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Protocol Registration and Results System

ID: EudraCT: 2006-0007084-89 Once-daily Oral Modified Release Hydrocortisone in Patients With Adrenal Insufficiency NCT00915343

Results Preview

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Participant Flow

Recruitment Details	
Pre-Assignment Details	Study consisted of Part A (cross-over) and Part B (open-label). Of the 64 participants started and completed Part A, 5 participants did not enter Part B (treatment switch=2, withdrawal by participant= 2, nausea and abnormal laboratory value=1), 59 started Part B of the study.

Arm/Group Title	Hydrocortisone MR OD Then Hydrocortisone TID - Part A	Hydrocortisone TID Then Hydrocortisone MR OD - Part A	Hydrocortisone MR Tablet OD - Part B (All 6 Months)	Total (Not public)
Arm/Group Description	Participants received novel once daily (OD) hydrocortisone modified release (MR) tablets in the first intervention period then hydrocortisone tablets thrice daily (TID) in the second intervention period, at the same total daily dose of 20 to 40 milligram (mg) for 12 weeks.	Participants received hydrocortisone tablets TID in the first intervention period then novel OD hydrocortisone MR tablets in the second intervention period, at the same total daily dose of 20 to 40 mg for 12 weeks.	Hydrocortisone MR tablets 20 to 40 mg orally OD for 6 months.	
Period Title: **Part A - First Intervention Period**				
Started	32	32	0	64
Completed	32	32	0	64
Not Completed	0	0	0	0
Period Title: **Part A - Second Intervention Period**				
Started	32	32	0	64
Completed	32	32	0	64
Not Completed	0	0	0	0

Period Title: **Part B - Open Label Period**

Started	0 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	0 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	59 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	59
Completed	0	0	57	57
Not Completed	0	0	2	2
Reason Not Completed				
Treatment switch	0	0	1	1
Did not attend the last visit	0	0	1	1
(Not Public)	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	Not Completed = 2 Total from all reasons = 2	

Baseline Characteristics

Arm/Group Title	Entire Study
▼ Arm/Group Description	Included all participants randomized to receive hydrocortisone MR tablets orally OD first or hydrocortisone tablets orally TID first; in any of the intervention periods during the 12-week cross-over period of Part A or hydrocortisone MR tablets orally OD during the 6-month open-label period of Part B.
Overall Number of Baseline Participants	63
▼ Baseline Analysis Population Description	Intention-To-Treat (ITT) set included all randomised participants who took at least 1 dose of study drug with assessments of any variables or with primary efficacy assessments including all pharmacokinetic (PK) samplings during any of the treatment periods.
Age, Continuous Mean (Standard Deviation) Units: years	47.3 (13.7)
Gender, Male/Female Measure Type: Number Units: participants	
Female	26
Male	37

Outcome Measures

1. Primary Outcome

Title:	Area Under the Concentration Time Curve From Zero to 24 Hours (AUC0-24h) of Total S-cortisol in Plasma After Multiple Doses During Part A
▼ Description:	AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The data for combined arm 1+2 after multiple doses were reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Part A: Intention-To-Treat (ITT) set included all randomised participants who took at least 1 dose of study drug with primary efficacy assessments including all pharmacokinetic (PK) samplings during either treatment period. Here "number of participants analysed" signifies those who were evaluable for the outcome measure.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	59	59
Mean (Standard Deviation) Units: hour*nanomole per liter	3962.0 (1079.6)	4879.6 (1194.4)

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Comparison of log S-cortisol AUC between OD and TID regimens was adjusted for both period effect and subject effect using generalized linear model (GLM) in statistical analysis system (SAS).

	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.806
	Confidence Interval	(2-Sided) 95% 0.753 to 0.862
	Estimation Comments	The quotient was defined as AUC0-24h for OD treatment divided by AUC0-24h for TID treatment.

2. Secondary Outcome

Title:	Maximal Concentration (Cmax1) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Cmax is a term that refers to the maximum (or peak) concentration that a drug achieves in the body after the drug has been administrated. Cmax1 is the Cmax after first dose of study drug. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	61	61
Mean (Standard Deviation) Units: nanomoles per liter	690.7 (109.2)	802.8 (136.2)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-111.989
	Confidence Interval	(2-Sided) 95% -133.980 to 89.999
	Estimation Comments	[Not specified]

3. Secondary Outcome

Title:	Maximal Concentration (Cmax2) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Cmax is a term that refers to the maximum (or peak) concentration that a drug achieves in the body after the drug has been administrated. Cmax2 is the Cmax after second dose of study drug. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	8	8
Mean (Standard Deviation)	553.8 (170.8)	446.9 (129.3)

Units: nanomoles per liter	

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0357
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of	Estimation Parameter	Other[Mean difference]

Estimation	Estimated Value	110.417
	Confidence Interval	(2-Sided) 95% 16.755 to 204.078
	Estimation Comments	[Not specified]

4. Secondary Outcome

Title:	Average Concentration of S-cortisol During the Dosing Interval at Steady State (Css,av) in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Css,av was calculated as the area under the S-cortisol concentration versus time curve during a dosing interval at steady state (AUCtau) divided by dosing interval (tau). Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	59	59
Mean (Standard Deviation) Units: nanomoles per liter	165.1 (45.0)	203.3 (49.8)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-38.076
	Confidence Interval	(2-Sided) 95% -50.276 to 25.876
	Estimation Comments	[Not specified]

5. Secondary Outcome

Title:	First Detectable Concentration (Cfirst) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	62	62
Mean (Standard Deviation) Units: nanomoles per liter	229.0 (169.8)	295.1 (203.2)

▼ Statistical Analysis 1 

Statistical	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A

Analysis Overview	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0033
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-65.782
	Confidence Interval	(2-Sided) 95% -109.201 to 22.362
	Estimation Comments	[Not specified]

6. Secondary Outcome

Title:	Concentration at 6 Hours (C6h) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	60	60

Mean (Standard Deviation) Units: nanomoles per liter	278.5 (134.9)	426.7 (135.2)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]

	Estimated Value	-148.015
	Confidence Interval	(2-Sided) 95% -189.469 to -106.561
	Estimation Comments	[Not specified]

7. Secondary Outcome

Title:	Concentration at 7 Hours (C7h) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	60	60
Mean (Standard Deviation) Units: nanomoles per liter	214.1 (106.8)	322.4 (110.0)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of	P-Value	<0.0001

Hypothesis	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-108.306
	Confidence Interval	(2-Sided) 95% -140.193 to -76.420
	Estimation Comments	[Not specified]

8. Secondary Outcome

Title:	Time to Peak Plasma Concentration (Tmax1) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Tmax is the time after administration of a drug when the maximum plasma concentration in the body is reached. Tmax1 is the Tmax after first dose of study drug. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	61	61
Median (Full Range) Units: hours	1.00 (0.38 to 5.00)	0.750 (0.292 to 2.750)

▼ Statistical Analysis 1 

Statistical Analysis	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A

Overview	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0214
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	0.270
	Confidence Interval	(2-Sided) 95% 0.028 to 0.512
	Estimation Comments	[Not specified]

9. Secondary Outcome

Title:	Time to Peak Plasma Concentration (Tmax2) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Tmax is the time after administration of a drug when the maximum plasma concentration in the body is reached. Tmax2 is the Tmax after second dose of study drug. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants	8	8

Analyzed		
Median (Full Range) Units: hours	5.00 (3.50 to 6.00)	6.00 (5.00 to 6.00)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0714
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of	Estimation Parameter	Other[Mean difference]

Estimation	Estimated Value	-1.042
	Confidence Interval	(2-Sided) 95% -2.098 to 0.015
	Estimation Comments	[Not specified]

10. Secondary Outcome

Title:	Time to First Detectable Concentration (Tfirst) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	62	62
Median (Full Range) Units: hours	0.229 (0.000 to 0.625)	0.208 (0.000 to 0.500)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical	P-Value	0.6687

Test of Hypothesis	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-0.007
	Confidence Interval	(2-Sided) 95% -0.038 to 0.024
	Estimation Comments	[Not specified]

11. Secondary Outcome

Title:	Time to Reach a Concentration of 200 Nanometers (nM) (T200) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	62	62
Median (Full Range) Units: hours	0.250 (0.000 to 0.750)	0.167 (0.063 to 0.563)

▼ Statistical Analysis 1 

Statistical	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A

Analysis Overview	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0280
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	0.049
	Confidence Interval	(2-Sided) 95% 0.006 to 0.093
	Estimation Comments	[Not specified]

12. Secondary Outcome

Title:	Drug Concentration Half-Life From 5 to 24 Hours (t1/2[5-24h]) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	t1/2[5-24h] is the time taken for the blood plasma concentration of a drug to halve from 5 to 24 hours. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description
Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.

Number of Participants Analyzed	17	17
Mean (Standard Deviation) Units: hours	7.32 (9.32)	1.84 (0.93)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0003
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	5.509
	Confidence Interval	(2-Sided) 95% 0.751 to 10.268
	Estimation Comments	[Not specified]

13. Secondary Outcome

Title:	Drug Concentration Half-Life From 5 to 14 Hours (t1/2[5-14h]) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	t1/2[5-14h] is the time taken for the blood plasma concentration of a drug to halve from 5 to 14 hours. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	52	52
Mean (Standard Deviation) Units: hours	4.60 (5.82)	18.4 (24.5)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-13.800
	Confidence Interval	(2-Sided) 95% -20.533 to -7.067
	Estimation Comments	[Not specified]

14. Secondary Outcome

Title:	Area Under the Concentration Time Curve (AUC) Between Specified Timepoints of Total S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body. AUC between specified timepoints included AUC0-4h, AUC4-12h, AUC6-12h, AUC12-24h, AUC0-10h, AUC4-10h, AUC6-10h, AUC10-24h, AUC(0-inf), AUC(24h-inf). Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported. Here, "N"signifies the number of participants evaluable for this outcome.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	63	63
Mean (Standard Deviation)		

Units: hour*nanomole per liter		
AUC0-4h (N=61, 61)	2053.7 (432.0)	1929.7 (409.9)
AUC4-12h (N=61, 61)	1491.8 (638.9)	2302.5 (669.3)
AUC6-12h (N=61, 61)	808.2 (386.3)	1607.6 (483.3)
AUC12-24h (N=61, 61)	306.2 (305.2)	576.6 (681.6)
AUC0-10h (N=61, 61)	3388.4 (915.0)	3768.7 (968.5)
AUC4-10h (N=61, 61)	1334.7 (582.5)	1839.0 (599.0)
AUC6-10h (N=61, 61)	651.1 (322.1)	1144.1 (404.6)
AUC10-24h (N=61, 61)	465.0 (352.2)	1058.0 (752.4)
AUC(0-inf) (N=52, 52)	3972.6 (1125.9)	5162.8 (1777.2)
AUC(24h-inf) (N=52, 52)	195.3 (568.1)	410.4 (1094.0)

▼ Statistical Analysis 1

Statistical Analysis	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC0-4h

Overview		
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0002
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	1.064
	Confidence Interval	(2-Sided) 95% 1.032 to 1.097
	Estimation Comments	The quotient was defined as AUC0-4h for OD treatment divided by AUC0-4h for TID treatment.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC4-12h
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.617
	Confidence Interval	(2-Sided) 95% 0.563 to 0.675

	Estimation Comments	The quotient was defined as AUC4-12h for OD treatment divided by AUC4-12h for TID treatment.

▼ Statistical Analysis 3

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC6-12h
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.472
	Confidence Interval	(2-Sided) 95% 0.424 to 0.525
	Estimation Comments	The quotient was defined as AUC6-12h for OD treatment divided by AUC6-12h for TID treatment.

▼ Statistical Analysis 4

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC12-24h
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0003
	Comments	[Not specified]
	Method	ANOVA

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.588
	Confidence Interval	(2-Sided) 95% 0.446 to 0.775
	Estimation Comments	The quotient was defined as AUC12-24h for OD treatment divided by AUC12-24h for TID treatment.

▼ Statistical Analysis 5 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC0-10h
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.894
	Confidence Interval	(2-Sided) 95% 0.856 to 0.935
	Estimation Comments	The quotient was defined as AUC0-10h for OD treatment divided by AUC0-10h for TID treatment.

▼ Statistical Analysis 6 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC4-10h
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.695
	Confidence Interval	(2-Sided) 95% 0.632 to 0.765
	Estimation Comments	The quotient was defined as AUC4-10h for OD treatment divided by AUC4-10h for TID treatment.

▼ Statistical Analysis 7

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC6-10h
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.540
	Confidence Interval	(2-Sided) 95% 0.482 to 0.605
	Estimation Comments	The quotient was defined as AUC6-10h for OD treatment divided by AUC6-10h for TID treatment.

▼

Statistical Analysis 8

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC10-24h
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.412
	Confidence Interval	(2-Sided) 95% 0.338 to 0.504
	Estimation Comments	The quotient was defined as AUC10-24h for OD treatment divided by AUC10-24h for TID treatment.

▼ Statistical Analysis 9 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC(0-inf)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of	Estimation Parameter	Other[Period-adjusted quotient]

Estimation	Estimated Value	0.776
	Confidence Interval	(2-Sided) 95% 0.714 to 0.843
	Estimation Comments	The quotient was defined as AUC(0-inf) for OD treatment divided by AUC(0-inf) for TID treatment.

▼ Statistical Analysis 10 ✓

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	AUC(24h-inf)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.8770
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	1.069
	Confidence Interval	(2-Sided) 95% 0.453 to 2.521
	Estimation Comments	The quotient was defined as AUC(24h-inf) for OD treatment divided by AUC(24h-inf) for TID treatment.

15. Secondary Outcome

Title:	Area Under the Concentration Time Curve During a Dosing Interval at Steady State (AUCtau) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body. AUCtau is defined as AUC during a dosing interval at steady state. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.

Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	59	59
Mean (Standard Deviation) Units: hour*nanomole per liter	3962.0 (1079.6)	4879.6 (1194.4)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.806
	Confidence Interval	(2-Sided) 95% 0.753 to 0.862
	Estimation Comments	The quotient was defined as AUCtau for OD treatment divided by AUCtau for TID treatment.

16. Secondary Outcome

Title:	Area Under the Concentration Time Curve During a Dosing Interval at Steady State Adjusted by Dose (AUCtau/Dose) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body. Participants in Arm 1 underwent standardised in-house PK sampling during 14 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	59	59
Mean (Standard Deviation) Units: hour per liter	0.048 (0.016)	0.061 (0.017)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.790
	Confidence Interval	(2-Sided) 95% 0.734 to 0.851
	Estimation Comments	The quotient was defined as AUCtau/dose for OD treatment divided by AUCtau/dose for TID treatment.

17. Secondary Outcome

Title:	Area Under the Concentration Time Curve From Zero to 24 Hours Adjusted by Dose (AUC0-24h/Dose) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	61	61
Mean (Standard Deviation)	0.047 (0.014)	0.060 (0.018)

Units: hour per liter		

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.785
	Confidence Interval	(2-Sided) 95% 0.741 to 0.831
	Estimation Comments	The quotient was defined as AUC0-24h/dose for OD treatment divided by AUC0-24h/dose for TID treatment.

18. Secondary Outcome

Title:	Area Under the Concentration Time Curve From Zero to 10 Hours Adjusted by Dose (AUC0-10h/Dose) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	61	61
Mean (Standard Deviation) Units: hour per liter	0.041 (0.012)	0.046 (0.013)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	0.885
	Confidence Interval	(2-Sided) 95% 0.844 to 0.926
	Estimation Comments	The quotient was defined as AUC0-10h/dose for OD treatment divided by AUC0-10h/dose for TID treatment.

19. Secondary Outcome

Title:	Area Under the Concentration Time Curve From Zero to 4 Hours Adjusted by Dose (AUC0-4h/Dose) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much and how long a drug stays in a body. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	61	61
Mean (Standard Deviation) Units: hour per liter	0.025 (0.005)	0.024 (0.006)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0020
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	1.053
	Confidence Interval	(2-Sided) 95% 1.020 to 1.086
	Estimation Comments	The quotient was defined as AUC0-4h/dose for OD treatment divided by AUC0-4h/dose for TID treatment.

20. Secondary Outcome

Title:	Average Concentration of S-cortisol During the Dosing Interval at Steady State Adjusted by Dose (Css,av/Dose) in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Css,av was calculated as the area under the S-cortisol concentration versus time curve during a dosing interval at steady state (AUCtau) divided by dosing interval (tau). Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	59	59
Mean (Standard Deviation) Units: per liter	0.002 (0.001)	0.003 (0.001)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-0.001
	Confidence Interval	(2-Sided) 95% -0.001 to -0.000
	Estimation Comments	[Not specified]

21. Secondary Outcome

Title:	Maximal Concentration Adjusted by Dose (Cmax1/Dose) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Cmax is a term that refers to the maximum (or peak) concentration that a drug achieves in the body after the drug has been administrated. Cmax1 is the Cmax after first dose of study drug. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	61	61
Mean (Standard Deviation) Units: per liter	0.008 (0.002)	0.010 (0.002)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-0.001
	Confidence Interval	(2-Sided) 95% -0.002 to -0.001
	Estimation Comments	[Not specified]

22. Secondary Outcome

Title:	Time to First Detectable Concentration Adjusted by Dose (Tfirst/Dose) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	62	62
Mean (Standard Deviation) Units: (hour per nanomole)*10^6	2.26 (1.69)	2.32 (1.43)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7827
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-0.055
	Confidence Interval	(2-Sided) 95% -0.444 to 0.334
	Estimation Comments	[Not specified]

23. Secondary Outcome

Title:	First Detectable Concentration Adjusted by Dose (Cfirst/Dose) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	62	62
Mean (Standard Deviation) Units: per liter	0.003 (0.002)	0.004 (0.002)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0015
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-0.001
	Confidence Interval	(2-Sided) 95% -0.001 to -0.000
	Estimation Comments	[Not specified]

24. Secondary Outcome

Title:	Percentage (%) of Area Under the Concentration Time Curve (AUC) Extrapolation of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	The percentage of AUC0-inf that is due to extrapolation from Tlast to infinity (AUC%Extrapolation) was calculated by using the formula AUC%extrapolation = 100*(AUC0-inf minus AUC0-t)/AUC0-inf. The function of this parameter was to provide information about what percentage of the theoretical curve (AUC0-inf) was possible to determine experimentally (AUC0-t). Therefore, on average, it is expected that the residual area (AUCextrapolation) is not greater than 20%. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description
Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	52	52
Mean (Standard Deviation) Units: percentage of AUC	10.1 (7.9)	9.26 (12.74)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other[Period-adjusted quotient]
	Estimated Value	6.098
	Confidence Interval	(2-Sided) 95% 2.940 to 12.646
	Estimation Comments	The quotient was defined as AUC Extrapolation for OD treatment divided by AUC Extrapolation for TID treatment.

25. Secondary Outcome

Title:	Percentage (%) of Fluctuation in Concentrations of S-cortisol at Steady State in Plasma After Single and Multiple Dosing During Part A
▼ Description:	Percentage of fluctuation was calculated by using formula 100*(Cmax-minimum plasma concentration [Cmin])/Cavg,ss. It was peak trough fluctuation within one dosing interval at steady state. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	59	59
Mean (Standard Deviation) Units: percentage of fluctuation	429.7 (117.3)	396.2 (99.0)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0396
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	33.532
	Confidence Interval	(2-Sided) 95% 1.734 to 65.329
	Estimation Comments	[Not specified]

26. Secondary Outcome

Title:	Accumulation Ratio (Rac) of S-cortisol in Plasma After Single and Multiple Dosing During Part A
▼ Description:	The Rac was calculated as area under the S-cortisol concentration versus time curve during a dosing interval at steady state (AUCtau) on Day 28 divided by AUC0-24h on Day 1. Participants in Arm 1 underwent standardised in-house PK sampling during 24 hours in order to assess single-dose PK of OD or TID regimen at the start of each study treatment period while participants in Arm 2 had a reduced PK sampling scheme of single dose PK on Days 1-2 and returned for multiple-dose PK sampling on Days 7-8. The average of single and multiple dosing for combined arm 1+2 was reported.
Time Frame:	Arm 1: Week 4, Week 16, Week 16 + 1 day, Week 28; Arm 2: Week 4, Week 4 + 7 days, Week 16, Week 16 + 7 days
Safety Issue?	No

▼ Outcome Measure Data

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	55	55
Mean (Standard Deviation)	1.11 (0.29)	1.03 (0.19)

Units: ratio		

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.1032
	Comments	[Not specified]
	Method	Other [Fisher's non-parametric permutation test]
	Comments	[Not specified]
Method of	Estimation Parameter	Other[Period-adjusted quotient]

Estimation	Estimated Value	0.080
	Confidence Interval	(2-Sided) 95% -0.017 to 0.177
	Estimation Comments	[Not specified]

27. Secondary Outcome

Title:	Comparison of Overall Patient Tolerability Score Between Once Daily and Thrice Daily Therapy, Assessed by Patient and Investigator – Part A
▼ Description:	Overall patient tolerability score assessed by patient and investigator, ranged from 1 (feeling poor on treatment) to 5 (feeling very well on treatment). The average total score ranges from 1 to 5 with a higher score representing better tolerability of the treatment. Questionnaire assessed by patient were "I have been very poorly on the treatment", "I haven't been very well (or less well) on the treatment", "I have been acceptably well on the treatment", "I have been well on the treatment" and "I have been very well on the treatment". Questionnaire assessed by investigator were "The patient has been feeling very poorly on the treatment", "The patient has not tolerated the treatment well", "The patient has tolerated the treatment less well", "The patient has tolerated the treatment well" and "The patient has tolerated the treatment very well".
Time Frame:	12 weeks
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	63	63
Mean (Standard Deviation) Units: scores on a scale		
Patient	4.28 (0.74)	4.36 (0.73)
Investigator	4.26 (0.73)	4.33 (0.73)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	Patient

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.3767
	Comments	[Not specified]
	Method	Other [Fisher's test]
	Comments	Fisher's non
Method of Estimation	Estimation Parameter	Other[least square mean]
	Estimated Value	-0.078
	Confidence Interval	(2-Sided) 95% -0.250 to 0.094
	Estimation Comments	[Not specified]

▼ Statistical Analysis 2 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	Investigator
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.4625
	Comments	[Not specified]
	Method	Other [Fisher's test]
	Comments	Fisher's non
Method of Estimation	Estimation Parameter	Other[least square mean]
	Estimated Value	-0.064
	Confidence Interval	(2-Sided) 95% -0.235 to 0.107
	Estimation Comments	[Not specified]

28. Secondary Outcome

Title:	Percentage (%) of Participants With Change From Baseline in Patient Tolerability Questionnaire at Month 6, Assessed by Patient and Investigator – Part B
▼ Description:	Patient tolerability questionnaire was assessed by both patient and investigator, the responses were as follows: improvement, no change, worsening and were reported.
Time Frame:	Baseline (week 0), month 6
Safety Issue?	No

▼ Outcome Measure Data

▼ Analysis Population Description

Part B ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during the entire 6-month period of Part B.
Number of Participants Analyzed	56
Measure Type: Number Units: percentage of participants	
Improvement (Patient)	10.7
Improvement (Investigator)	14.0
No change (Patient)	73.2
No change (Investigator)	70.0
Worsening (Patient)	16.1
Worsening (Investigator)	16.0

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
	Comments	Patient
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of	P-Value	0.6072

Hypothesis	Comments	[Not specified]
	Method	Sign test
	Comments	[Not specified]

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
	Comments	Investigator
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	1.0000
	Comments	[Not specified]
	Method	Sign test
	Comments	[Not specified]

29. Secondary Outcome

Title:	Comparison of Quality of Life (QoL) Assessed by Short Form-36 Survey (SF-36) For Physical and Mental Component Score Between Once Daily and Thrice Daily Therapy- Part A
▼ Description:	The SF-36 was a questionnaire used to assess physical functioning and is made up of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Transforming and standardizing these domains lead to the calculation of the physical and mental component summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A higher value corresponds to better well-being.
Time Frame:	12 weeks
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.

Number of Participants Analyzed	61	61
Mean (Standard Deviation) Units: scores on a scale		
Physical component	49.3 (9.1)	50.0 (9.9)
Mental component	51.1 (7.3)	49.8 (9.3)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	Comparison of Quality of Life (QoL) Assessed by Short Form-36 Survey (SF-36) For Physical Component Score
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.3332
	Comments	[Not specified]
	Method	Other [Fisher's test]

	Comments	Fisher's non-parametric two-sample permutation test
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-0.6
	Estimation Comments	[Not specified]

▼ Statistical Analysis 2 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	Comparison of Quality of Life (QoL) Assessed by Short Form-36 Survey (SF-36) For Mental Component Score
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.3405
	Comments	[Not specified]
	Method	Other [Fisher's test]
	Comments	Fisher's non-parametric two-sample permutation test
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	0.9
	Estimation Comments	[Not specified]

30. Secondary Outcome

Title:	Change From Baseline to 6 Months in Quality of Life (QoL) Assessed by Short Form-36 Survey (SF-36) For Physical and Mental Component Score - Part B
▼ Description:	The SF-36 was a questionnaire used to assess physical functioning and is made up of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Transforming and standardizing these domains lead to the calculation of the physical and mental component summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A higher value in the SF-36 questionnaire corresponds to better well-being.
Time Frame:	Baseline (week 0), month 6
Safety Issue?	No

▼ Outcome Measure Data

▼ Analysis Population Description
Part B ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during the entire 6-month period of Part B.
Number of Participants Analyzed	54
Mean (Standard Deviation) Units: scores on a scale	
Physical component	0.390 (4.374)
Mental component	-0.896 (5.913)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
	Comments	Change From Baseline to 6 months in Quality of Life (QoL) Assessed by Short Form-36 Survey (SF-36) For Physical Component Score
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.8418
	Comments	[Not specified]
	Method	Other [Wilcoxon Signed Rank]

	Comments	[Not specified]

▼ Statistical Analysis 2 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
	Comments	Change From Baseline to 6 months in Quality of Life (QoL) Assessed by Short Form-36 Survey (SF-36) For Mental Component Score
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.3550
	Comments	[Not specified]
	Method	Other [Wilcoxon Signed Rank test]
	Comments	[Not specified]

31. Secondary Outcome

Title:	Comparison of Quality of Life (QoL) Assessed by Fatigue Impact Scale (FIS) Total Score Between Once Daily and Thrice Daily Therapy - Part A
▼ Description:	FIS is a subject-reported scale that qualifies the impact of fatigue on daily life in participants. It consisted of 40 statements that measure fatigue in 3 areas: physical, cognitive, and psychosocial. This 40-item scale evaluates the construct of perceived impact of fatigue on everyday life. Respondents rated each statement using a 5-point Likert-type scale ranging from 0 (no problem) to 4 (extreme problem). A total score ranged from 0 to 160. A lower value corresponds to better well-being.
Time Frame:	12 weeks
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	62	61

Mean (Standard Deviation) Units: scores on a scale	22.6 (25.4)	26.4 (30.3)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0823
	Comments	[Not specified]
	Method	Other [Fisher's]
	Comments	Fisher's non-parametric two-sample permutation test

Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-2.9
	Estimation Comments	[Not specified]

32. Secondary Outcome

Title:	Change From Baseline to 6 Months in Quality of Life (QoL) Assessed by Fatigue Impact Scale (FIS) Total Score - Part B
▼ Description:	FIS is a subject-reported scale that qualifies the impact of fatigue on daily life in participants. It consisted of 40 statements that measure fatigue in 3 areas: physical, cognitive, and psychosocial. This 40-item scale evaluates the construct of perceived impact of fatigue on everyday life. Respondents rated each statement using a 5-point Likert-type scale ranging from 0 (no problem) to 4 (extreme problem). A total score ranged from 0 to 160. A lower value corresponds to better well-being.
Time Frame:	Baseline (week 0), month 6
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part B ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during the entire 6-month period of Part B.
Number of Participants Analyzed	56
Mean (Standard Deviation) Units: scores on a scale	-1.09 (12.49)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.5982
	Comments	[Not specified]

	Method	Other [Wilcoxon Signed Rank test]
	Comments	[Not specified]

33. Secondary Outcome

Title:	Comparison of Quality of Life (QoL) Assessed by Psychological General Well Being (PGWB) Total Scores Between Once Daily and Thrice Daily Therapy- Part A
▼ Description:	The PGWB consists of 22 self-administered items rated on a scale from 1 (worst level of well-being) to 6 (maximum level of well-being) with a total score ranging from 22 to 132. A higher score represents better well-being.
Time Frame:	12 weeks
Safety Issue?	No

▼ Outcome Measure Data

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	62	61
Mean (Standard Deviation) Units: scores on a scale	110.5 (14.0)	107.7 (17.3)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0632
	Comments	[Not specified]
	Method	Other [Fisher's test]

	Comments	Fisher's non-parametric two-sample permutation test
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	2.3
	Estimation Comments	[Not specified]

34. Secondary Outcome

Title:	Change From Baseline to 6 Months in Quality of Life (QoL) Assessed by Psychological General Well Being (PGWB) Total Scores- Part B
▼ Description:	The PGWB consists of 22 self-administered items rated on a scale from 1 (worst level of well-being) to 6 (maximum level of well-being) with a total score ranging from 22 to 132. A higher score represents better well-being.
Time Frame:	Baseline (week 0), month 6
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

Part B ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during the entire 6-month period of Part B.
Number of Participants Analyzed	55
Mean (Standard Deviation) Units: scores on a scale	-0.739 (9.687)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.8676
	Comments	[Not specified]

	Method	Other [Wilcoxon Signed Rank test]
	Comments	[Not specified]

35. Secondary Outcome

Title:	Change From Baseline to 12 Weeks in Diurnal Fatigue Questionnaire for Day Average of Once Daily Therapy - Part A
▼ Description:	Diurnal fatigue was assessed at 8 ante meridian (AM), at 12 AM and at 4 post meridian (PM) by a visual analogue scale (VAS) based on 8 domains (energy, relaxed, less alert, moody, mental fatigue, intellectually slow, difficulty focusing, physical activity). Mean values were calculated for the morning (8 AM), the day (12 AM), the evening (4 PM) and mean per day (mean of 8 AM, 12 AM and 4 PM) were analyzed with score range from 0 to 100. A lower value corresponds to better well-being.
Time Frame:	Baseline (week 0), Week 12
Safety Issue?	No

▼ Outcome Measure Data

▼ Analysis Population Description

ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A
▼ Arm/Group Description:	During the 4-week run-in period prior to the first intervention period during Part A, participants on a twice-a-day (BID) regimen were transferred to a thrice-a-day (TID) regimen while maintaining the same total daily hydrocortisone dose. In the first and second intervention periods during Part A, participants were randomised to novel once daily (OD) treatment with hydrocortisone modified release (MR) tablets 20 to 40 milligram (mg) orally and the treatment continued for 12 weeks and returned every 4 weeks for study drug dispensation.
Number of Participants Analyzed	47
Mean (Standard Deviation) Units: scores on a scale	-3.1 (12.1)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical	P-Value	0.9700

Test of Hypothesis	Comments	[Not specified]
	Method	Other [Wilcoxon Signed Rank test]
	Comments	[Not specified]

36. Secondary Outcome

Title:	Change From Baseline to 6 Months in Diurnal Fatigue Questionnaire for Day Average- Part B
▼ Description:	Diurnal fatigue scores (Visual Analog Scale [VAS] scores of energy, relaxed, less alert, moody, mental fatigue, intellectually slow, difficulty focusing, physical activity) were analyzed with score range from 0 to 100. A lower value corresponds to better well-being.
Time Frame:	Baseline (week 0), month 6
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

Part B ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during the entire 6-month period of Part B.
Number of Participants Analyzed	44
Mean (Standard Deviation) Units: scores on a scale	-0.180 (7.943)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.2624
	Comments	[Not specified]
	Method	Other [Wilcoxon Signed Rank test]

	Comments	[Not specified]

37. Secondary Outcome

Title:	Comparison on Participant Compliance Between Once Daily and Thrice Daily Therapy - Part A
▼ Description:	Compliance was calculated as actual consumption/expected consumption Compliance = (Number of dispensed tablets - Number of returned tablets)/(Number of days during the study period x daily Number of hydrocortisone tablets when taking the ordinary daily dose).
Time Frame:	Weeks 4 up to 28
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Part A ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	58	58
Mean (Standard Deviation) Units: percentage use	104.8 (7.5)	103.1 (13.2)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	1.28
	Estimation Comments	[Not specified]

38. Secondary Outcome

Title:	Participant Compliance- Part B
▼ Description:	Compliance was calculated as actual consumption/expected consumption Compliance = (Number of dispensed tablets - Number of returned tablets)/(Number of days during the study period x daily Number of hydrocortisone tablets when taking the ordinary daily dose).
Time Frame:	Up to Month 6 follow-up
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Part B ITT population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during the entire 6-month period of Part B.
Number of Participants Analyzed	58
Mean (Standard Deviation) Units: percentage use	102.3 (12.8)

39. Secondary Outcome

Title:	Comparison on Participant Preference by Questionnaire Between Once Daily and Thrice Daily Therapy-Part A
▼ Description:	Participant Preference Questionnaire consisted of the following set of questions: 1. How large was the benefit with OD compared to TID and the responses were recorded as considerably poorer, somewhat poorer, comparable, large, very large; 2. How strongly concur with the following statement: I prefer novel OD to conventional TID and the responses were recorded as strongly disagree, disagree, neutral, strongly, very strongly; 3. How strongly concur with the following statement: I prefer conventional TID to novel OD and the responses were recorded as strongly disagree, disagree, neutral, strongly, very strongly.
Time Frame:	Weeks 16 up to 28
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Part A ITT population

Arm/Group Title	Hydrocortisone OD Versus TID
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study. Hydrocortisone tablets 20 to 40 mg

	orally TID during Part A of the study.
Number of Participants Analyzed	63
Measure Type: Number Units: percentage of preference	
Benefit compared OD to TID: Considerably poorer	3.8
Benefit compared OD to TID: Somewhat poorer	5.7
Benefit compared OD to TID: Comparable	5.7
Benefit compared OD to TID: Large	20.8
Benefit compared OD to TID: Very large	64.2
Prefer OD to TID: Strongly disagree	3.7
Prefer OD to TID: Disagree	3.7
Prefer OD to TID: Neutral	5.6
Prefer OD to TID: Strongly	25.9
Prefer OD to TID: Very strongly	61.1
Prefer TID to OD: Strongly disagree	39.6
Prefer TID to OD: Disagree	35.4
Prefer TID to OD: Neutral	12.5
Prefer TID to OD: Strongly	4.2
Prefer TID to OD: Very strongly	8.3

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Hydrocortisone OD Versus TID
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Sign test
	Comments	[Not specified]

40. Secondary Outcome

Title:	Comparison on 24-hour Urinary Free Cortisol Between Once Daily and Thrice Daily Therapy-Part A
▼ Description:	[Not specified]
Time Frame:	12 weeks
Safety Issue?	Yes

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Part A Safety population consisted of all randomised patients who took at least one dose of study medication. Safety population with participants evaluable for this outcome.

Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A
▼ Arm/Group Description:	Hydrocortisone MR tablets 20 to 40 mg orally OD during Part A of the study.	Hydrocortisone tablets 20 to 40 mg orally TID during Part A of the study.
Number of Participants Analyzed	36	37
Mean (Standard Deviation) Units: nanomoles per 24 hours	385.7 (178.8)	425.9 (278.8)

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Hydrocortisone MR Tablet OD - Part A, Hydrocortisone Tablet TID - Part A
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0034
	Comments	[Not specified]

	Method	Other [Wilcoxon Signed Rank test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Mean difference]
	Estimated Value	-272.3
	Estimation Comments	[Not specified]

Adverse Events

Time Frame	Part A (24 weeks) and Part B (6 months)				
Additional Description					
Source Vocabulary Name	MedDRA				
Assessment Type	Non-systematic Assessment				
Arm/Group Title	Hydrocortisone MR Tablet OD - Part A	Hydrocortisone Tablet TID - Part A	Hydrocortisone MR Tablet OD - Part B (First 3 Months)	Hydrocortisone MR Tablet OD - Part B (Second 3 Months)	Hydrocortisone MR Tablet OD - Part B (All 6 Months)
▼ Arm/Group Description	Hydrocortisone modified release (MR) tablets 20 to 40 mg orally, once daily (OD) during the 12-week period of Part A.	Hydrocortisone tablets 20 to 40 mg orally, thrice daily (TID) during the 12-week period of Part A.	Hydrocortisone MR tablets 20 to 40 mg orally, once daily (OD) during the first 3 months of Part B (6 months).	Hydrocortisone MR tablets 20 to 40 mg orally, once daily (OD) during the second 3 months of Part B (6 months).	Hydrocortisone MR tablets 20 to 40 mg orally, once daily (OD) during the entire 6-month period of Part B.

▼ Serious Adverse Events

	Hydrocortisone MR Tablet OD - Part A		Hydrocortisone Tablet TID - Part A		Hydrocortisone MR Tablet OD - Part B (First 3 Months)		Hydrocortisone MR Tablet OD - Part B (Second 3 Months)		Hydrocortisone MR Tablet OD - Part B (All 6 Months)	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	6/64 (9.38%)		2/64 (3.12%)		2/59 (3.39%)		4/57 (7.02%)		6/59 (10.17%)	
Gastrointestinal disorders										
Pancreatitis	0/64 (0%)	0	0/64 (0%)	0	0/59 (0%)	0	1/57 (1.75%)	1	1/59 (1.69%)	1

acute [A]										
Hepatobiliary disorders										
Cholelithiasis [A]	0/64 (0%)	0	0/64 (0%)	0	0/59 (0%)	0	1/57 (1.75%)	1	1/59 (1.69%)	1
Infections and infestations										
Gastroenteritis [A]	4/64 (6.25%)	4	2/64 (3.12%)	2	1/59 (1.69%)	1	0/57 (0%)	0	1/59 (1.69%)	1
Influenza [A]	1/64 (1.56%)	1	0/64 (0%)	0	0/59 (0%)	0	0/57 (0%)	0	0/59 (0%)	0
Pneumonia [A]	1/64 (1.56%)	1	0/64 (0%)	0	0/59 (0%)	0	0/57 (0%)	0	0/59 (0%)	0
Varicella [A]	0/64 (0%)	0	0/64 (0%)	0	0/59 (0%)	0	1/57 (1.75%)	1	1/59 (1.69%)	1
Renal and urinary disorders										
Nephrolithiasis [A]	0/64 (0%)	0	0/64 (0%)	0	1/59 (1.69%)	1	0/57 (0%)	0	1/59 (1.69%)	1
Surgical and medical procedures										
Surgical and medical procedures [A]	0/64 (0%)	0	0/64 (0%)	0	0/59 (0%)	0	1/57 (1.75%)	1	1/59 (1.69%)	1

Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA

▼ Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%

	Hydrocortisone MR Tablet OD - Part A		Hydrocortisone Tablet TID - Part A		Hydrocortisone MR Tablet OD - Part B (First 3 Months)		Hydrocortisone MR Tablet OD - Part B (Second 3 Months)		Hydrocortisone MR Tablet OD - Part B (All 6 Months)	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	29/64 (45.31%)		25/64 (39.06%)		12/59 (20.34%)		16/57 (28.07%)		23/59 (38.98%)	
Gastrointestinal disorders										

Diarrhoea [A]	1/64 (1.56%)	1	0/64 (0%)	0	0/59 (0%)	0	4/57 (7.02%)	5	4/59 (6.78%)	5
General disorders										
Fatigue [A]	8/64 (12.5%)	10	3/64 (4.69%)	3	4/59 (6.78%)	4	2/57 (3.51%)	2	6/59 (10.17%)	6
Infections and infestations										
Gastroenteritis [A]	8/64 (12.5%)	9	2/64 (3.12%)	2	4/59 (6.78%)	4	0/57 (0%)	0	4/59 (6.78%)	4
Influenza [A]	8/64 (12.5%)	8	2/64 (3.12%)	2	1/59 (1.69%)	1	4/57 (7.02%)	4	5/59 (8.47%)	5
Nasopharyngitis [A]	7/64 (10.94%)	9	15/64 (23.44%)	16	1/59 (1.69%)	1	6/57 (10.53%)	6	7/59 (11.86%)	7
Investigations										
Blood thyroid stimulating hormone increased [A]	1/64 (1.56%)	1	3/64 (4.69%)	3	2/59 (3.39%)	2	1/57 (1.75%)	1	3/59 (5.08%)	3
Nervous system disorders										
Headache [A]	2/64 (3.12%)	4	5/64 (7.81%)	7	1/59 (1.69%)	1	1/57 (1.75%)	1	2/59 (3.39%)	2

Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA

Limitations and Caveats

[Not Specified]

More Information

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

If a multicentre publication is not submitted within twelve (12) months after conclusion, abandonment or termination of the Study at all sites, or after Sponsor confirms there shall be no multicentre Study publication, the Institution and/or such Principal Investigator may publish the results from the Institution site individually.

Results Point of Contact

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