>0,13</td><td>-10</td><td>-0,03</td></tr>
<tr><td>6. Non specific</td><td>22</td><td>0,07</td><td>0</td><td>0</td><td>22</td><td>0,07</td></tr>
<tr><td>7. Anaphylaxis</td><td>30</td><td>0,10</td><td>0</td><td>0</td><td>30</td><td>0,1</td></tr>
<tr><td>8. Severe anaphylaxis</td><td>1</td><td>0,00</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>9. Local and systemic</td><td>7</td><td>0,02</td><td>0</td><td>0</td><td>7</td><td>0,02</td></tr>
<tr><td>10. Total local</td><td>537</td><td>1,75</td><td>0</td><td>0</td><td>537</td><td>1,75</td></tr>
<tr><td>11. Total systemic</td><td>162</td><td>0,53</td><td>46</td><td>0,15</td><td>116</td><td>0,38</td></tr>
</table>
</td>
</tr>
<tr>
<td>For safety issue, it's easy to figure out SCIT-related AEs in most cases and the AEs in the control groups is not necessary to demonstrate the safety profile of SCIT</td>
<td>The benefit of this study is to obtain evidence-based information on how large the Side Effects (urticaria, angioedema, asthma, rhinoconjunctivitis, anaphylaxis) in the allergic rhinitis group receiving SCIT also occurred in the allergic rhinitis group who did not receive SCIT.</td>
</tr>
</table>

Author Responses to Reviewer's Comments (Reviewer 1)

(Page 2)

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<table>
<tr>
<td>However, it may be interesting to know if SCIT reduced respiratory infections in this population</td>
<td>Subject in the SCIT group experienced a 0.03% lower incidence of rhinoconjunctivitis than the non-SCIT group, and 0.078% of rhinoconjunctivitis in non-SCIT was caused by infection, while in SCIT, it was only 0.030%.
(we have added this statement to the manuscript)

<table>
<tr><td rowspan="2">Side effects (SE)/ Adverse Events (AE)</td><td colspan="2">SCIT group</td><td colspan="2">non-SCIT group</td></tr>
<tr><td>n</td><td>%</td><td>n</td><td>%</td></tr>
<tr><td>Rhinoconjungtivitis</td><td></td><td></td><td></td><td></td></tr>
<tr><td>• all</td><td>30</td><td>0.100</td><td>40</td><td>0.130</td></tr>
<tr><td>• allergy</td><td>21</td><td>0.070</td><td>16</td><td>0.052</td></tr>
<tr><td>• infection</td><td>9</td><td>0.030</td><td>24</td><td>0.078</td></tr>
</table>
</td>
</tr>
<tr>
<td>For efficacy issue, how did the authors assure the patients in the two groups followed the same medication treatment protocol in a retrospective cohort study?</td>
<td>All of the subjects we studied were from a large cohort of public and private pediatric immunological allergy patients managed by the Division of Allergy-Immunology, Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital for research and development of allergy care in children since 2001. All parents of patients in the cohort have agreed that their children will receive medical treatment, monitor the course of the disease, and disease outcomes by standard operating procedures for research and patient care in the Allergy-Immunology Division. Department of Pediatrics, Faculty of Medicine, Airlangga University, Dr. Soetomo General Academic Hospital. A monitoring form for allergy patients who received SCIT or not (which was held by the doctor and by the patient's parent/caregiver) was used by Dr. Soetomo General Academic Hospital for more than 20 years for data collection and monitoring of allergy patients.
(we have added this statement to the manuscript)</td>
</tr>
<tr>
<td>The authors need to explain the method to match the two groups, by gender, age or other variables? Some demographic characteristics were not balanced in the two groups, which might have impact on efficacy and safety of SCIT.</td>
<td>The eight matched variables were: age, sex, weight, height, family history of allergies, symptoms, and treatment scores at SCIT initiation and comorbid atopic conditions (asthma, conjunctivitis, and atopic dermatitis) during the year before SCIT initiation.
We did not match the two groups based on the AR-associated condition (Table 1).

Although asthma, bronchitis, and sinusitis were found to be unbalanced in the two groups (P=0.000), however, our analysis showed that asthma, bronchitis, and sinusitis did not significantly differentiate safety from SCIT and non-SCIT:

<table>
<tr><td colspan="7">Multivariate Tests[a]</td></tr>
<tr><td>Effect</td><td>Side Effects (SE) or Adverse Events (AE)</td><td>Value</td><td>F</td><td>Hypothesis df</td><td>Error df</td><td>Sig.</td></tr>
<tr><td rowspan="5">Group * Asthma

Group= SCIT vs non-SCIT</td><td>Pillai's Trace</td><td>0,001</td><td>.111[b]</td><td>18,000</td><td>2164,000</td><td>1,000</td></tr>
<tr><td>Wilks' Lambda</td><td>0,999</td><td>.111[b]</td><td>18,000</td><td>2164,000</td><td>1,000</td></tr>
<tr><td>Hotelling's Trace</td><td>0,001</td><td>.111[b]</td><td>18,000</td><td>2164,000</td><td>1,000</td></tr>
<tr><td>Roy's Largest Root</td><td>0,001</td><td>.111[b]</td><td>18,000</td><td>2164,000</td><td>1,000</td></tr>
<tr><td>Pillai's Trace</td><td>0,003</td><td>.406[b]</td><td>18,000</td><td>2164,000</td><td>0,987</td></tr>
</table>
</td>
</tr>
</table>

Author Responses to Reviewer's Comments (Reviewer 1)

(Page 3)

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Group * Bronchitis **Group= SCIT vs non-SCIT**	Wilks' Lambda	0,997	.406[b]	18,000	2164,000	0,987
	Hotelling's Trace	0,003	.406[b]	18,000	2164,000	0,987
	Roy's Largest Root	0,003	.406[b]	18,000	2164,000	0,987
Group * Sinusitis **Group= SCIT vs non-SCIT**	Pillai's Trace	0,001	.131[b]	18,000	2164,000	1,000
	Wilks' Lambda	0,999	.131[b]	18,000	2164,000	1,000
	Hotelling's Trace	0,001	.131[b]	18,000	2164,000	1,000
	Roy's Largest Root	0,001	.131[b]	18,000	2164,000	1,000

Tests of Between-Subjects Effects

Effect	Side Effects (SE) or Adverse Events (AE)	Side Effects (SE) or Adverse Events (AE)	df	Mean Square	F	Sig.
Group * Asthma **Group= SCIT vs non-SCIT**	Local_only_3	0,039	1	0,039	0,532	0,466
	Local_only_6	0,051	1	0,051	0,839	0,360
	Local_only_9	0,010	1	0,010	0,210	0,647
	Local_only_12	0,018	1	0,018	1,081	0,299
	Local_only_18	2,978E-05	1	2,978E-05	0,003	0,958
	Urticaria_3	1,135E-07	1	1,135E-07	0,000	0,998
	Urticaria_6	4,436E-06	1	4,436E-06	0,003	0,955
	Urticaria_9	0,000	1	0,000		
	Urticaria_12	3,131E-06	1	3,131E-06	0,000	0,986
	Urticaria_18	0,000	1	0,000		
	Angioedema_3	3,833E-06	1	3,833E-06	0,008	0,927
	Angioedema_6	0,000	1	0,000		
	Angioedema_9	3,833E-06	1	3,833E-06	0,008	0,927
	Angioedema_12	0,000	1	0,000		
	Angioedema_18	0,000	1	0,000		
	Asthma_3	0,000	1	0,000	0,063	0,802
	Asthma_6	0,000	1	0,000	0,063	0,802
	Asthma_9	4,560E-05	1	4,560E-05	0,014	0,905
	Asthma_12	0,000	1	0,000		
	Asthma_18	4,560E-05	1	4,560E-05	0,014	0,905
	Rhinoconjungtivitis_3	0,000	1	0,000	0,060	0,807
	Rhinoconjungtivitis_6	0,001	1	0,001	0,115	0,735
	Rhinoconjungtivitis_9	0,000	1	0,000		
	Rhinoconjungtivitis_12	0,000	1	0,000		
	Rhinoconjungtivitis_18	0,000	1	0,000		

Author Responses to Reviewer's Comments (Reviewer 1)

(Page 4)

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		Non_specific_Symptoms_3	0,000	1	0,000		
		Non_specific_Symptoms_6	3,110E-05	1	3,110E-05	0,006	0,937
		Non_specific_Symptoms_9	0,000	1	0,000		
		Non_specific_Symptoms_12	0,000	1	0,000		
		Non_specific_Symptoms_18	3,110E-05	1	3,110E-05	0,006	0,937
		Anaphylaxis_3	0,001	1	0,001	0,132	0,717
		Anaphylaxis_6	0,001	1	0,001	0,132	0,717
		Anaphylaxis_9	0,000	1	0,000		
		Anaphylaxis_12	0,000	1	0,000		
		Anaphylaxis_18	0,000	1	0,000		
		Severe_Anaphilaxis_3	3,833E-06	1	3,833E-06	0,008	0,927
		Severe_Anaphilaxis_6	0,000	1	0,000		
		Severe_Anaphilaxis_9	0,000	1	0,000		
		Severe_Anaphilaxis_12	0,000	1	0,000		
		Severe_Anaphilaxis_18	0,000	1	0,000		
		Local_Sistemic_3	1,997E-05	1	1,997E-05	0,009	0,925
		Local_Sistemic_6	4,929E-07	1	4,929E-07	0,001	0,974
		Local_Sistemic_9	4,929E-07	1	4,929E-07	0,001	0,974
		Local_Sistemic_12	0,000	1	0,000		
		Local_Sistemic_18	0,000	1	0,000		
	Group * Bronchitis **Group= SCIT vs non-SCIT**	Local_only_3	0,227	1	0,227	3,095	0,079
		Local_only_6	0,038	1	0,038	2,280	0,131
		Local_only_9	0,112	1	0,112	2,354	0,125
		Local_only_12	0,038	1	0,038	2,280	0,131
		Local_only_18	0,001	1	0,001	0,112	0,738
		Urticaria_3	0,001	1	0,001	0,080	0,777
		Urticaria_6	3,801E-05	1	3,801E-05	0,028	0,868
		Urticaria_9	0,000	1	0,000		
		Urticaria_12	0,001	1	0,001	0,058	0,810
		Urticaria_18	0,000	1	0,000		
		Angioedema_3	2,053E-06	1	2,053E-06	0,004	0,947
		Angioedema_6	0,000	1	0,000		
		Angioedema_9	2,053E-06	1	2,053E-06	0,004	0,947
		Angioedema_12	0,000	1	0,000		
		Angioedema_18	0,000	1	0,000		
		Asthma_3	1,426E-05	1	1,426E-05	0,003	0,953
		Asthma_6	1,426E-05	1	1,426E-05	0,003	0,953
		Asthma_9	0,000	1	0,000	0,058	0,809
		Asthma_12	0,000	1	0,000		

		Asthma_18	0,000	1	0,000	0,058	0,809
		Rhinoconjungtivitis_3	1,935E-05	1	1,935E-05	0,004	0,950
		Rhinoconjungtivitis_6	9,231E-05	1	9,231E-05	0,011	0,917
		Rhinoconjungtivitis_9	0,000	1	0,000		
		Rhinoconjungtivitis_12	0,000	1	0,000		
		Rhinoconjungtivitis_18	0,000	1	0,000		
		Non_specific_Symptoms_3	0,000	1	0,000		
		Non_specific_Symptoms_6	2,670E-05	1	2,670E-05	0,005	0,942
		Non_specific_Symptoms_9	0,000	1	0,000		
		Non_specific_Symptoms_12	0,000	1	0,000		
		Non_specific_Symptoms_18	2,670E-05	1	2,670E-05	0,005	0,942
		Anaphylaxis_3	0,000	1	0,000	0,069	0,793
		Anaphylaxis_6	0,000	1	0,000	0,069	0,793
		Anaphylaxis_9	0,000	1	0,000		
		Anaphylaxis_12	0,000	1	0,000		
		Anaphylaxis_18	0,000	1	0,000		
		Severe_Anaphilaxis_3	2,053E-06	1	2,053E-06	0,004	0,947
		Severe_Anaphilaxis_6	0,000	1	0,000		
		Severe_Anaphilaxis_9	0,000	1	0,000		
		Severe_Anaphilaxis_12	0,000	1	0,000		
		Severe_Anaphilaxis_18	0,000	1	0,000		
		Local_Sistemic_3	3,532E-08	1	3,532E-08	0,000	0,997
		Local_Sistemic_6	4,223E-06	1	4,223E-06	0,009	0,923
		Local_Sistemic_9	4,223E-06	1	4,223E-06	0,009	0,923
		Local_Sistemic_12	0,000	1	0,000		
		Local_Sistemic_18	0,000	1	0,000		
	Group * Sinusitis **Group= SCIT vs non-SCIT**	Local_only_3	0,045	1	0,045	0,610	0,435
		Local_only_6	0,018	1	0,018	0,287	0,592
		Local_only_9	0,002	1	0,002	0,052	0,820
		Local_only_12	0,006	1	0,006	0,345	0,557
		Local_only_18	0,002	1	0,002	0,175	0,676
		Urticaria_3	0,002	1	0,002	0,160	0,689
		Urticaria_6	1,957E-05	1	1,957E-05	0,014	0,905
		Urticaria_9	0,000	1	0,000		
		Urticaria_12	0,002	1	0,002	0,145	0,703
		Urticaria_18	0,000	1	0,000		
		Angioedema_3	4,227E-06	1	4,227E-06	0,009	0,923
		Angioedema_6	0,000	1	0,000		
		Angioedema_9	4,227E-06	1	4,227E-06	0,009	0,923

Author Responses to Reviewer's Comments (Reviewer 1)

(Page 6)

https://www.mdpi.com/2073-4409/11/9/1584/review_report

		Angioedema_12	0,000	1	0,000		
		Angioedema_18	0,000	1	0,000		
		Asthma_3	0,000	1	0,000	0,110	0,740
		Asthma_6	0,000	1	0,000	0,110	0,740
		Asthma_9	0,000	1	0,000	0,080	0,778
		Asthma_12	0,000	1	0,000		
		Asthma_18	0,000	1	0,000	0,080	0,778
		Rhinoconjungtivitis_3	0,001	1	0,001	0,123	0,726
		Rhinoconjungtivitis_6	0,002	1	0,002	0,226	0,634
		Rhinoconjungtivitis_9	0,000	1	0,000		
		Rhinoconjungtivitis_12	0,000	1	0,000		
		Rhinoconjungtivitis_18	0,000	1	0,000		
		Non_specific_Symptoms_3	0,000	1	0,000		
		Non_specific_Symptoms_6	0,000	1	0,000	0,073	0,787
		Non_specific_Symptoms_9	0,000	1	0,000		
		Non_specific_Symptoms_12	0,000	1	0,000		
		Non_specific_Symptoms_18	0,000	1	0,000	0,073	0,787
		Anaphylaxis_3	0,002	1	0,002	0,239	0,625
		Anaphylaxis_6	0,002	1	0,002	0,239	0,625
		Anaphylaxis_9	0,000	1	0,000		
		Anaphylaxis_12	0,000	1	0,000		
		Anaphylaxis_18	0,000	1	0,000		
		Severe_Anaphilaxis_3	4,227E-06	1	4,227E-06	0,009	0,923
		Severe_Anaphilaxis_6	0,000	1	0,000		
		Severe_Anaphilaxis_9	0,000	1	0,000		
		Severe_Anaphilaxis_12	0,000	1	0,000		
		Severe_Anaphilaxis_18	0,000	1	0,000		
		Local_Sistemic_3	8,313E-05	1	8,313E-05	0,036	0,849
		Local_Sistemic_6	2,174E-06	1	2,174E-06	0,005	0,945
		Local_Sistemic_9	2,174E-06	1	2,174E-06	0,005	0,945
		Local_Sistemic_12	0,000	1	0,000		
		Local_Sistemic_18	0,000	1	0,000		

The medication scores were not recorded in the study, the international guideline	We have data regarding medication scores and added it to the manuscript in Table 4.

Author Responses to Reviewer's Comments (Reviewer 1)

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suggested to evaluate the efficacy of SCIT by combined symptom and medication score in AR patients.	
It should be noted some patients would dropped out of SCIT within 18 months, which might weaken their conclusion.	In contrast to many previous studies, our study focused on the incidence of local SE and systemic SE purely due to SCIT in pediatric patients with AR. Focus on them for 18 months, continue to receive HDMI SCIT with high compliance, with or without side effects. And from this study, information was obtained on how many children consistently followed SCIT despite having local SE and systemic SE. So the conclusion of this research, we write like this: "Our study concluded that in pediatric patients with AR who received HDM SCIT for 18 months with high adherence, some experienced significant local SE and systemic SE due to SCIT, but this did not interfere with the course of AR treatment or the effectiveness of SCIT"
The quality of allergen extracts has a significant impact on SCIT safety and efficacy, and the WAO recommend to provide product-based evidence of immunotherapy. I suggest the authors focus on the risk factors related to SCIT-related AEs and efficacy, which will be more interesting to readers, but instead of the direct comparison of safety data with different allergen	Thank you for the advice. Currently, following this study, we are investigating the risk factors associated with AE and the efficacy of our local SCIT product. In ongoing research, we also compare the safety and efficacy data between our local SCIT products and imported products that have already been on the market.

Second Review Report Form for Reviewer 1

https://www.mdpi.com/2073-4409/11/9/1584/review_report

Journal	Cells (ISSN 2073-4409)
Manuscript ID	cells-1680618
Type	Article
Title	Safety Profile and Issues of Subcutaneous Immunotherapy in the Treatment of Children with Allergic Rhinitis
Authors	Anang Endaryanto * , Ricardo Adrian Nugraha
Section	Stem Cells
Abstract	To evaluate safety profiles among allergic rhinitis children who got house dust mites subcutaneous immunotherapy. A retrospective cohort study had been done from 2015 until 2020 to investigate any side effects of subcutaneous immunotherapy among rhinitis children due to house dust mite allergy. Among 1098 patients who received house dust mite subcutaneous immunotherapy injections, there were 284 patients (25.87%) who had side effects, and side effects that occurred was 699 times or 2.27% of the 30,744 subcutaneous immunotherapy injections given. This study demonstrates a few incidences of systemic reactions associated with house dust mite subcutaneous immunotherapy. Local reactions are common; however it does not interfere with the effectiveness of subcutaneous immunotherapy.

Review Report Form

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English language and style
( ) Extensive editing of English language and style required
( ) Moderate English changes required
(x) English language and style are fine/minor spell check required
( ) I don't feel qualified to judge about the English language and style

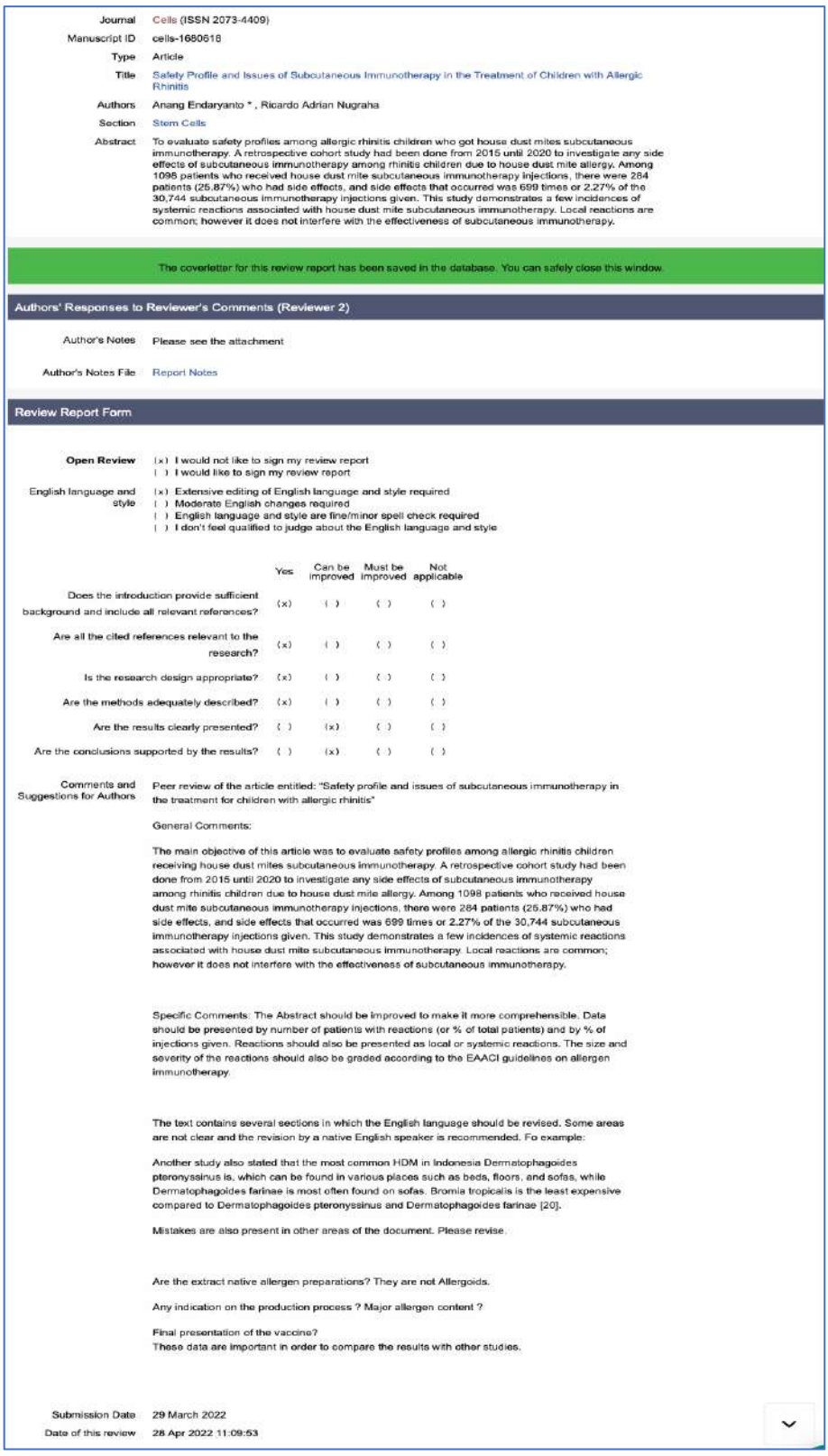
	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Are all the cited references relevant to the research?	(x)	( )	( )	( )
Is the research design appropriate?	( )	(x)	( )	( )
Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	(x)	( )	( )	( )
Are the conclusions supported by the results?	(x)	( )	( )	( )

Comments and Suggestions for Authors: The authors need to clarify the criteria of SCIT-related AE in the draft.

Submission Date: 29 March 2022
Date of this review: 04 May 2022 10:17:41

First Review Report Form for Reviewer 2

https://www.mdpi.com/2073-4409/11/9/1584/review_report



Journal	Cells (ISSN 2073-4409)
Manuscript ID	cells-1680618
Type	Article
Title	Safety Profile and Issues of Subcutaneous Immunotherapy in the Treatment of Children with Allergic Rhinitis
Authors	Anang Endaryanto *, Ricardo Adrian Nugraha
Section	Stem Cells
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Authors' Responses to Reviewer's Comments (Reviewer 2)

Author's Notes	Please see the attachment
Author's Notes File	Report Notes

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(x) Extensive editing of English language and style required
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Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Are all the cited references relevant to the research?	(x)	( )	( )	( )
Is the research design appropriate?	(x)	( )	( )	( )
Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

Peer review of the article entitled: "Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis"

General Comments:

The main objective of this article was to evaluate safety profiles among allergic rhinitis children receiving house dust mites subcutaneous immunotherapy. A retrospective cohort study had been done from 2015 until 2020 to investigate any side effects of subcutaneous immunotherapy among rhinitis children due to house dust mite allergy. Among 1098 patients who received house dust mite subcutaneous immunotherapy injections, there were 284 patients (25.87%) who had side effects, and side effects that occurred was 699 times or 2.27% of the 30,744 subcutaneous immunotherapy injections given. This study demonstrates a few incidences of systemic reactions associated with house dust mite subcutaneous immunotherapy. Local reactions are common; however it does not interfere with the effectiveness of subcutaneous immunotherapy.

Specific Comments: The Abstract should be improved to make it more comprehensible. Data should be presented by number of patients with reactions (or % of total patients) and by % of injections given. Reactions should also be presented as local or systemic reactions. The size and severity of the reactions should also be graded according to the EAACI guidelines on allergen immunotherapy.

The text contains several sections in which the English language should be revised. Some areas are not clear and the revision by a native English speaker is recommended. Fo example:

Another study also stated that the most common HDM in Indonesia Dermatophagoides pteronyssinus is, which can be found in various places such as beds, floors, and sofas, while Dermatophagoides farinae is most often found on sofas. Bromia tropicalis is the least expensive compared to Dermatophagoides pteronyssinus and Dermatophagoides farinae [20].

Mistakes are also present in other areas of the document. Please revise.

Are the extract native allergen preparations? They are not Allergoids.

Any indication on the production process ? Major allergen content ?

Final presentation of the vaccine?
These data are important in order to compare the results with other studies.

Submission Date	29 March 2022
Date of this review	28 Apr 2022 11:09:53

Author Responses to Reviewer's Comments (Reviewer 2)

(Page 1)

https://www.mdpi.com/2073-4409/11/9/1584/review_report

Reviewer 2

Specific Comments: The Abstract should be improved to make it more comprehensible. Data should be presented by number of patients with reactions (or % of total patients) and by % of injections given. Reactions should also be presented as local or systemic reactions. The size and severity of the reactions should also be graded according to the EAACI guidelines on allergen immunotherapy.	Abstract has been improved to be as follows: **Abstract:** This study aimed to evaluate safety issues of house dust mites subcutaneous immunotherapy (SCIT) among allergic rhinitis (AR) children. A retrospective cohort study was done between 2015 until 2020 to investigate the side effects of SCIT among AR children due to house dust mite allergy. Among 1098 patients who received house dust mite subcutaneous immunotherapy injections, 284 patients (25.87%) had side effects (SE). SE was found to be 699 times higher or 2.27% of the 30,744 subcutaneous immunotherapy injections. A total of 17.9% of patients had local SE during SCIT administration. Systemic side effects occurred in 8.38% of children receiving SCIT and in 0.53% of the total population who got SCIT injections. Only 2/92 (2.18%) of patients got an allergic reaction within 30 minutes of injection, and these patients responded well to antiallergic medication. Severe anaphylaxis occurred in 0.091% of the 1098 patients in the SCIT group and 0.0033% of the 30,774 SCIT injections. Systemic SE after SCIT occurred in 8.38% of patients receiving SCIT or 0.53% of the total number of SCIT injections. Anaphylactic episodes occurred in 16 patients (1.46%) and 15 patients (1.37%) who had first and second episodes. One severe attack was found, and it was resolved with adrenaline. This study demonstrates that in pediatric patients with AR who received HDM SCIT for 18 months with high adherence, some experienced significant local SE and systemic SE due to SCIT, but this did not interfere with the course of AR treatment or the effectiveness SCIT (we have added this abstract revision to the manuscript)

Author Responses to Reviewer's Comments (Reviewer 2)

(Page 2)

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The text contains several sections in which the English language should be revised. Some areas are not clear and the revision by a native English speaker is recommended. Fo example: Another study also stated that the most common HDM in Indonesia Dermatophagoides pteronyssinus is, which can be found in various places such as beds, floors, and sofas, while Dermatophagoides farinae is most often found on sofas. Bromia tropicalis is the least expensive compared to Dermatophagoides pteronyssinus and Dermatophagoides farinae [20]. Mistakes are also present in other areas of the document. Please revise.	We have revised as follows: The type of HDM allergen content in SCIT used in this study was based on previous research in Indonesia, which stated that the most common types of HDM allergen found in Indonesia were *Dermatophagoides pteronyssinus* (87%), *Dermatophagoides farinae* (7%), and *Bromia tropicalis* (6%) [19]. Another study on HDM in Indonesia informed that *Bromia tropicalis* is the least common compared to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. *Dermatophagoides pteronyssinus* can be found in various places such as beds, floors, and sofas. Meanwhile, *Dermatophagoides farinae* is often found on the sofas [20]. (we have added this revision to the manuscript)
Are the extract native allergen preparations? They are not Allergoids.	Yes, the extract are native allergen preparations, not Allergoids.
Any indication on the production process ? Major allergen content ? Final presentation of the vaccine? These data are important in order to compare the results with other studies.	• House dust mite allergen immunotherapy (SCIT) is processed and produced by Teaching Industry Allergen - Airlangga University - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. • Major allergen content is *Dermatophagoides pteronyssinus* extract with 11.3-26.6 ng/mL

Accepted for Publication
6 Mei 2022

Email Airlangga University - [Cells] Manuscript ID: cells-1680618 - Accepted for Publication 09/05/22 16.52

ANANG ENDARYANTO <anang.endaryanto@fk.unair.ac.id>

[Cells] Manuscript ID: cells-1680618 - Accepted for Publication

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Cc: Ricardo Adrian Nugraha <ricardo.adrian.nugraha-2019@fk.unair.ac.id>, Cells Editorial Office <cells@mdpi.com>, Anna Zhao <anna.zhao@mdpi.com>

Dear Dr. Endaryanto,

Congratulations on the acceptance of your manuscript, and thank you for your interest in submitting your work to Cells:

Manuscript ID: cells-1680618
Type of manuscript: Article
Title: Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis
Authors: Anang Endaryanto *, Ricardo Adrian Nugraha
Received: 29 March 2022
E-mails: anang.endaryanto@fk.unair.ac.id, ricardo.adrian.nugraha-2019@fk.unair.ac.id
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We invite you to proofread your manuscript to ensure that this is the final version that can be published and confirm that you will require no further changes from hereon:

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Type of manuscript: Article
Title: Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis
Authors: Anang Endaryanto *, Ricardo Adrian Nugraha
Received: 29 March 2022
E-mails: anang.endaryanto@fk.unair.ac.id, ricardo.adrian.nugraha-2019@fk.unair.ac.id
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Kind regards,
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Manuscript Resubmitted 7 Mei 2022	ANANG ENDARYANTO <anang.endaryanto@fk.unair.ac.id> **[Cells] Manuscript ID: cells-1680618 - Manuscript Resubmitted** 1 pesan **Cells Editorial Office** <cells@mdpi.com> 7 Mei 2022 11.17 Balas Ke: Anna Zhao <anna.zhao@mdpi.com>, Cells Editorial Office <cells@mdpi.com> Kepada: Anang Endaryanto <anang.endaryanto@fk.unair.ac.id> Cc: Ricardo Adrian Nugraha <ricardo.adrian.nugraha-2019@fk.unair.ac.id> Dear Dr. Endaryanto, Thank you very much for resubmitting the modified version of the following manuscript: Manuscript ID: cells-1680618 Type of manuscript: Article Title: Safety profile and issues of subcutaneous immunotherapy in the treatment for children with allergic rhinitis Authors: Anang Endaryanto *, Ricardo Adrian Nugraha Received: 29 March 2022 E-mails: anang.endaryanto@fk.unair.ac.id, ricardo.adrian.nugraha-2019@fk.unair.ac.id Submitted to section: Stem Cells, https://www.mdpi.com/journal/cells/sections/stem_cells A member of the editorial office will be in touch with you soon regarding progress of the manuscript. Kind regards, Cells Editorial Office Postfach, CH-4020 Basel, Switzerland Office: St. Alban-Anlage 66, CH-4052 Basel Tel. +41 61 683 77 34 (office) Fax +41 61 302 89 18 (office) E-mail: cells@mdpi.com https://www.mdpi.com/journal/cells/
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Double check 8 Mei 2022	ANANG ENDARYANTO <anang.endaryanto@fk.unair.ac.id> **Re: [Cells] cells-1680618-Double check** 2 pesan **Sarah.Liu** <sarah.liu@mdpi.com> 8 Mei 2022 10.27 Balas Ke: anna.zhao@mdpi.com Kepada: anang.endaryanto@fk.unair.ac.id Cc: ricardo.adrian.nugraha-2019@fk.unair.ac.id, Cells Editorial Office <cells@mdpi.com>, anna.zhao@mdpi.com Dear Dr. Endaryanto, Thanks for your proofreading. However, we noted you added a information "Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials", but we did not find the Supplementary Materials. We changed this information to "Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article". Please check and confirm. Please feel free to contact us if any questions and we look forward to hearing from you. P.S.: Stay safe and healthy. Kind regards, Sarah Liu Section Managing Editor MDPI Branch Office, Beijing Room 1110, Jincheng Center, No. 21 Cuijingbeili, Tongzhou District, Beijing 101101, China Skype: 1542897540; Tel.: 010-5730-8682 www.mdpi.com Disclaimer: The information and files contained in this message are confidential and intended solely for the use of the individual or entity to whom they are addressed. If you have received this message in error, please notify me and delete this message from your system. You may not copy this message in its entirety or in part, or disclose its contents to anyone. **cells-1680618.docx** 2581K
Paper has been published 9 Mei 2022 https://www.mdpi.com/2073-4409/11/9/1584/htm	ANANG ENDARYANTO <anang.endaryanto@fk.unair.ac.id> **[Cells] Manuscript ID: cells-1680618; doi: 10.3390/cells11091584. Paper has been published.** 2 pesan **Cells Editorial Office** <cells@mdpi.com> 9 Mei 2022 13.59 Balas Ke: Anna Zhao <anna.zhao@mdpi.com>, Cells Editorial Office <cells@mdpi.com> Kepada: Anang Endaryanto <anang.endaryanto@fk.unair.ac.id> Cc: Cells Editorial Office <cells@mdpi.com>, Anna Zhao <anna.zhao@mdpi.com> Dear Dr. Endaryanto, We are pleased to inform you that "Safety Profile and Issues of Subcutaneous Immunotherapy in the Treatment of Children with Allergic Rhinitis" by Anang Endaryanto ", Ricardo Adrian Nugraha has been published in Cells and is available online: Abstract: https://www.mdpi.com/2073-4409/11/9/1584 HTML Version: https://www.mdpi.com/2073-4409/11/9/1584/htm PDF Version: https://www.mdpi.com/2073-4409/11/9/1584/pdf You are receiving this email at the request of the authors. We would be happy to keep you updated about new issue releases of Cells. Please enter your e-mail address in the box at https://www.mdpi.com/journal/cells/toc-alert/ to receive notifications. We also invite you to consider Cells and other open access MDPI journals when publishing your next article. A full list is available at https://www.mdpi.com/about/journals. Kind regards, Cells Editorial Office Postfach, CH-4020 Basel, Switzerland Office: St. Alban-Anlage 66, CH-4052 Basel Tel. +41 61 683 77 34 (office) Fax +41 61 302 89 18 (office) E-mail: cells@mdpi.com https://www.mdpi.com/journal/cells/