No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis

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Background: Long-term safety of topical calcineurin inhibitors is not well understood. APPLES (A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis; NCT00475605) examined incidence of lymphoma and other cancers in a pediatric population with atopic dermatitis.

Objective: To quantify incident malignancies during 10 years in children with atopic dermatitis who used topical tacrolimus for ≥6 weeks.

Methods: Standardized incidence ratios for cancer events were analyzed relative to sex-, age-, and race-matched control data from national cancer registries.

Results: There were 7954 eligible patients enrolled at 314 sites in 9 countries. During 44,629 person-years, 6 confirmed incident cancers occurred (standardized incidence ratio, 1.01; 95% confidence interval, 0.37-2.20). No lymphomas occurred.

Limitations: Observational prospective cohort study.

Conclusion: The cancer incidence was as expected, given matched background data. This finding provides no support for the hypothesis that topical tacrolimus increases long-term cancer risk in children with atopic dermatitis. (J Am Acad Dermatol 2020;83:375-81.)

Key words: atopic dermatitis; cancer risk; lymphoma; skin cancer; tacrolimus; topical calcineurin inhibitors.

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Conflicts of interest: Dr Paller is an investigator for AbbVie, Anaptysbio, Celgene, Eli Lilly, Galderma, Incyte, LEO Pharma Inc, Janssen, Novartis, and Sanofi-Regeneron, and is a consultant with honorarium for AbbVie, Amgen, Asana, Celgene, Dermavant, Dermira, Galderma, Eli Lilly, Forte, LEO Pharma Inc, Menlo, Novartis, Pfizer, Regeneron, and Sanofi-Genzyme. Dr Fölster-Holst is a consultant, speaker, and clinical researcher for Almirall Hermal, Beiersdorf AG, Johnson & Johnson, LEO Pharma Inc, Neubourg GmbH, Novartis, Pierre Fabre, Pfizer, Procter & Gamble, Regeneron Pharmaceuticals, and Sanofi-Aventis. Dr Margolis is a consultant on atopic dermatitis for Pfizer, LEO Pharma Inc, and Sunovion, an advisor for the National Eczema Association, and receives research support from Valeant. Drs Chen, Diepgen, Elmets, and Pollock have no conflicts of interest to declare.

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IRB approval status: An Institutional Review Board or Independent Ethics Committee for each participating site approved the study protocol.

This work is dedicated to the memory of Thomas L. Diepgen.

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Atopic dermatitis (AD) requires long-term treatment to prevent and manage flares.[1-3] Whereas spontaneous remissions occur often in childhood or adolescence,[4,5] longitudinal analysis suggests ≥50% of patients continue to experience symptoms beyond age 20.[6] Because AD may require lifelong treatment, therapeutics must be held to stringent standards of long-term safety.

Topical treatment, the mainstay of AD care,[1] traditionally employs topical corticosteroids (TCSs) and the topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus.[7] TCI treatment differs in crucial respects from systemic calcineurin inhibition used in transplantation medicine. Penetration of topical tacrolimus beyond the stratum corneum is poor, thus limiting systemic exposure.[8] Nevertheless, the drug's immunosuppressive effect raises a theoretical possibility that topical administration could increase the risk of cutaneous or other cancers. Indeed, isolated melanoma and lymphoma cases have been reported, although the observed rates are not in excess of the population incidence. No clear epidemiologic evidence supports a causal relationship.[9-11]

In 2005 and 2006, United States (US) and European regulators issued warnings advising that continuous long-term use of topical tacrolimus and pimecrolimus should be avoided.[12,13] These authorities required prospective safety studies to clarify any actual cancer risk posed by topical TCIs. APPLES (A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis; NCT00475605) examined whether topical treatment with tacrolimus 0.03% or 0.1% ointment increases children's long-term risk of malignancy under actual-use conditions.

CAPSULE SUMMARY

- In the APPLES (A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis) cohort of children exposed to tacrolimus ointment for atopic dermatitis, the cancer incidence during a 10-year period closely matched expectations for an age- and sex-matched control population.
- This result, which proved robust to potential biases introduced by patient attrition, provides support for current United States and international atopic dermatitis treatment guidelines.

METHODS

Patients

After consent, children with AD could be included if their first exposure to tacrolimus ointment occurred before age 16 and if they used tacrolimus for ≥6 weeks. Patients with previously diagnosed cancers were eligible for inclusion. There were no restrictions on treatment during the study. No medication was supplied through APPLES. Patients' TCI exposure after enrollment was not quantified.

At baseline and annually thereafter, patients underwent a physical examination, including skin and lymph node evaluation. AD severity was evaluated every other year. Families responded twice yearly to a questionnaire or telephone interview regarding the child's AD therapy and any hospital or specialist contacts. Planned subject study duration was 10 years, with the final clinic visit allowed from 9.75 years.

All potential cancer events were reviewed by an independent Endpoint Review Committee. Incident malignancies other than nonmelanoma skin cancer were included in the primary analysis.

The protocol for this observational study was approved by an Institutional Review Board or an Independent Ethics Committee for each participating site.

Statistical analysis

The primary end point was the standardized incidence ratio (SIR), which is the ratio of observed events to expected events, for any Endpoint Review Committee-adjudicated malignancy. For each country, the expected number of cancer events was calculated using data from national registries, including Surveillance, Epidemiology, and End Results (US) and International Agency for Research on Cancer (Poland, United Kingdom, France, and Austria). For all countries, analyses were stratified based on patient sex and 5-year age groups (0-4 years, 5-9 years, etc.) For the US, Surveillance, Epidemiology, and End Results data also permitted stratification based on race.

Cancer incidence was calculated based on study follow-up time to the patient's last contact with their study center (patients who discontinued for any reason, including withdrawn consent or loss to follow-up) or the time at which patients were censored from the study. Censoring occurred at the final follow-up appointment (for patients observed for ≥9.75 years) or on January 31, 2019 (for those remaining in the study with <9.75 years of follow-up when the study was terminated). To determine the potential impact of biased exposure assessment, person-time was accumulated starting from the

Abbreviations used:

AD:	atopic dermatitis
APPLES:	A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis
CI:	confidence interval
JOELLE:	Joint European Longitudinal Lymphoma and Skin Cancer Evaluation
SIR:	standardized incidence ratio
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroid
US:	United States

date of enrollment (time 0 analysis), from 6 months after tacrolimus initiation, or the date of enrollment (whichever was later; month 6 analysis).

The study aimed to enroll 8000 patients to detect a ≥3-fold increase in overall cancer incidence with 95% confidence relative to a background population matched on country of residence, age, sex, and (where possible) race. No imputation was applied for missing data. A planned sensitivity analysis examined the effect on SIR for the whole population, given different hypothetical event rates among patients after they were lost to follow-up.

RESULTS

Patient enrollment and study termination

Sites in North America and Western Europe began enrolling patients in May 2005. By August 2012, 314 sites in 9 countries (Germany, Austria, Canada, France, Ireland, Netherlands, Poland, United Kingdom, and US) had enrolled 8071 patients. In July 2018, the US Food and Drug Administration determined that continued observations were unlikely to alter the study's findings with regard to cancer incidence and approved terminating the study early. Data collection ended on January 31, 2019.

The analysis included 7954 of the 8071 patients enrolled. As shown in Fig 1, 7 patients died, and 1454 (18.3%) withdrew consent. An additional 4368 (54.9%) were considered lost to follow-up because they failed to make contact with their study center at year 10 or because, on the study completion date, they had been enrolled for <9.75 years and had had no contact for ≥6 months despite a final campaign to reach those who had not withdrawn consent. Therefore, 2125 patients (26.7%) completed the study, including 1176 who completed with 10 years of follow-up and 949 who were censored at study completion. Median follow-up duration was 6.4 years.

The 7 patient deaths occurred in North America. Causes of death were trauma (car accident or violence) in 4, aspiration/esophageal atresia in 1, secondary to cerebral palsy in 1, and 1 patient with a complex medical history who died of causes that were deemed unrelated to tacrolimus exposure or AD.

Baseline characteristics

Patients' baseline characteristics and demographics (Table I) were similar between the North American and European subpopulations, except as noted. Approximately half of patients were girls, 50.0% had moderate to severe AD at the time of enrollment, and 74.3% had experienced moderate to severe AD symptoms at some point.

Mean age at enrollment was 7.1 years (median, 6.0 years), with peak enrollment at age 3 years. Mean ± SD age at AD onset was 2.3 ± 3.5 years, with the first dose of a topical TCI at 5.4 ± 4.2 years. Skin types varied between locations, consistent with racial differences between North America and Europe. Overall, 40.5% were of phototype IV to VI. Darker skin types were seen in 50.8% of North American patients and in 14.7% of European patients (Table I and data not shown).

The mean ± SD time between first use of tacrolimus and enrollment in APPLES was 1.8 ± 2.2 years. Mean (median) ages of first exposure to tacrolimus and pimecrolimus were 5.7 (4.7) years and 4.8 (3.5) years, respectively. Before enrollment, estimated mean ± SD TCI exposure was 885 ± 1963 grams of tacrolimus ointment and 608 ± 1413 grams of pimecrolimus cream.

Excluding tacrolimus, the most common prior AD treatments were topical corticosteroids (84% of patients), pimecrolimus (32%), and oral steroids (28%). Other prior treatments included cyclosporine (2%), topical tar (5%), and ultraviolet B (4%). Few patients (<1%) had been exposed to ultraviolet A. However, in addition to therapeutic ultraviolet exposure, 1% (2% in Europe) reported having previously used a tanning bed (data not shown).

Malignancies diagnosed before enrollment

Cancers identified before enrollment in APPLES were not included in the SIR calculation below. Of 8 prior cancers, 6 (2 neuroblastomas, 1 acute lymphocytic leukemia, 1 T-cell acute lymphocytic leukemia, 1 alveolar sarcoma, and 1 ependymoma) were diagnosed before the initial tacrolimus exposure. Two malignancies were diagnosed after initiation of tacrolimus but before enrollment in APPLES, namely, 1 case of acute lymphocytic leukemia (diagnosed 2.0 years after the first tacrolimus exposure) and 1

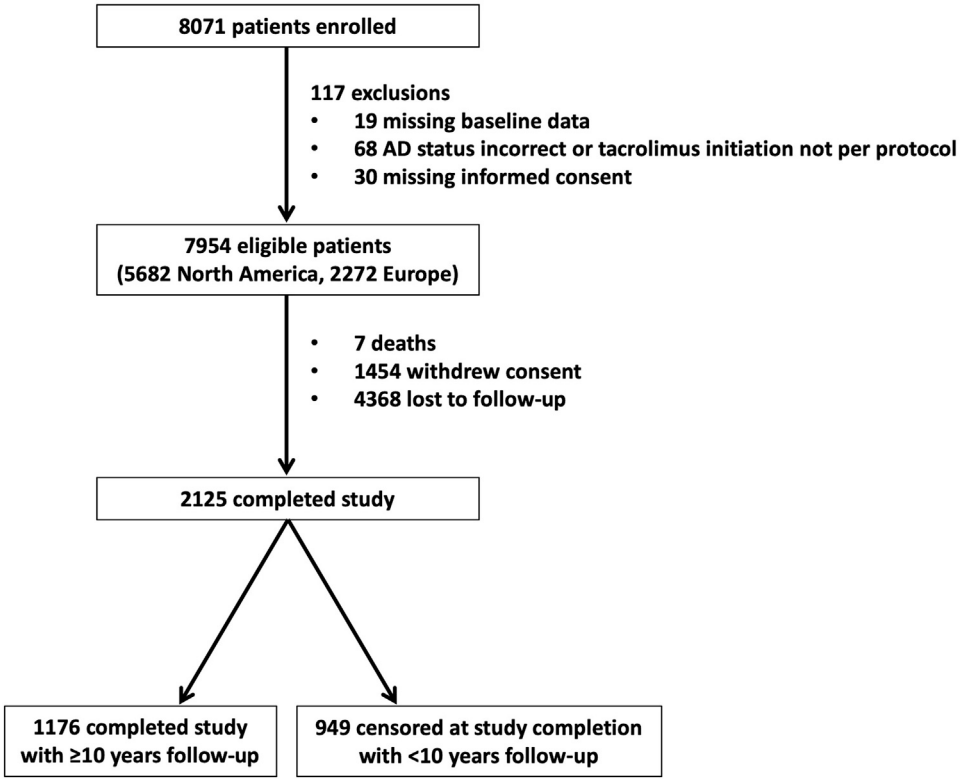

Fig 1. Patient inclusion and disposition. *AD*, Atopic dermatitis.

lymphocyte-predominant non-Hodgkin lymphoma (diagnosed 2.8 years after first exposure).

Incident cancers

After enrollment, 63 events were submitted to the Endpoint Review Committee for adjudication. Among the 54 events determined not to be incident malignancies, 26 were benign cutaneous lesions such as nevi, warts, or dermatofibromas; 5 female patients had benign breast neoplasias. For 3 events in 3 individuals (unspecified abnormal skin biopsy finding, cervical disorder, and bone neoplasm), there were insufficient data to determine whether the event was a malignancy.

Six events in 6 individuals were deemed incident cancers, namely, 1 cutaneous tumor (a spitzoid melanoma) and 5 other cancers, consisting of chronic myeloid leukemia, alveolar rhabdomyosarcoma, carcinoid tumor of the appendix, spinal cord neoplasm, and malignant paraganglioma in 1 patient each. No nonmelanoma skin cancers or incident lymphomas were observed.

The spitzoid melanoma (2.3 mm thick) developed on the knee of a 14-year old Asian boy with moderate to severe AD who had used tacrolimus since age 7. The tumor was characterized as a childhood-type spitzoid melanoma featuring desmoplastic intradermal proliferation of enlarged melanocytes with significant nuclear atypia. Comparative genomic hybridization identified a deletion of distal 1q and segmental loss of 3p, with evidence of genomic instability consistent with melanoma.

The other 5 malignancies occurred in children ranging from 10.4 to 16.0 years, whose duration of tacrolimus exposure ranged from 4.1 to 10.9 years. No pattern was evident with regard to patient age at diagnosis or time since first dose of tacrolimus (Table II).

Observed and expected cancer incidences

As reported in Table III, the observed rate of all incident cancers, which was 6 events per 44,629 person-years (month 6 analysis), was consistent with expectations for a population matched by age, sex, race, and country of origin. We found no significant divergence between the number of observed and expected incident cancers; the overall SIR was 1.01 (95% confidence interval [CI], 0.37-2.20). Examining male and female incidence separately, SIRs for each included the null value of 1.0. The CIs were wide, reflecting the very low number of cancers. Time 0 analysis was similar, including the same 6 events in 45,279 person-years, corresponding to a SIR of 0.99 (95% CI, 0.36-2.16) (not shown).

Table I. Patient demographics and atopic dermatitis (*AD*) history at baseline*

	All patients (N = 7954)		North America (n = 5682)		Europe (n = 2272)	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Female sex	4166	52.4	3043	53.6	1123	49.4
Race/ethnicity						
White	4041	50.8	2001	35.2	2040	89.8
Black/African American	2404	30.2	2352	41.4	52	2.3
Asian	428	5.4	317	5.6	111	4.9
White Hispanic/Latino	698	8.8	692	12.2	6	0.3
Black Hispanic/Latino	95	1.2	93	1.6	2	0.1
Other	285	3.6	224	3.9	61	2.7
Age at enrollment, y						
<2	582	7.3	480	8.4	102	4.5
2-4	2293	28.8	1659	29.2	634	27.9
5-7	1800	22.6	1280	22.5	520	22.9
8-16	3060	38.5	2131	37.5	929	40.9
>16	218	2.7	131	2.3	87	3.8
Skin phototype						
Type I	723	9.1	429	7.6	294	12.9
Type II	2224	28.0	1127	19.8	1097	48.3
Type III	1784	22.4	1237	21.8	547	24.1
Type IV-VI	3222	40.5	2889	50.8	333	14.7
Prior tanning bed use	96	1.2	49	0.9	47	2.1
Current AD severity						
Clear	362	4.6	250	4.4	112	4.9
Mild	3609	45.4	2513	44.2	1096	48.2
Moderate	3273	41.1	2428	42.7	845	37.2
Severe	705	8.9	488	8.6	217	9.6
History of moderate-severe AD	5911	74.3	4254	74.9	1657	72.9
Comorbidities						
Allergies other than hay fever	2868	36.1	2134	37.6	734	32.3
Hay fever	2171	27.3	1514	26.6	657	28.9
Asthma	2461	30.9	1825	32.1	636	28.0
Allergies, hay fever, and asthma	873	11.0	622	10.9	251	11.0

*For each category, there were ≤10 missing data points and for demographic data (race, sex, age, phototype), ≤5 values were missing.

Table II. Age and duration of tacrolimus exposure among the 6 patients with incident malignancies

Incident malignancy	Age at cancer diagnosis, y	Time from first exposure to topical tacrolimus to cancer diagnosis, y
Alveolar rhabdomyosarcoma	16.0	10.9
Carcinoid tumor of the appendix	12.3	9.3
Chronic myeloid leukemia	15.3	4.1
Malignant paraganglioma	14.9	5.4
Spinal cord neoplasm	10.4	4.6
Spitzoid melanoma	14.8	7.6

A sensitivity analysis examined the effect of unidentified incident cancers occurring in patients after they were lost to follow-up, a period covering 27,676 unobserved person-years of experience. The analysis evaluated the effect of altering the hypothetical cancer incidence rate during this unobserved period. Table IV reveals that if the hypothetical event rate during the unobserved period were 3.0-times greater than background incidence, for a total of 20 events (6 observed plus 14 hypothetical events), the SIR would then be significantly greater than 1.00. Conversely, assuming an unobserved event rate up to 2.7-times greater than the background rate, no significant difference would be detected between the hypothetical mean cancer incidence and the population background incidence.

Table III. Standardized incidence ratio for all cancers (month 6 analysis)

Variable	Total
Observed person-years	44,629
Incidence of all cancers	
Expected cases	5.95
APPLES observed cases	6
Standardized incidence ratio (95% CI)	1.01 (0.37-2.20)

APPLES, A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis; *CI*, confidence interval.

Table IV. Sensitivity analysis of standardized incidence ratio (*SIR*) for all cancers*

Increased incidence (-fold)†	Observed incidents	Observed plus hypothetical incidents‡	SIR, mean (95% CI)
1.0	6	11	1.02 (0.51-1.83)
1.5	6	13	1.21 (0.64-2.07)
2.0	6	15	1.40 (0.78-2.30)
2.5	6	18	1.67 (0.99-2.65)
3.0	6	20	1.86 (1.14-2.87)

CI, Confidence interval.

*The SIR analysis here assumes a range of incidence rates, from 1.0- to 3.0-times the sex-, age-, and nationality-matched background incidence, occurring in patients after loss to follow-up.

†Relative to control population incidence.

‡Rounded to whole number.

DISCUSSION

APPLES is an international, longitudinal, observational cohort study in which patients received AD care from pediatricians and dermatologists using local standards of care. Along with another long-term safety study on topical TCIs,[14] APPLES provides direct prospective data to address longstanding hypotheses about cancer risk for children using these products for AD.[10,11,14,15]

Resolution of this issue is complicated by the need to disentangle the intrinsic cancer risk related to AD from incremental TCI treatment effects; some but not all studies have reported higher overall cancer incidence in patients with AD.[16] The possibility that AD treatments could contribute to such elevated risk also remains undecided. For instance, Arellano et al[15] found no evidence of a significant lymphoma risk associated with treatment with TCIs or TCSs but indicated that lymphoma risk might be intrinsically elevated in patients with more severe AD. Conversely, a 2011 US Food and Drug Administration report revisiting published and unpublished cases of lymphoma in children with AD suggested that although no causal relationship could be established, T-cell lymphoma risk might increase in proportion to cumulative tacrolimus exposure.[17]

In previous safety surveys, occasional observations of lymphomas have raised the possibility of a heightened risk of lymphoma or other cancers in patients with AD treated with TCIs. Such observations have proved difficult to interpret,[10] partly due to uncertainty regarding the possible interaction between baseline lymphoma risk and atopic disease or AD severity.[11,18]

The key finding in APPLES was that incidence of all cancers closely matched the expected rate in age- and sex-matched populations from the countries represented in the study. The 6 incident cancers identified were diverse, likely with unique etiologies. The timing of the diagnosis was not associated with the initiation of tacrolimus or enrollment in APPLES. The calculated incidence of malignancies in APPLES (SIR, 1.01; 95% CI, 0.37-2.20) provides no evidence for increased cancer risk with tacrolimus exposure and excludes the hypothesized tripling of cancer risk that the study was statistically powered to detect. This incidence was similar to the equivalent estimate (SIR, 1.2; 95% CI, 0.5-2.8) in a pediatric longitudinal cohort study of the Pediatric Eczema Elective Registry (25,000 person-years of follow-up) examining children exposed to pimecrolimus.[19]

Another large prospective study has reported interim results that provide further context to the current observations. The Joint European Longitudinal Lymphoma and Skin Cancer Evaluation (JOELLE), conducted using health care databases from 4 European countries, examined lymphoma and skin cancer incidences in individuals using tacrolimus or pimecrolimus, using propensity score matching to allow comparison with patients using TCS. Interim analysis of JOELLE pediatric data shows a borderline excess risk associated with tacrolimus use, relative to TCSs. The authors conclude that a causal relationship between tacrolimus exposure and incident lymphoma, if any, must be a small effect. Direct comparison between APPLES and JOELLE is complicated by the complete absence of incident lymphomas in APPLES and by the fact that other malignancies, such as the diverse spectrum of solid tumor diagnoses observed in APPLES, were not assessed in JOELLE.[14]

Limitations and strengths

Limitations of APPLES are common to observational studies, including the risk of biased enrollment or biased dropout, or both, as well as recall bias that

might affect reporting of patients' medical and treatment histories.

The study size represented a compromise between feasibility and the desire for sufficient power to detect an increase in risk of malignancies, given the rarity of these events among children and adolescents. APPLES was not powered to detect specific cancer types; for this reason, the primary end point was quantification of total incident malignancies.

The precision of the analysis is further limited by patient attrition, a problem that was anticipated for a long-term observational study with primary data collection, particularly one involving children and adolescents. To minimize patient attrition, study sites were encouraged to enroll patients from their own practice and to collect extensive contact information so that patients could be more easily located if they lost contact.

In addition, a planned sensitivity analysis addressed the possibility of bias associated with patient drop out; that is, the possibility that cancer incidence might occur at a higher rate in patients who had been lost to follow-up, relative to patients who remained in the study. This sensitivity analysis showed that unobserved cancer events would need to occur at a rate >2.7-times higher than the control incidence for the total hypothetical incidence to significantly exceed the expected incidence of pediatric malignancies over 10 years. Thus, it appears that neither AD itself nor tacrolimus exposure was associated with heightened risk of cancer in this pediatric population.

CONCLUSION

In this prospective evaluation of our cohort of approximately 8000 children with AD who were treated with tacrolimus ointment, 1 cutaneous malignancy and no instances of lymphoma were observed over the duration of the study. Malignancies were observed at the expected rate for the age-, sex- and, where possible, race-matched general population. This conclusion is robust to varying assumptions about cancer incidence among patients lost to follow-up. Thus, APPLES found no evidence to support the hypothesized increased cancer risk in children with AD treated with tacrolimus ointment.

A complete listing of APPLES study sites is available at https://data.mendeley.com/datasets/sxgkpjdxsw/1. We gratefully acknowledge the study center personnel and patients and also thank John Ashkenas, PhD, for medical writing support, made possible by LEO Pharma in accordance with Good Publication Practice guidelines.

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