Public Assessment Report
for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Wynzora
(calcipotriol and Betamethasone dipropionate)

DK/W/0030/pdWS/001

Marketing Authorisation Holder: Almirall, S.A.

Rapporteur:	DK
Finalisation procedure (day 120):	28-11-2022

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Wynzora
INN (or common name) of the active substance(s):	Calcipotriol and Betamethasone dipropionate
MAH:	Almirall, S.A.
Currently approved Indication(s)	Wynzora is indicated for topical treatment of mild to moderate psoriasis vulgaris, including scalp psoriasis, in adults.
Pharmaco-therapeutic group (ATC Code):	D05AX52
Pharmaceutical form(s) and strength(s):	50 micrograms/g + 0.5 mg/g cream

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2, 4.8, 5.1 and 5.2.
No PL changes are proposed.

II. RECOMMENDATION

The MAH should submit a Type IB variation within 30 days applying for the proposed changes to the approved SmPC.

Proposed change in Section 4.2 Posology and method of administration

Paediatric population

The safety and efficacy of Wynzora Cream in children below 18 years have not been established.

Currently available data in children aged 12 to 17 years are described in sections 4.8, 5.1 and 5.2.

Proposed additional text in Section 4.8 Undesirable effects

Paediatric population

In an uncontrolled clinical trial with 7 subjects aged 12 to 17 years no adverse reactions were reported. See section 5.1 for further details regarding the trial.

In this limited sample, no clinically relevant differences have been observed between the safety profiles of Wynzora cream in adult and adolescent populations.

Proposed additional text in Section 5.1 Pharmacodynamic properties

Paediatric population
HPA axis suppression was evaluated in 7 adolescent subjects aged 12 to 17 years with extensive psoriasis involving 10.5-16% of the body surface area (including scalp). Treatment consisted of once daily application of Wynzora Cream to the body and scalp for up to 8 weeks. The mean weekly dose up to Week 8 was 27.2 g. Adrenal suppression was not observed in any subjects (N=6) after 4 or 8 weeks of treatment (one subject had an abnormal ACTH-stimulated cortisol at baseline and discontinued the trial prematurely). There were no changes in calcium metabolism.

Proposed change in Section 5.2 Pharmacokinetic properties

One of 27 (3.7%) *adult* subjects had quantifiable levels of calcipotriol at Week 4. For the major metabolite of calcipotriol, MC1080, 3 of 27 (11.1%) subjects had quantifiable levels at Week 4. No subjects had quantifiable levels of calcipotriol or MC1080 at Week 8.

For betamethasone dipropionate, there were 3 *adult* subjects (11.1%) with quantifiable levels of betamethasone dipropionate at Week 4. The major metabolite of betamethasone dipropionate, betamethasone 17-propionate (B17P), was quantifiable in 13 subjects (48.1%) at Week 4. No subjects had quantifiable levels of betamethasone dipropionate at Week 8, whereas 7 out of 17 (41.2%) subjects with quantifiable levels of B17P at Week 8.

Paediatric population

In a study including 7 adolescent patients (6 provided PK data), calcipotriol and its metabolite MC1080 were below the lower limit of quantification in all plasma samples at Week 4. Betamethasone dipropionate were below the lower limit of quantification in all plasma samples at Week 4. The metabolite, betamethasone 17-propionate (B17P), was quantifiable in 3 of 6 (50%) subjects.

III. INTRODUCTION

On 2 March 2022, the MAH submitted a completed paediatric study for Wynzora, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH proposed the following regulatory action: SmPC changes are proposed in sections 4.2, 4.8, 5.1 and 5.2.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

The investigational medicinal product used in the submitted study MC2-01-C6 was MC2-01 cream (developmental code for Wynzora® Cream), a fixed combination product containing calcipotriol 50 micrograms/g, a vitamin D analogue, and betamethasone dipropionate (BDP) equivalent to 0.5 mg/g betamethasone, a potent steroid.

Wynzora® Cream was approved in the European Union (EU) via the Decentralised Procedure (positive End of Procedure letter was received June 29, 2021). The indication in the EU is topical treatment of mild to moderate psoriasis vulgaris, including scalp psoriasis, in adults.

There is no specific paediatric formulation.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report(s) for:

Trial no.: MC2-01-C6: A multicentre, open-label, single-group maximal use trial, evaluating the safety and pharmacokinetic profile of the active ingredients and their metabolites after application of MC2-01 cream in adolescent subjects (age 12 to 16 years, 11 months) with extensive psoriasis vulgaris.

2. Clinical study

➢ Description

This was a phase 2, open-label, single-group, multicentre trial in which the investigational product, MC2-01 cream, was investigated in adolescent subjects (age 12 to 16 years, 11 months) with clinically diagnosed extensive psoriasis vulgaris.

The trial included a maximum of 6 weeks screening period, an 8-week treatment period, and a maximum 4-week post-treatment follow-up period.

Subjects who fulfilled all inclusion and none of the exclusion criteria at Day 0/Visit 1 were enrolled in the trial and applied MC2-01 cream topically once daily to affected areas for 8 weeks.

➢ Methods

- Objective(s)

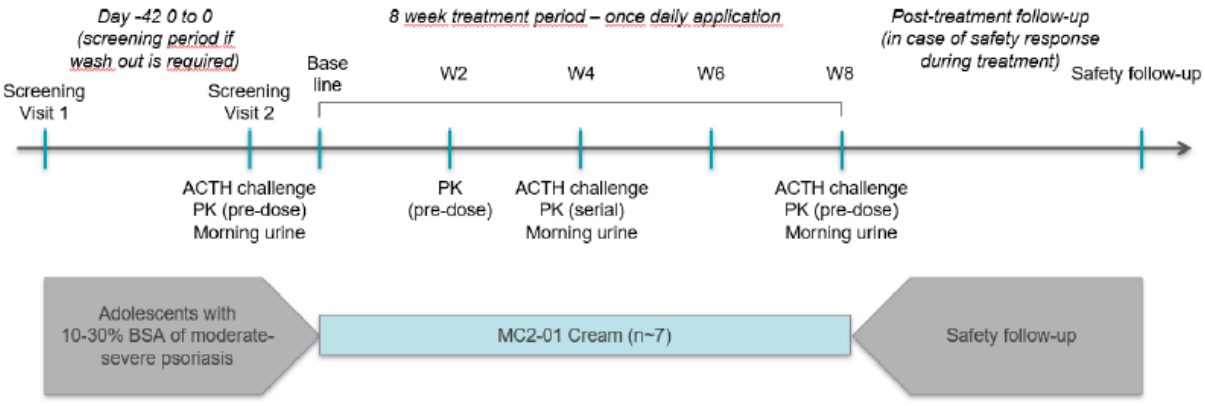
  The primary objectives were to evaluate the effect of MC2-01 cream on the HPA axis and calcium metabolism following once daily topical application under maximum-use conditions in subjects with extensive psoriasis vulgaris.

  The secondary objective was to evaluate the pharmacokinetic profile of the active ingredients and their main metabolites following once daily topical application of MC2-01 cream under maximum-use conditions in adolescent subjects (age 12 to 16 years, 11 months) with extensive psoriasis vulgaris.

- Study design

  An outline of the trial design for trial MC2-01-C6 is depicted in Figure 2.

Figure 2: MC2-01-C6 - clinical trial design



- Study population /Sample size

  The trial included generally healthy male or female subjects between 12 to 16 years, 11-month of age with a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration that involved the body (trunk and/or limbs), with or without scalp. This indication had to be confirmed by the following inclusion criteria: Physician's Global Assessment (PGA) of disease severity of at least moderate severity on the treatment area and a treatment area involving 10-30% of the body (trunk and/or limbs) and scalp. Furthermore, a normal HPA axis function including a serum cortisol concentration above 4.5 mcg/dL (160 nmol/l) before ACTH challenge and equal or above 18 mcg/dL (500 nmol/l) 30 minutes after ACTH challenge at screening was a requirement for inclusion.

  Blood samples for PK assessments were collected at:
  • SV2 (baseline sample)
  • Week 2 (single time point before application of IMP)
  • Week 4 before application of IMP and then at 1, 3, and 5 hours after the application
  • Week 8 (single time point. Subject should not apply IMP on the day of the Week 8 visit)

  Initially it was planned to enroll about 30 subjects at approximately 12 sites in Europe (10 sites were initiated in Germany, Czech Republic and Hungary). The choice of sample size in this trial was based on regulatory considerations with respect to common practice in maximum use studies. For the PK population, the aim was to have at least 20 subjects included that have at least completed Week 4 visit (Visit 3).

- Treatments

  Each subject eligible for the trial was treated with MC2-01 cream once-daily for 8 weeks. There was no reference product used in this trial.

- Outcomes/endpoints

  Primary endpoint
  HPA axis: Subjects with serum cortisol level of less than 18 mcg/dL at 30 minutes after ACTH challenge test at Week 4 and Week 8. Serum cortisol was measured by the DiaSorin LIAISON® immunoassay. A 30-minute post-stimulation level below 18 mcg/dL (500 nmol/l) was defined as an adrenal suppression.

  Calcium metabolism
  Changes from Baseline to Week 4 and Week 8 in:
  o Albumin corrected serum calcium
  o Ratio of urinary calcium to creatinine (spot analysis, second morning urine sample)

  Secondary endpoints
  Plasma PK parameters (AUC0-t, AUC0-5, Cmax and Tmax) were assessed at Week 4. Blood samples were assayed for concentrations of the active ingredients (BDP and CAL) and for their main metabolites MC1080 and betamethasone 17-propionate, respectively.

  Further safety endpoints
  o Adverse events (AEs) and serious adverse events (SAEs)
  o Local skin reaction (LSR)
  o Changes in safety laboratory test results

- Changes in ECGs
- Changes in vital signs and physical examinations

Other endpoints

- The proportion of subjects with treatment success, defined as a minimum 2-point decrease from baseline in the Physicians Global Asessment (PGA) on the body (trunk and/or limbs), and with or without scalp at Week 4 and Week 8

- Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale (PTCS)

- Statistical Methods

The choice of sample size in this trial is not based on statistical considerations, but rather on regulatory considerations with respect to common practice in maximum use studies evaluating pharmacokinetic profiles and evidence of HPA safety.

Statistical analysis was performed using SAS 9.4. All endpoints were analysed using descriptive statistics.

PK parameters AUC_{0-5} and C_{max} were calculated using standard formulas inserting the lower limit of quantification (LLOQ) for non-quantifiable levels of the analyte; therefore, AUC_{0-5} is an upper limit in case at least one time-point showed a non-quantifiable level of the analyte, and Cmax is an upper limit in case all time points showed non-quantifiable levels of the analyte. For a given analyte, the PK parameters AUC_{0-t} and T_{max} were calculated if at least one time-point shows a quantifiable level of the analyte.

The analysis populations were defined in the clinical trial protocol as follows:

- Safety population: all subjects who are enrolled in the trial and dispensed the trial medication at Visit 1/Day 0, excluding subjects who return all of the trial medication unused. The Safety population was used for all safety analyses other than evaluation of the HPA-axis

- PK population: all subjects in the Safety population who have received the planned application of treatment at the Week 4 visit and have had at least one blood draw for PK assessment at Week 4

- HPA population: all subjects in the Safety population that show normal HPA function at SV2. The HPA population was used for the HPA axis suppression analysis.

➢ **Results**

- Recruitment/ Number analysed

Based on recommendation from FDA the MC2-01-C6 trial was subject to a temporary halt after 9 subjects had provided informed consent/assent and 7 subjects had been enrolled. The sponsor decided not to re-initiate the MC2-01-C6 trial following the receival of the NDA approval letter.

Seven (7) subjects have been enrolled in the trial and treated with IMP and were included in the Interim Safety population.

One out of the 7 subjects discontinued the trial prematurely at study day 29 due to a major protocol deviation: the subject had no normal HPA axis function at screening and missed the inclusion criteria.

This one subject was excluded from the HPA population as it did not show normal HPA function at SV2. In addition, it was excluded from PK population as no Week 4 PK assessment was performed due to early discontinuation of the subject.

- Baseline data

4 (57.1 %) of the subjects were male. The mean age was 14.7 years with an age range between 12 and 16 years. All subjects were white (100%) and Non-Latino and Non-Hispanic.

The mean body mass index (BMI) was 25.72 kg/m^2 and ranged between 21.3 and 35.3 kg/m^2.

The mean duration of psoriasis at study start (ICF date) averaged about 3 years. Overall, the duration varied with a range between 1 and more than 6 years.

PGA of psoriasis severity on the treatment area at Visit 1 (baseline value) was in line with the inclusion criteria (at least moderate). All subjects had a moderate PGA (PGA score=3) showing a moderate disease severity.

At Baseline about 13% of the body surface area (BSA) in total was affected by psoriasis (mean = 13.43%) with a range between 10.5% and 16.0%.

Assessor's comment

Inclusion criteria for the MC2-01-C6 trial included having a treatment area between 10% and 30% of the BSA on the body and scalp. For enrolled subjects, the percentage of BSA affected by psoriasis was at the lower end of this range, between 10.5 % and 16.0 %. The latter actual figures should be reflected in the SmPC. Furthermore, for transparency reasons, the number of subjects enrolled should be stated. Hence, the MAH is asked to amend the first sentence of its proposed additional text in SmPC section 5.1 as follows ("Red" will highlight new text and "~~crossed out~~" text will highlight deletions):

"*Paediatric population*

HPA axis suppression was evaluated in 7 adolescent subjects age 12 to 17 years with extensive psoriasis involving ~~10-30~~10.5-16.0% of the body surface area (including scalp)." (**OC, see LoQ**)

- Efficacy results

Physicians Global Assessment

During treatment phase all subjects show a clear improvement of psoriasis severity starting early in treatment phase from Week 2 on. At Week 4 the PGA of all 7 subjects improved from 'moderate' to 'mild' or 'almost clear'.

All in all, 6 out of the 7 treated subjects reached treatment success during treatment phase (see Text Table 12-4). Only one single subject did not reach a treatment success during treatment phase. However, this subject missed several IMP applications and had a low compliance rate. Treatment compliance in the first 4 weeks for this subject were 72.4% and in the last 4 weeks treatment compliance was 66.7%.

Another subject that was a treatment success at Week 6, had psoriasis at mild intensity at Week 8 (Visit 5) and was not a treatment success at Week 8 (Visit 5). The subject missed 12 applications

in the period between the Week 6 and the Week 8 visits and this may explain the increase in psoriasis intensity from Week 6 to Week 8.

Text Table 12-4: PGA treatment success – Interim Safety population

		Total (N = 7)
Overall	n' (%)	7 (100.0)
	n (%)	6 (85.7)
	95% CI	42.1, 99.6
Week 4/ Visit 3	n' (%)	7 (100.0)
	n (%)	4 (57.1)
	95% CI	18.4, 90.1
Week 8/ Visit 5	n' (%)	6 (85.7)
	n (%)	4 (66.7)
	95% CI	22.3, 95.7

PGA=Physician global assessment.
N: the number of subjects in the Interim Safety population. n: the number of subjects within a specific category.
n': the number of valid observations.
Confidence interval (CI) is calculated using Clopper-Pearson method.
Treatment success is defined as at least 2-point decrease from Baseline in the PGA on the trunk, limbs, and scalp.
Source: Table 14.4.1.2

Psoriasis Treatment Convenience Scale (PTCS) score at Week 2, 4, and 8

The total sum score as well as subjects' answers to each separate question confirmed efficacy of the IMP and convenience with the IMP treatment at each visit of treatment phase.

Assessor's comment

The design (open, uncontrolled) and size (n=7) of the prematurely discontinued study MC2-01-C6 does not allow for conclusions regarding efficacy of MC2-01 cream in adolescents. It is accordingly endorsed that the MAH has not proposed to include in the SmPC any data on efficacy assessments from the submitted study.

- Safety results

Extent of Exposure

Duration of IMP treatment and IMP exposure

According to the trial protocol, subjects who completed the trial should have applied the IMP once daily for a period of 56±2 days (until Week 8 visit).

Text Table 10-9 displays the treatment duration and the number of missed doses for the overall trial and for the period from start of IMP to Week 4 visit, which was the timepoint of PK analysis sampling (scheduled at study day 29±2).

The mean duration of treatment was 53.7 days (median=56 days) in total and 28.3 days (median=29 days) up to Week 4 visit.

The mean number of exposure days was 47.7 (median=51) in total and 26.3 (median=27) up to Week 4 visit.

Text Table 10-9: Extend of Exposure – Interim Safety Population

	Up to Week 4 /Visit 3	Total treatment period Up to Week 8
	Total (N = 7)	Total (N = 7)
Total duration of IMP treatment (days)		
n	7	7
Mean	28.3	53.7
SD	1.0	12.2
Median	29.0	56.0
Q1, Q3	27.0, 29.0	54.0, 61.0
Min, Max	27, 29	27, 63
Extent of exposure (days)		
n	7	7
Mean	26.3	47.7
SD	2.7	11.5
Median	27.0	51.0
Q1, Q3	25.0, 28.0	41.0, 56.0
Min, Max	21, 29	26, 61
Number of missed doses [1]		
n [1]	5	6
Mean	2.8	7.0
SD	2.9	7.2
Median	2.0	3.5
Q1, Q3	1.0, 2.0	2.0, 14.0
Min, Max	1, 8	1, 18

N: the number of subjects in the Interim Safety population.
n: the number of valid measurements or the number of subjects within a specific category.
Percentages are calculated as (100 x n/N).
Total duration (days) is defined as (date of the last dose – date of the first dose + 1).
Extent of exposure (days) is defined as (number of required days – number of missed doses).
Compliance is estimated as [100% * (number of required days – number of missed doses)/ number of required days]. Periods of approved discontinuations are not taken into account in the calculation of extent of exposure and compliance.
[1] Only subjects with at least one missed dose were included into this summary.
Source: Table 14.1.13.1 and Table 14.1.13.3

Amount of IMP exposure

According to the protocol subjects applied the IMP topically once daily to affected areas. They should apply enough IMP to treat the entire affected areas and rub in gently to ensure that the plaques were saturated with the medication.

Text Table 10-10 shows the amount of IMP used during the whole treatment period (Visit 1 to Week 8 visit) and during the period from start of IMP to Week 4 (Visit 3), which was the timepoint of PK analysis sampling (scheduled at study day 29±2).

The mean amount of IMP used during the total treatment period was about 222 g (median ≈138 g) and about 94 g (median ≈59 g) from start of IMP up to Week 4 (see Text Table 10-10).

Text Table 10-10: Amount of IMP Exposure – Interim Safety Population

	Up to Week 4 /Visit 3	Total treatment period up to Week 8
	Total (N = 7)	Total (N = 7)
Total amount of IMP used (g)		
n	7	7
Mean	94.000	222.163
SD	78.997	202.772
Median	58.880	137.860
Q1, Q3	41.080, 178.140	77.160, 501.860
Min, Max	27.98, 233.16	27.98*, 508.68
Average weekly amount of IMP used (g)		
n	7	7
Mean	23.417	27.226
SD	20.210	23.908
Median	14.212	15.820
Q1, Q3	9.916, 42.999	9.645, 56.520
Min, Max	7.25[1], 60.45	7.25, 65.06

N: the number of subjects in the Interim Safety population.
n: the number of valid measurements or the number of subjects within a specific category. Percentages are calculated as (100 x n/N).
Total dose (g) is assessed as (weight of the tube dispensed – weight of the tube returned) summed over all tubes used and returned. Lost and unused tubes were not accounted for in the calculation of total dose.
[1] Min value of 27.98g results from one subject, which discontinued with Week 4 visit
Source: Table 14.1.13.1 and **Table** 14.1.13.3

Measurement of Treatment Compliance

For assessment of treatment compliance, subjects were asked to complete a dosing diary documenting the daily application during the entire treatment period.

The mean compliance was consistently high with about 90% (median=94.44%) in the total treatment period (start of IMP to Week 8) and more than 93% (median=96.3%) in the period up to Week 4.

2 subjects revealed a low compliance rate during the treatment phase:

- Subject #11002 missed 12 applications between Week 4 (Visit 3) and Week 8 (Visit 5). Consequently, the compliance rate between Week 4 (Visit 3) and Week 8 (Visit 5) was 61.3%, only. Of the 13 IMP applications missed between Week 4 and the Week 8 visit, 12 of these missed applications were in the period between the Week 6 and the Week 8 visits.
- Compliance rate between Visit 1 and Week 4 (Visit 3) was 96.6%.
- Subject #11001 missed several applications throughout the trial resulting in low compliance rate:
- Compliance rate between Visit 1 and Week 2 (Visit 2) was 68.8%
- Compliance rate between Visit 1 and Week 4 (Visit 3) was 72.4%, in the last week prior to the PK evaluation at Week 4 (Visit 3) only one application was missed.
- Compliance rate between Week 4 (Visit 3) and Week 8 (Visit 5) was 66.7%

Assessor's comment

The currently approved SmPC in Europe for Wynzora® Cream (with an adult-only indication) recommends that the maximum daily dose should not exceed 15 g. On the basis of BSA to body mass ratio considerations, the MAH's critical expert overview states (page 12) that in the US, "*the maximal weekly use of MC2-01 cream in adolescence is proposed limited to 60 g*". While the current FDA label for Wynzora® Cream in fact includes no adolescent indication or proposed posology in this age group, such information has been incorporated in the US prescribing information for Taclonex® Topical Suspension, the tradename for Daivobet® Gel in the US. Hence, the latter states that "*Patients age 12 to 17 years should not use more than 60 grams per week.*"[1]

Based on the cited US prescribing information and in accordance with the fact that in Trial MC2-01-C6, range of percentage of BSA affected by psoriasis was at the lower end of the inclusion criterium of 10%-30% BSA involvement, "maximal usage" conditions were not achieved in the majority of MC2-01 cream-treated adolescent subjects in the submitted study: According to Text Table 10-10 reproduced above, the mean weekly IMP dose up to Week 4 was 23.4 g (range from 7.25 g to 60.45 g). For transparency reasons and with an eye to contextualize results for PK as well as data on potential effects on HPA axis and calcium metabolism, the MAH is asked to provide, in its proposed additional text in SmPC section 5.1, data for extent of IMP exposure up to Week 4 in trial MC2-01-C6 in terms of average amount of product used per week. **(OC, see LoQ)**

1.TACLONEX Topical Suspension prescribing information. US Food and Drug Administration. Available online at

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=T&ai=0 (accessed on May 16, 2022).

Pharmacokinetics

BDP, CAL and its metabolite MC1080 were below the LLOQ in all plasma samples of all subjects. The metabolite of BDP, betamethasone 17-propionate, was quantifiable in 3 out of 6 (50 %) subjects with C_{max} ranging from 36.3-75.2 pg/mL and an AUC_{0-5} ranging from 164 pg*h/mL to 314 pg*h/mL.

When comparing the systemic exposures of B17P after MC2-01 cream administration in MC2-01-C6 and MC2-01-C3 trial conducted in adults (see further details in the Summary of Product Characteristics (SmPC) Section 5.2 Pharmacokinetic properties) [SIC]. It should be noted that comparison is based on a limited number of samples in both trials with B17P levels above the LLOQ. Furthermore, there were a difference in the patient populations in the two trials, with MC2-01-C6 subjects having a mean affected BSA of 13.7%, and the MC2-01-C3 subjects had a mean affected BSA of 25%. B17P was quantifiable in 13 of 27 subjects (48%) at Week 4 in MC2-01-C3 with a mean C_{max} and AUC_{0-7} of 96 pg/mL and 419 pg*h/mL, respectively. In MC2-01-C6 3 subjects out of 6 (50%) had measurable levels of B17P at Week 4 with a mean C_{max} of 37.5 pg/ml, and mean AUC_{0-5} of 162 pg*h/ml. The lower mean C_{max} and the lower AUC may reflect the difference in BSA affected in the two populations, suggesting that the bioavailability of BDP were in the same range.

Assessor's comment

Sensitive and adequately validated liquid chromatography-tandem mass spectrometric methods (LC-MS/MS) were used to quantify BDP, CAL and their respective metabolites B17P and MC1080 in plasma samples collected in study MC2-01-C6. The only quantifiable analyte was B17P, which was above the LLOQ in 3 out of 6 subjects. Although the half-life of B17P is relatively long and PK measurements at Week 8 were limited to single time point trough evaluation, the data presented in Text Table 12-1 above do not overall indicate accumulation of the quantifiable BDP metabolite.

Overall, the submitted adolescent Trial MC-01-C6 demonstrates very low systemic exposure to Wynzora® Cream's active substances and their main metabolites. It is endorsed that there appears to be no clinically meaningful difference in the relative bioavailability of BDP in adolescents vs. adults based on comparison of results from the currently submitted study and those of the MUsT in adults (study MC2-01-C3), with the latter reviewed during the initial Wynzora MAA.

For transparency reasons, in the MAH's proposed "*Paediatric population*" sub-section added to SmPC section 5.2, the number of subjects enrolled should be stated initially (**OC, see LoQ**).

HPA axis

The 30 minutes ACTH stimulated cortisol values for all subjects that completed the trial were included in the HPA population (N=6). None of the subjects within the HPA population showed an HPA axis suppression at any timepoint.

Assessor's comment

Based on a conservative choice of cut-off value of serum cortisol level 30 min after ACTH challenge below 18 mcg/dL (500 nmol/l), no subject showed HPA axis suppression at Week 4 or Week 8. These results (and those pertaining to calcium metabolism, see below) should be interpreted with caution, given the previously mentioned limitations, i.e. low number of enrolled subjects in a prematurely halted trial, low treatment adherence in two of six subjects with average weekly IMP dose applied for the total study population not meeting conditions of maximal use.

Calcium metabolism

In the present trial, all levels of uncorrected serum calcium were normal, whereas there was one subject (# 11001) that had levels of albumin corrected serum calcium that were constant at all visits but were marginally below the lower limit of reference. This subject had marginally elevated serum calcium at SV2 (baseline value) and levels decreased to normal during the trial.

Furthermore, no subjects had PTH levels below lover limit of reference.

Assessor's comment

In study MC2-01-C6, there were no laboratory parameter findings indicating effects of MC2-01 cream on calcium metabolism.

Adverse events

- In total, there were 4 adverse events in 3 of the 7 subjects. The adverse events were the following: nasopharyngitis, tonsillitis, dysuria, and acne. All the adverse events were treatment emergent and of mild intensity. None of the adverse events were deemed treatment related.

- There were no serious adverse events during the trial.

- There were no subjects with perilesional or lesional LSR [local skin reaction] during the trial neither before first IMP application (Visit 1) nor throughout the entire treatment phase. In addition, not any subject reported a symptom of burning or pain after IMP application throughout the total treatment phase.

Assessor's comment

No treatment-related adverse events or new adverse events were observed.

3. Discussion on clinical aspects

Assessor's comment

Wynzora® Cream (development code: MC2-01 cream) is a fixed combination product containing calcipotriol 50 micrograms/g, a vitamin D analogue, and betamethasone dipropionate (BDP) 0.5 mg/g, a potent steroid. The product is approved for topical treatment of mild to moderate psoriasis vulgaris, including scalp psoriasis, in adults.

With the current procedure, the MAH is submitting the final paediatric study report for MC2-01-C6, a maximal usage trial in adolescents and applies for related amendments to SmPC sections 4.2, 4.8, 5.1 and 5.2. No indication or posology in adolescents is applied for. As off-label use in adolescents is likely, it is of value to investigate the safety of the product in this age group, with special focus on evaluation of HPA axis suppression.

Trial MC2-01-C6 was an international, multicentre, prospective, open-label, non-controlled maximal use trial (MUsT), designed to evaluate the safety and PK profile of the active ingredients and their metabolites after application of MC2-01 cream for an 8-week treatment period in adolescent subjects (age 12 to 16 years, 11 months) with extensive psoriasis vulgaris affecting 10-30% of the body surface area (including scalp).

The PK results indicated that systemic absorption of the product is marginal also in the adolescent population: No plasma sample had a quantifiable concentration of BDP, CAL or the latter's metabolite MC1080, with the former's main metabolite B17P measurable at concentrations close to the LLOQ in 3 out of 6 subjects. No evidence of HPA axis suppression or influence on calcium metabolism was observed, and no treatment-related adverse event or any new adverse event was recorded.

Trial MC2-01-C6, initially planned to enrol 30 subjects and conducted in accordance with an FDA-requested Paediatric Study Plan, was prematurely halted after the FDA waived the requirement to conduct studies in paediatric subjects. Consequently, the actually provided study enrolled only 7 subjects, of which 6 completed (1 subject was discontinued after adrenal suppression was seen as baseline). This sample size is a major limitation. Further limitations to the value of the submitted safety data include a relatively low percentage of affected BSA in the context of a MUsT (mean of 13.4%, upper range 16.0%) and accordingly low average amount of IMP used per week (<30 g); this should be reflected in the update to SmPC section 5.1. **(OC, see LoQ)**

V. PPDAR REQUEST FOR SUPPLEMENTARY INFORMATION

Question 1 (SmPC, section 5.1, Pharmacodynamic properties):

For transparency reasons and with an eye to contextualize results for PK as well as data on potential effects on HPA axis and calcium metabolism, the MAH is asked to implement the following revisions to its proposed additional text ("Red" will highlight new text and "~~crossed-out~~" text will highlight deletions):

"*Paediatric population*

HPA axis suppression was evaluated in 7 adolescent subjects age 12 to 17 years with extensive psoriasis involving ~~10-30~~10.5-16.0% of the body surface area (including scalp)." Treatment consisted of once daily application of Wynzora Cream to the body and scalp for up to 8 weeks. The mean weekly dose up to Week 4 was 23.4 g. Adrenal suppression was not observed in any subjects (N=6) after 4 or 8 weeks of treatment (one subject had an abnormal ACTH-stimulated cortisol at baseline and discontinued the trial prematurely). There were no changes in calcium metabolism.

Question 2 (SmPC, section 5.2, Pharmacokinetic properties):

For transparency reasons, the MAH is asked to implement the following revisions to its proposed additional text ("Red" will highlight new text and "~~crossed-out~~" text will highlight deletions):

"*Paediatric population*

In a study including 7 adolescent patients (6 provided PK data), ~~C~~calcipotriol and its metabolite MC1080 were below the lower limit of quantification in all plasma samples at Week 4. Betamethasone dipropionate were below the lower limit of quantification in all plasma samples at Week 4. The metabolite, betamethasone 17-propionate (B17P), was quantifiable in 3 of 6 (50%) subjects."

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1 (SmPC, section 5.1, Pharmacodynamic properties):

For transparency reasons and with an eye to contextualize results for PK as well as data on potential effects on HPA axis and calcium metabolism, the MAH is asked to implement the following revisions to its proposed additional text ("Red" will highlight new text and "~~crossed-out~~" text will highlight deletions):

"*Paediatric population*

HPA axis suppression was evaluated in 7 adolescent subjects age 12 to 17 years with extensive psoriasis involving ~~10-30~~10.5-16.0% of the body surface area (including scalp)." Treatment consisted of once daily application of Wynzora Cream to the body and scalp for up to 8 weeks. The mean weekly dose up to Week 4 was 23.4 g. Adrenal suppression was not observed in any subjects (N=6) after 4 or 8 weeks of treatment (one subject had an abnormal ACTH-stimulated cortisol at baseline and discontinued the trial prematurely). There were no changes in calcium metabolism.

MAH´s response to Question 1

The Applicant agrees to implement the requested revision to the initial text proposed by MAH in section 5.1 of the SmPC related to the involving % of the body surface area, according with the data provided in page age 65 in the Interim Clinical Report.

Text Table 10-5: Baseline Disease Characteristics – Interim Safety population

	Total (N = 7)
Duration of disease [months][1]	
Mean	39.86
SD	25.19
Median	36.24
Min, Max	12.1, 74.5
Fitzpatrick skin type at Screening [n (%)]	
I	0
II	2 (28.6)
III	4 (57.1)
IV	1 (14.3)
V	0
VI	0
PGA at Visit 1/ Baseline [n (%)]	
0 – Clear	0
1 – Almost clear	0
2 – Mild	0
3 – Moderate	7 (100.0)
4 – Severe	0
Mean	3.0
SD	0.0
Median	3.0
Min, Max	3, 3
Total BSA involvement at Visit 1/ Baseline [n (%)]	
Mean	13.43
SD	2.32
Median	13.50
Min, Max	10.5, 16.0
BSA involvement scalp at Visit 1/ Baseline [n (%)]	
Mean	2.0
SD	1.2
Median	2.0
Min, Max	1, 4
BSA involvement body[2] at Visit 1/ Baseline [n (%)]	
Mean	11.43
SD	2.28
Median	11.00
Min, Max	8.5, 15.0

BMI=Body Mass Index; BSA=Body Surface Area; PGA=Physician Global Assessment.
N: number of subjects in Interim Safety population. n: the number of valid measurements or the number of subjects within a specific category. Percentages are calculated as (100 x n/N).
[1] Duration of disease is calculated in months as (date of informed consent – date of diagnosis + 1) / 30.4375.
[2] Body= neck, trunk and/or limbs
Source: Table 14.1.7 and Table 14.1.8

Considering that the study was finalized at week 8, and in accordance with the provided in page 72 in the Interim Clinical Report

Text Table 10-10: Amount of IMP Exposure – Interim Safety Population

	Up to Week 4 /Visit 3	Total treatment period up to Week 8
	Total (N = 7)	Total (N = 7)
Total amount of IMP used (g)		
n	7	7
Mean	94.000	222.163
SD	78.997	202.772
Median	58.880	137.860
Q1, Q3	41.080, 178.140	77.160, 501.860
Min, Max	27.98, 233.16	27.98*, 508.68
Average weekly amount of IMP used (g)		
n	7	7
Mean	23.417	27.226
SD	20.210	23.908
Median	14.212	15.820
Q1, Q3	9.916, 42.999	9.645, 56.520
Min, Max	7.25[1], 60.45	7.25, 65.06

N: the number of subjects in the Interim Safety population.
n: the number of valid measurements or the number of subjects within a specific category. Percentages are calculated as (100 x n/N).
Total dose (g) is assessed as (weight of the tube dispensed – weight of the tube returned) summed over all tubes used and returned. Lost and unused tubes were not accounted for in the calculation of total dose.
[1] Min value of 27.98g results from one subject, which discontinued with Week 4 visit
Source: Table 14.1.13.1 and **Table** 14.1.13.3

Since the approved duration for treatment included is up to 8 weeks; the applicant proposes to include the mean weekly dose up to 8 weeks which is 27.2 g.

"*Paediatric population*
HPA axis suppression was evaluated in 7 adolescent subjects aged 12 to 17 years with extensive psoriasis involving ~~10-30~~10.5-16.0% of the body surface area (including scalp)." Treatment consisted of once daily application of Wynzora Cream to the body and scalp for up to 8 weeks. The mean weekly dose up to Week 48 was 27.2~~3.4~~ g. Adrenal suppression was not observed in any subjects (N=6) after 4 or 8 weeks of treatment (one subject had an abnormal ACTH-stimulated cortisol at baseline and discontinued the trial prematurely). There were no changes in calcium metabolism. "

The updated version of the SmPC is provided as word version in the working documents folder (clean and highlighted word versions).

Assessment of the Applicant's response

The MAH's response is endorsed.

Rationale:

As highlighted by the MAH, the recommended treatment period is up to 8 weeks. In further considering that primary endpoints of the submitted study MC2-01-C6 included evaluation of HPA axis suppression (and calcium metabolism) at both Week 4 and Week 8, the MAH's proposal to include the mean weekly dose up to 8 weeks is acceptable.

Conclusion: Issue resolved.

Question 2 (SmPC, section 5.2, Pharmacokinetic properties):

For transparency reasons, the MAH is asked to implement the following revisions to its proposed additional text ("Red" will highlight new text and "~~crossed out~~" text will highlight deletions):

"*Paediatric population*

In a study including 7 adolescent patients (6 provided PK data), ~~C~~calcipotriol and its metabolite MC1080 were below the lower limit of quantification in all plasma samples at Week 4. Betamethasone dipropionate were below the lower limit of quantification in all plasma samples at Week 4. The metabolite, betamethasone 17-propionate (B17P), was quantifiable in 3 of 6 (50%) subjects."

MAH´s response to Question 2

The Applicant agrees to implement the requested revisions to the initial text proposed by MAH in section 5.2 of the SmPC.

The updated version of the SmPC is provided as word version in the working documents folder (clean and highlighted word versions).

Assessment of the Applicant's response

It is endorsed that the requested revisions have been implemented in the updated SmPC.

Conclusion: Issue resolved.

VII. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH has responded satisfactorily to the raised questions.

- **Recommendation**

The MAH should submit a Type IB variation within 30 days applying for the proposed changes to the approved SmPC.

Proposed change in Section 4.2 Posology and method of administration

Paediatric population

The safety and efficacy of Wynzora Cream in children below 18 years have not been established.

Currently available data in children aged 12 to 17 years are described in sections 4.8, 5.1 and 5.2.

Proposed additional text in Section 4.8 Undesirable effects

Paediatric population

In an uncontrolled clinical trial with 7 subjects aged 12 to 17 years no adverse reactions were reported. See section 5.1 for further details regarding the trial.

In this limited sample, no clinically relevant differences have been observed between the safety profiles of Wynzora cream in adult and adolescent populations.

Proposed additional text in Section 5.1 Pharmacodynamic properties

Paediatric population
HPA axis suppression was evaluated in 7 adolescent subjects aged 12 to 17 years with extensive psoriasis involving 10.5-16% of the body surface area (including scalp). Treatment consisted of once daily application of Wynzora Cream to the body and scalp for up to 8 weeks. The mean weekly dose up to Week 8 was 27.2 g. Adrenal suppression was not observed in any subjects (N=6) after 4 or 8 weeks of treatment (one subject had an abnormal ACTH-stimulated cortisol at baseline and discontinued the trial prematurely). There were no changes in calcium metabolism.

Proposed change in Section 5.2 Pharmacokinetic properties

One of 27 (3.7%) *adult* subjects had quantifiable levels of calcipotriol at Week 4. For the major metabolite of calcipotriol, MC1080, 3 of 27 (11.1%) subjects had quantifiable levels at Week 4. No subjects had quantifiable levels of calcipotriol or MC1080 at Week 8.

For betamethasone dipropionate, there were 3 *adult* subjects (11.1%) with quantifiable levels of betamethasone dipropionate at Week 4. The major metabolite of betamethasone dipropionate, betamethasone 17-propionate (B17P), was quantifiable in 13 subjects (48.1%) at Week 4. No

subjects had quantifiable levels of betamethasone dipropionate at Week 8, whereas 7 out of 17 (41.2%) subjects with quantifiable levels of B17P at Week 8.

Paediatric population

In a study including 7 adolescent patients (6 provided PK data), calcipotriol and its metabolite MC1080 were below the lower limit of quantification in all plasma samples at Week 4. Betamethasone dipropionate were below the lower limit of quantification in all plasma samples at Week 4. The metabolite, betamethasone 17-propionate (B17P), was quantifiable in 3 of 6 (50%) subjects.