Diurnal Group plc

Analyst Day

11 December 2018

Date of Preparation: December 2018 Code: CORP-GB-0023

Analyst Day:
Challenges and Current Treatment Options for Congenital Adrenal Hyperplasia

Prof John Newell-Price – The University of Sheffield, UK

Date of Preparation: December 2018 Code: CORP-GB-0023

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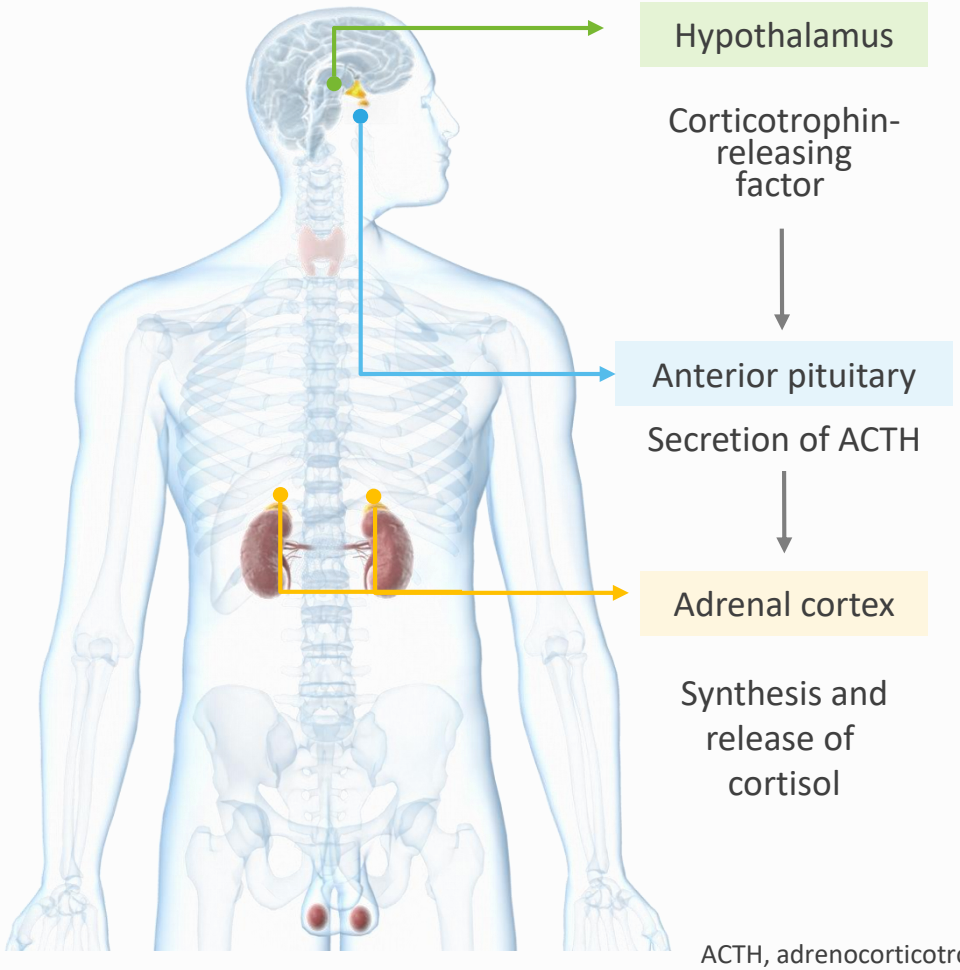
The Hypothalamic-Pituitary-Adrenal axis

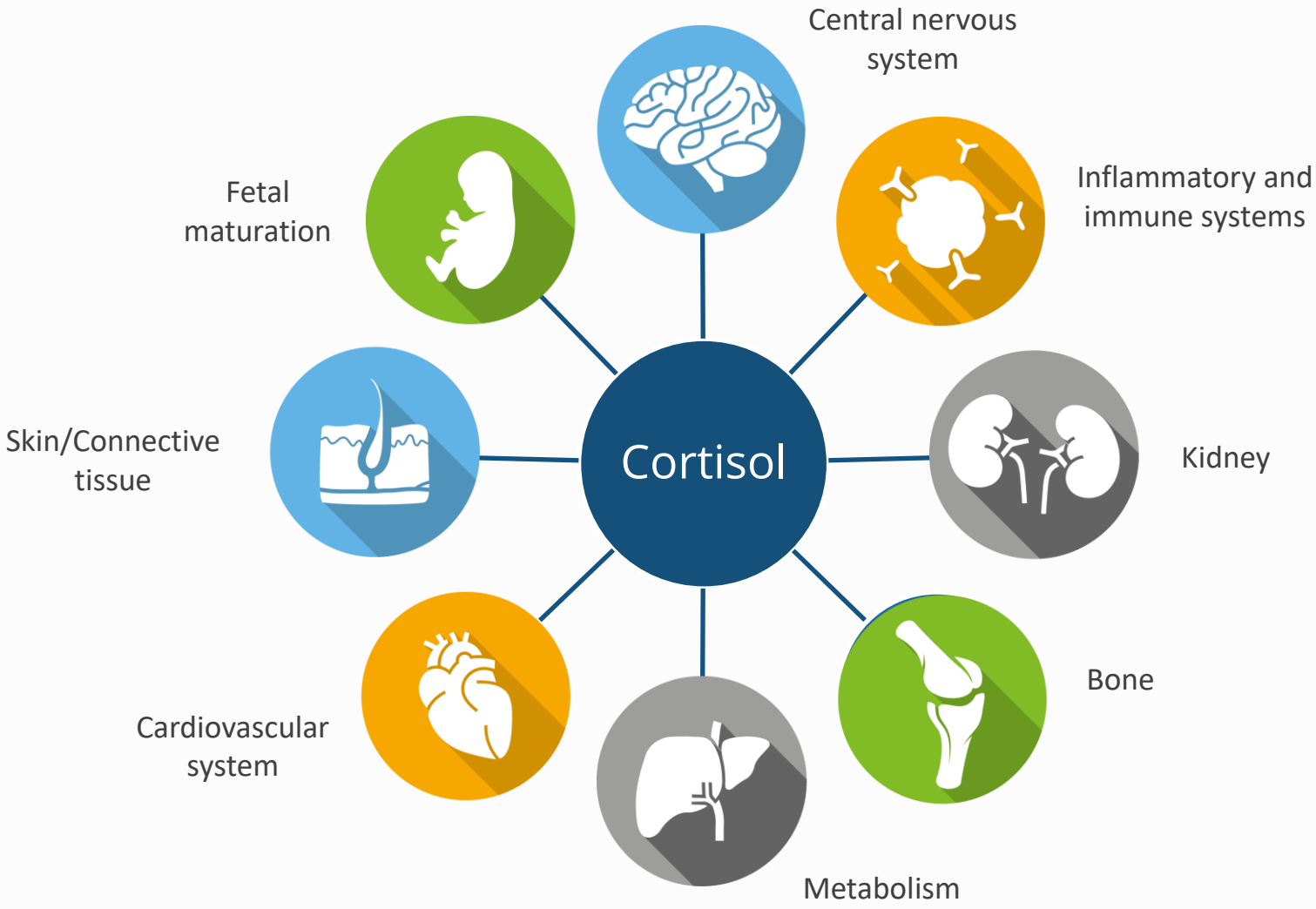


- The Hypothalamo-Pituitary-Adrenal axis (HPA) consists of the[1]
  - hypothalamus
  - pituitary gland
  - adrenal cortex
- The HPA has a pivotal role in cortisol production[1]
- Cortisol release is regulated by a pacemaker in the suprachiasmatic nucleus within the hypothalamus[2]

ACTH, adrenocorticotropic hormone.
Figure based on Hardy, et al. 2012.

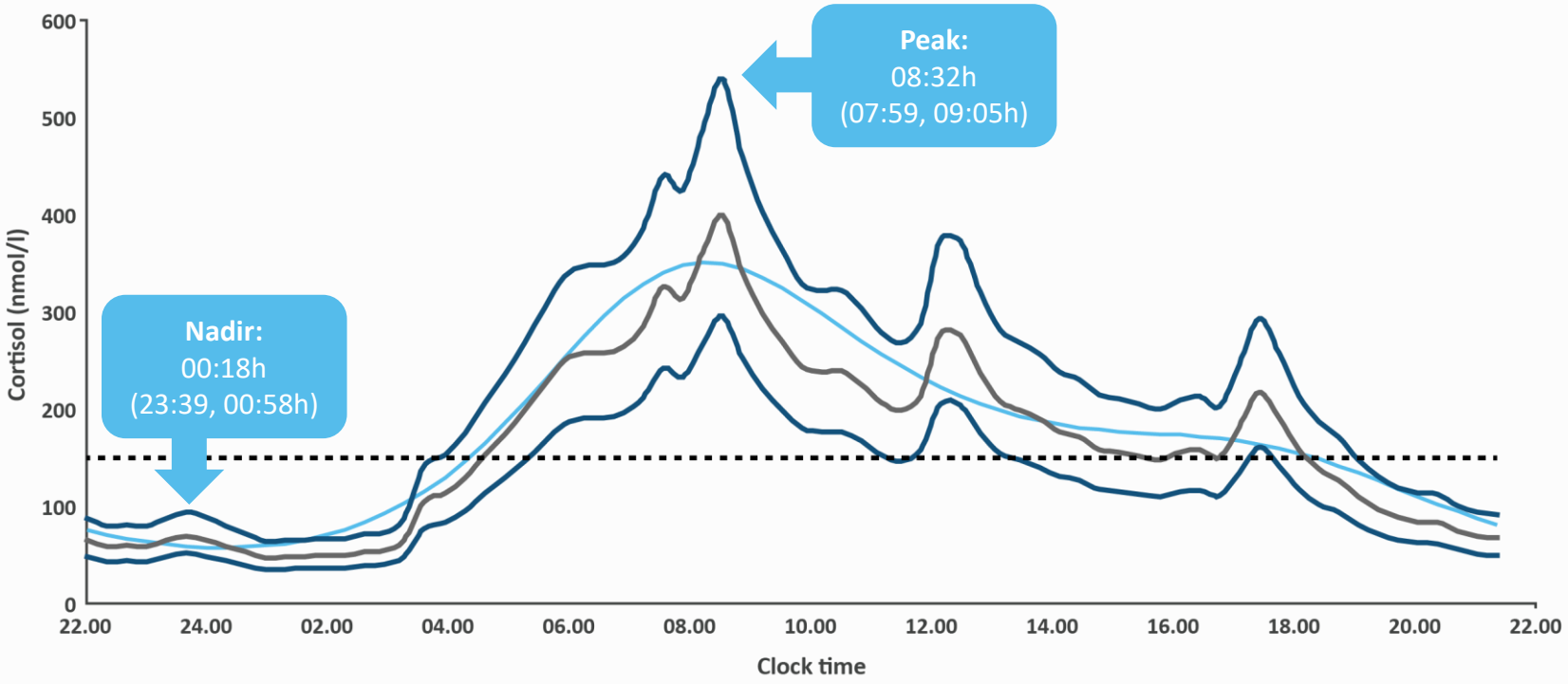
References: 1. Hardy A, et al. Swiss Med Wkly 2012; 142: w13650; 2. Chan S, et al. Ther Adv Endocrinol Metab 2010; 1: 129–38.

Cortisol is an essential steroid hormone affecting multiple systems



Nussey S, et al. The adrenal gland. In: Endocrinology: An integrated approach. Oxford BIOS Scientific Publishers; 2001.

Cortisol levels follow a predictable 24-hour pattern

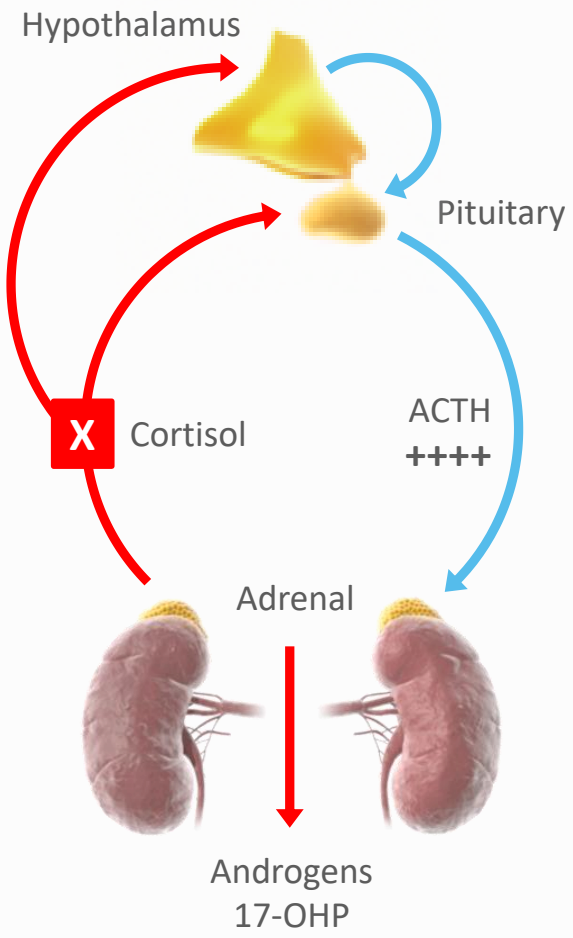


— Geometric mean (95% confidence interval ± 2 standard deviations (—) of serum cortisol concentration based on 20-min sampling over 24 hours in 33 healthy subjects.
— Average of harmonic regressions for individual subjects' data.
····· Mean (95% CI) mesor (midline indicating statistic of rhythm): 144 nmol/l (116, 157 nmol/l).

Adapted from Debono M, et al. J Clin Endocrinol Metal 2009; 94: 1548–54.

What is Congenital Adrenal Hyperplasia (CAH)?

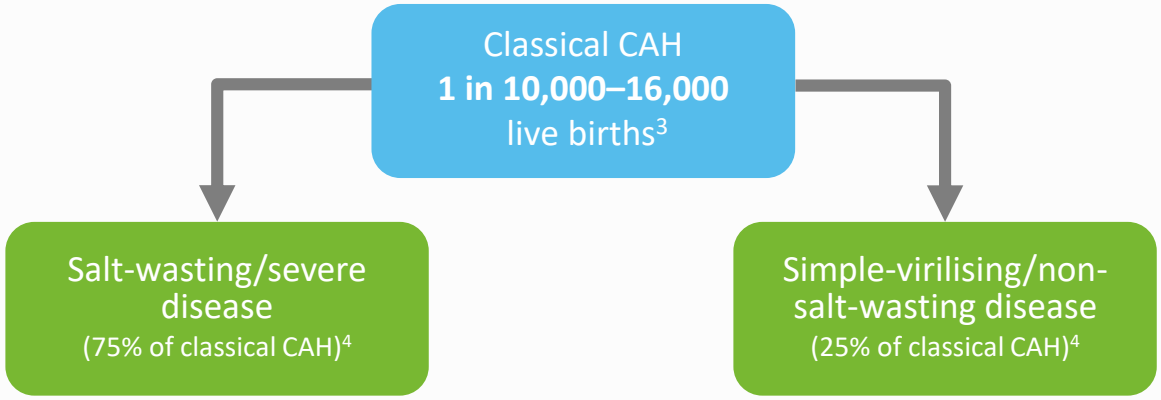
What is CAH?



- Congenital enzyme deficiency results in cortisol deficiency which untreated results in death through an adrenal crisis
- The lack of cortisol feedback results in high ACTH drive causing hyperplasia of the adrenals and increased secretion of adrenal precursor hormones
- High precursor hormones are androgens and cause virilisation of females, short stature and infertility

CAH is a group of autosomal recessive disorders of the adrenal system

- CAH is typified by impaired production of essential steroid hormones (aldosterone and cortisol) and an excess and/or deficiency of mineralocorticoids and androgens[1–3]
- Two subtypes of CAH are recognised[2]
  - Subtypes are primarily identified based on the severity of cortisol insufficiency and levels of cortisol precursors[3]



References: 1. Auchus R, et al. J Clin Endocrinol Metab 2013; 98: 2645–65; 2. Speiser P, et al. J Clin Endocrinol Metab 2010; 95: 4133–60; 3. Huynh T, et al. Clin Biochem Rev 2009; 30: 75–86; 4. Nimkarn S, et al. 21-hydroxylase-deficient congenital adrenal hyperplasia. In GeneReviews®, eds Pagon RA, Adam MP, Ardinger HH, et al. Seattle (WA): University of Washington, Seattle; 1993–2016. Available from http://www.ncbi.nlm.nih.gov/books/NBK1171/. Last accessed 11/1/16.

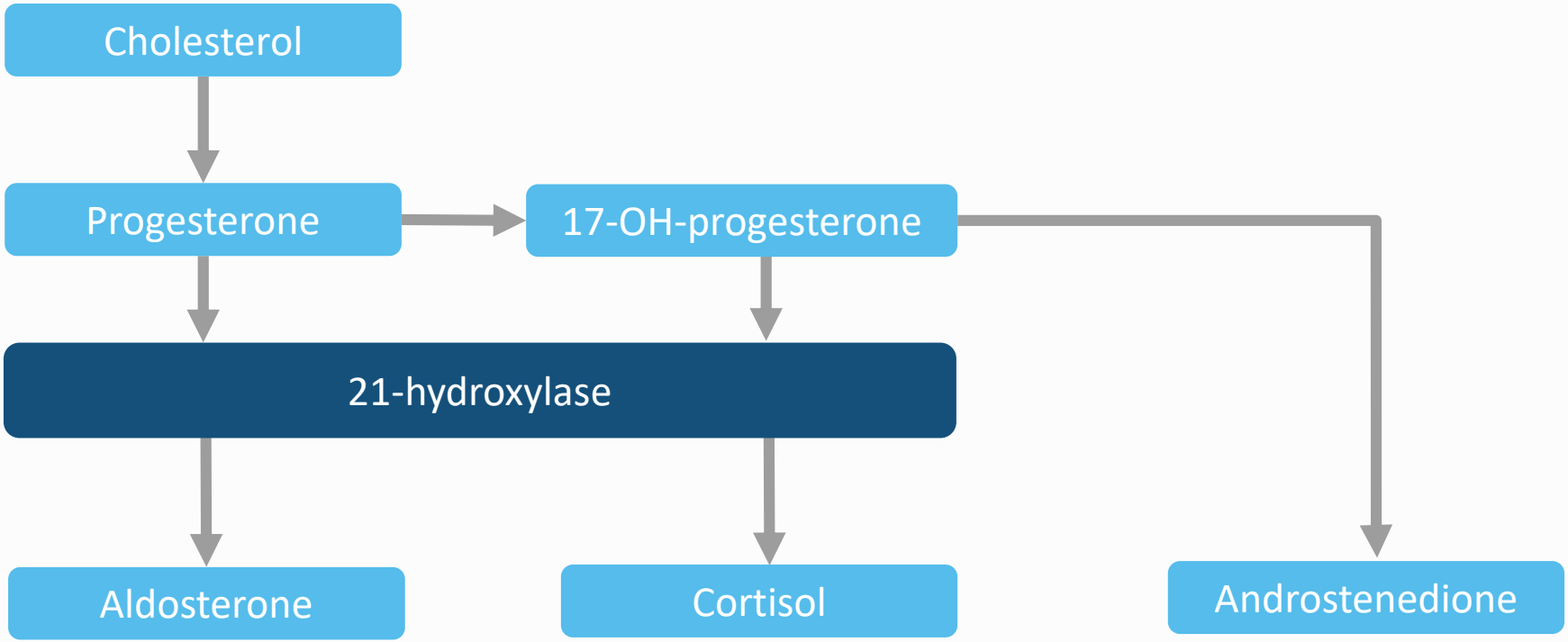
Genetics of CAH

- Classical and non-classical CAH are both most commonly caused by deficiencies of the enzymes 21-hydroxylase or 11-beta hydroxylase in the adrenal pathway[1,2]

	21-hydroxylase	11-beta-hydroxylase
Incidence	90% of CAH[1]	8–9% of CAH[1]
Gene	*CYP21A2*[3]	*CYP11B1*[4]
Mutations	• At least nine mutations known[1] • Many leave the enzyme with some degree of functionality[1] • Recent data indicate that *CYP21A2* genotype does not always correlate clearly with phenotype[5]	• Multiple gene abnormalities identified[1] • Lead to a spectrum of impairment from severe to partial[1]

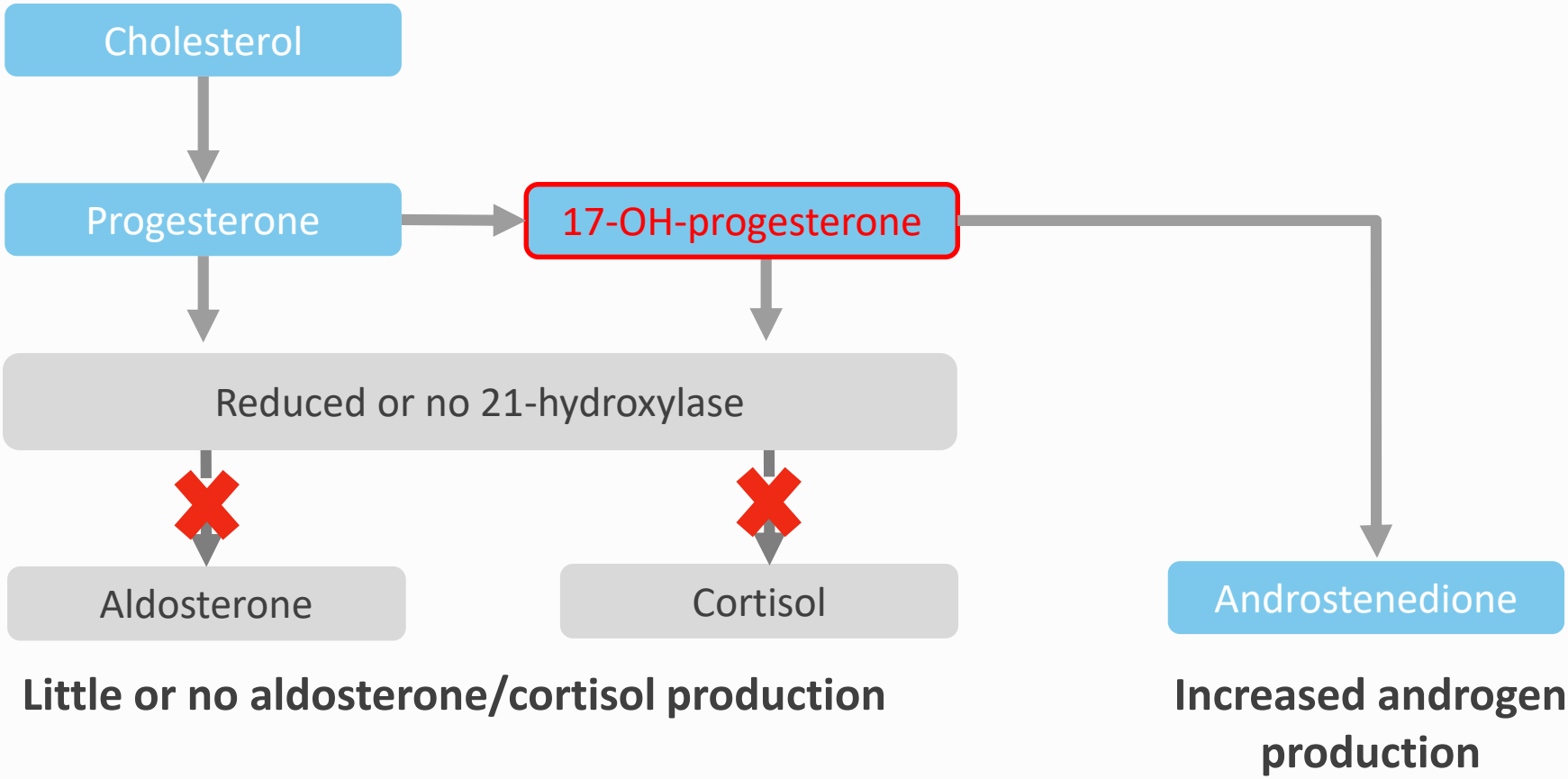
References: 1. Deaton M, et al. Am Fam Physician 1999; 59: 1190–96; 2. Witchel S et al. Int J Ped Endo 2010: Art IC 625105; 3. Kolahdouz M, et al. Adv Biomed Res 2015; 4: 189; 4. White P. Endocrinol Metab Clin North Am 2001; 30: 61–79; 5. Krone N, et al. J Clin Endocrinol Metab 2013; 98: E346–54.

21-hydroxylase is essential for cortisol production



Deaton M, et al. Am Fam Physician 1999; 59: 1190–96.

Loss of 21-hydroxylase activity disrupts cortisol production in CAH



Deaton M, et al. Am Fam Physician 1999; 59: 1190–96.

Clinical presentation

Classical CAH is associated with negative long-term health outcomes (1)

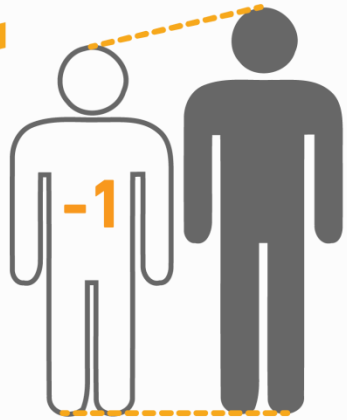
Fertility[1]

IRREGULAR MENSES
⅓ women

33% BOYS **TART** 44% MEN

TART: TESTICULAR ADRENAL REST TUMOUR

Smaller Stature[1]

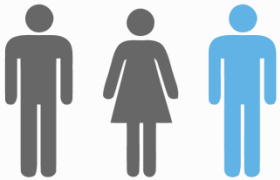


Standard deviation score

Metabolic effects[1,2]

DIABETES MELLITUS

2.8x vs controls



OBESITY
⅓ OF ADULTS

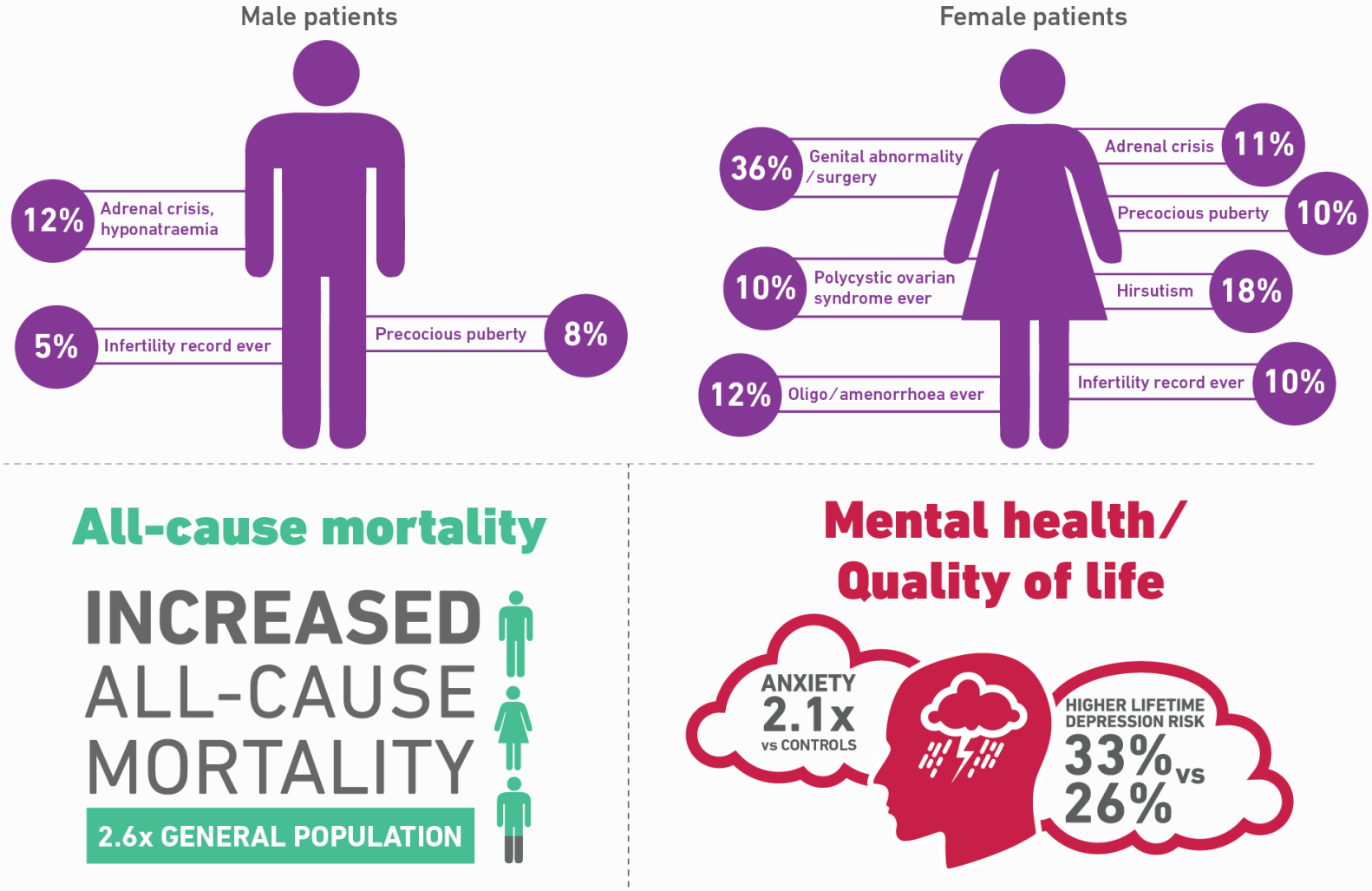
METABOLIC SYNDROME
18% ADULTS

HYPERTENSION

1.6x vs controls

References: 1. Finkielstain G, et al. J Clin Endocrinol Metab 2012; 97: 4429–38; 2. Stewart P et al. Defining and exploring the excessive healthcare burden of adrenal insufficiency. Abstract GP.01.02, presented at 17th European Congress of Endocrinology, 16–20 May 2015.

Classical CAH is associated with negative long-term health outcomes (2)



Jenkins-Jones S, et al. The burden of illness of congenital adrenal hyperplasia in the United Kingdom: a retrospective, observational study. Poster PND4, presented at ISPOR 18th Annual European Congress 7-11 November 2015.

Treatment

Adults with classical CAH should receive individualised therapy

- Therapies focus on: the prevention of adrenal crisis; prevention of long-term consequences of adrenal replacement therapies; and the restoration of fertility where desired[1]
- Hydrocortisone or long-acting glucocorticoids are recommended on or close to attainment of linear growth[2]

Drug	Total daily dose	Daily distribution (no. doses)
Maintenance therapy		
Hydrocortisone	15–25 mg	2–3
Prednisone	5–7.5 mg	2
Fludrocortisone	0.05–0.2 mg	1
Dexamethasone	0.25–0.5 mg	1
Hydrocortisone stress dosing		
100 mg initial parenteral dose, followed by 3–4 times maintenance dose IV every 6 hours		

References: 1. Auchus R. Int J Ped Endocrinol 2010; 2010: Art614107; 2. Speiser P, et al. J Clin Endocrinol Metab 2010; 95: 4133–60.

Adults with classical CAH require ongoing monitoring

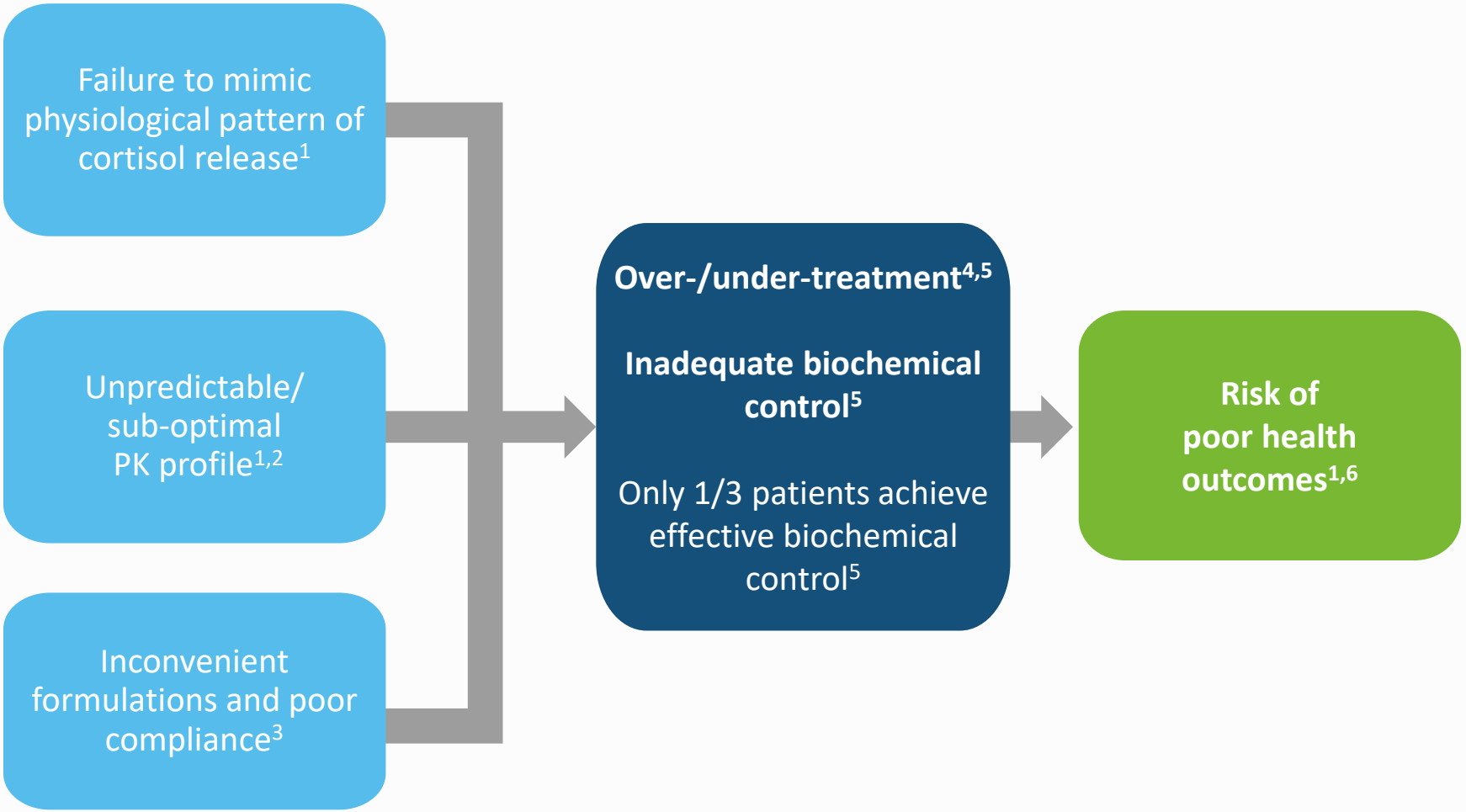
Monitoring and evaluations should be carried out according to individual needs[1]

- 6-12 month treatment assessments should include[2]
  - hormone measurements
  - physical examination
- Additional monitoring may be carried for:
  - fecundity and fertility[1]
  - testicular adrenal rest tumours (TART)[2]
  - weight[1]
  - lipid profile[1]
  - blood pressure[1]
  - bone mineral density[1]

References: 1. Nimkarn S, et al. 21-hydroxylase-deficient congenital adrenal hyperplasia. In GeneReviews®, eds Pagon RA, Adam MP, Ardinger HH, et al. Seattle (WA): University of Washington, Seattle; 1993–2016. Available from http://www.ncbi.nlm.nih.gov/books/NBK1171/. Last accessed 7/3/17. 2. Speiser P, et al. J Clin Endocrinol Metab 2010; 95: 4133–60.

Unmet needs

Current hydrocortisone therapies risk over- or under-treatment



References: 1. Chan S, et al. Ther Adv Endocrinol Metab 2010; 1: 1291383; 2. CORDIS/TAIN Periodic Report. Available from http://cordis.europa.eu/result/rcn/144089_en.html. Last accessed 11/1/16; 3. Auchus R. Int J Pediatr Endocrinol 2010; 2010: 614107; 4. Peacey S, et al. Clin Endocrinol (Oxf) 1997; 48: 266–61; 5. Han T, et al. Nat Rev Endocrinol 2014; 10: 115–24; 6. Debono M, et al. Best Pract Res Clin Endocrinol Metab 2009; 23: 221–32.

In adults, conventional hydrocortisone therapies do not mirror circadian release of cortisol

- Current therapies have a short plasma half-life and cannot replicate natural circadian variation of hydrocortisone[1–3]

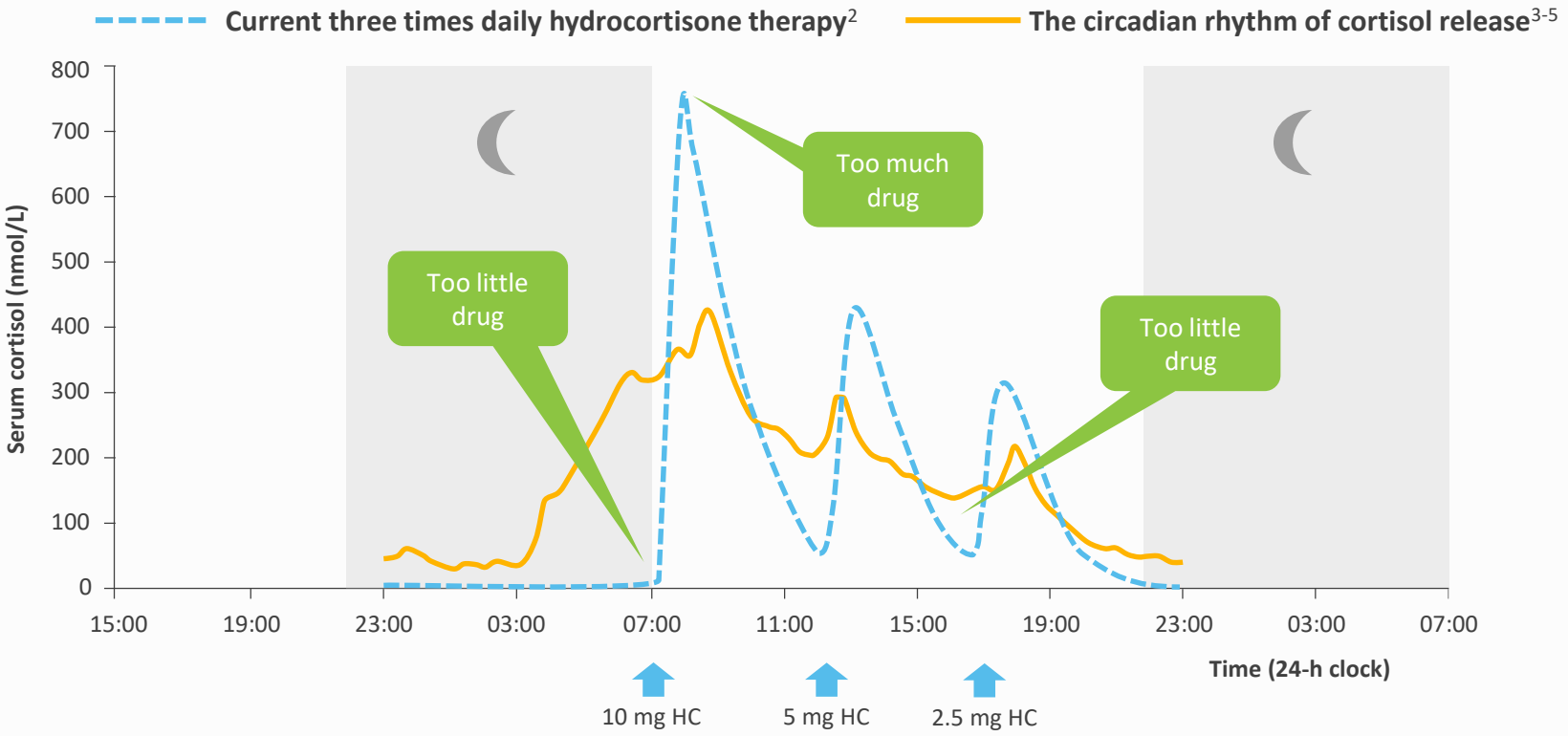
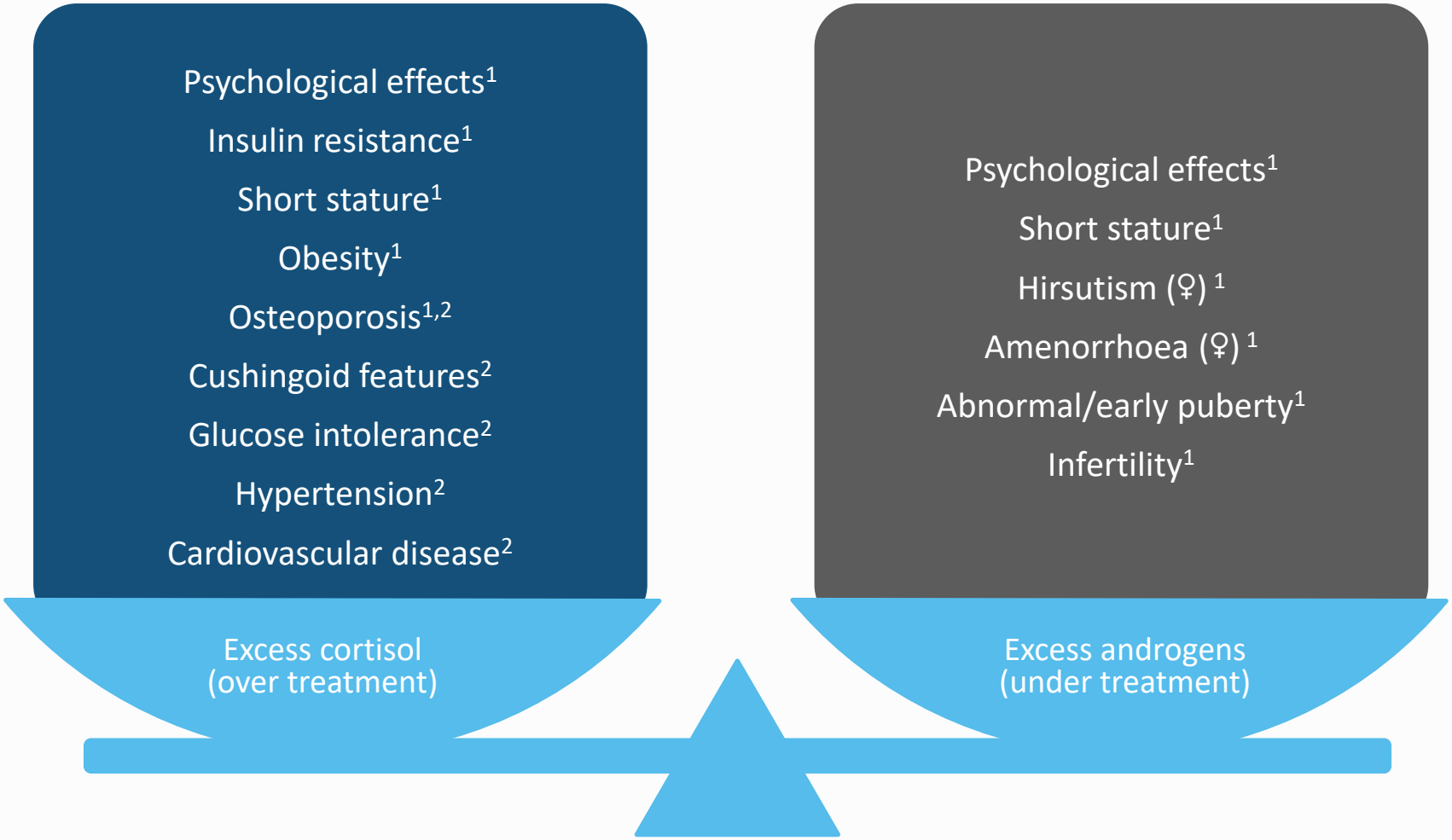


Figure based on Mah et al., and Debono et al.

References: 1. Chan S, et al. Ther Adv Endocrinol Metab 2010; 1: 1291383; 2. Mah P, et al. Clin Endocrinol 2004; 61: 367–75; 3. Debono M, et al. J Clin Endocrinol Metab 2009; 94: 1548–54; 4. Debono M, et al. Presented at 94th Annual meeting of the Endocrine Society. Presentation no. MON-480. Available from: http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2012.AHPAA.1.MON-480. Last accessed 17/3/16; 5. Darzy K, et al. J Clin Endocrinol 2005; 90: 5217–25.

Over- and under-treatment result in multiple adverse outcomes



References: 1. Han T, et al. Nat Rev Endocrinol 2014; 10: 115–24; 2. Debono M, et al. Best Pract Res Clin Endocrinol Metab 2009; 23: 221–32.

Replicating circadian variation in cortisol levels is an important unmet need

Diurnal

Lack of cortisol rhythmicity and inappropriate dosing is associated with poor health outcomes[1–3]

Replicating circadian cortisol levels may improve biochemical control of Congenital Adrenal Hyperplasia (CAH) and health status[4]

New formulations of modified release cortisol may help reduce morbidity and mortality in CAH[5]

1. Plat L, et al. J Clin Endocrinol Metab 1999; 84: 3082–92; 2. Han T, et al. Nat Rev Endocrinol 2014; 10: 115–24; 3. Debono M, et al. Best Pract Res Clin Endocrinol Metab 2009; 23: 221–32; 4. Whitaker M, et al. Clin Endocrinol (Oxf) 2014; 80: 554–61; 5. Chan S, et al. Ther Adv Endocrinol Metab 2010; 1: 129138.

Summary

- Patients with CAH have impaired production of cortisol and aldosterone and aberrant levels of mineralocorticoids and androgens[1–3]
- Classical CAH may be fatal if left untreated; classical disease is associated with multiple poor outcomes throughout sufferers' lives[4–7]
- Classical CAH requires life-long treatment to replace cortisol and to normalise excessive androgen secretion[2]
- Current hydrocortisone therapies fail to mimic natural circadian variation[8]
- CAH still results in significant increased morbidity and mortality[7, 9]
- New therapies are needed that mimic the body's natural circadian cortisol release and improve patient outcomes[8]

1. Auchus R, et al. J Clin Endocrinol Metab 2013; 98: 2645–65; 2. Speiser P, et al. J Clin Endocrinol Metab 2010; 95: 4133–60; 3. Huynh T, et al. Clin Biochem Rev 2009; 30: 75–86; 4. US National Institutes of Health/National Institute of Child Health and Human Development. What are the symptoms of congenital adrenal hyperplasia (CAH)? Available from https://www.nichd.nih.gov/health/topics/cah/conditioninfo/Pages/symptoms.aspx. Last accessed 7/3/17; 5. Finkielstain G, et al. J Clin Endocrinol Metab 2012; 97: 4429–38; 6. Stewart P, et al. Defining and exploring the excessive healthcare burden of adrenal insufficiency. Abstract GP.01.02, presented at 17th European Congress of Endocrinology, 16–20 May 2015. 7. Jenkins-Jones S, et al. The burden of illness of congenital adrenal hyperplasia in the United Kingdom: a retrospective, observational study. Poster PND4, presented at ISPOR 18th Annual European Congress 7–11 November 2015; 8. Chan S, et al. Ther Adv Endocrinol Metab 2010; 1: 1291383; 9. Falhammar H, et al. J Clin Endocrinol Metab 2014;99:E2715–21.

Analyst Day:
Chronocort® - European Study Update

John Porter, MBBS PhD – Medical Director

Date of Preparation: December 2018 Code: CORP-GB-0023

11 December 2018

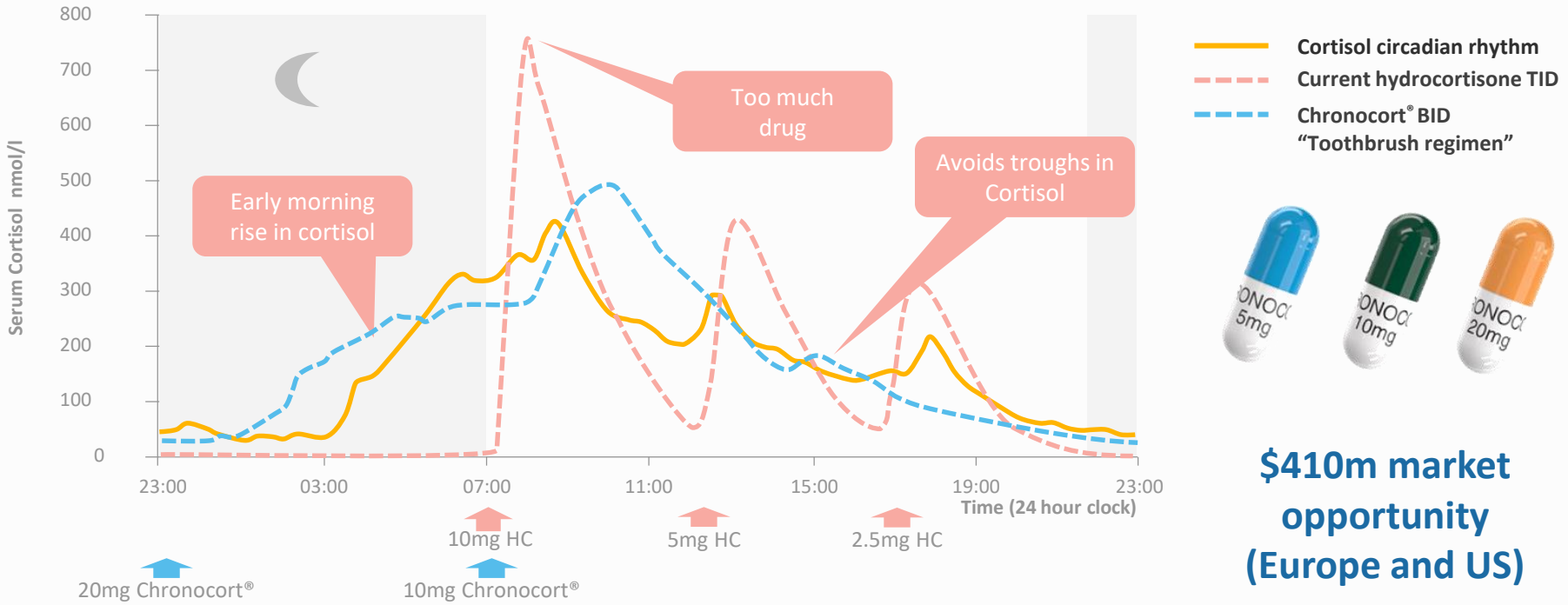
Chronocort®: Targeting effective disease control in adults

Chronocort® – innovative drug delivery solution:

- Delayed release coat allows pH triggered release in GI tract

Chronocort® – improved disease control:

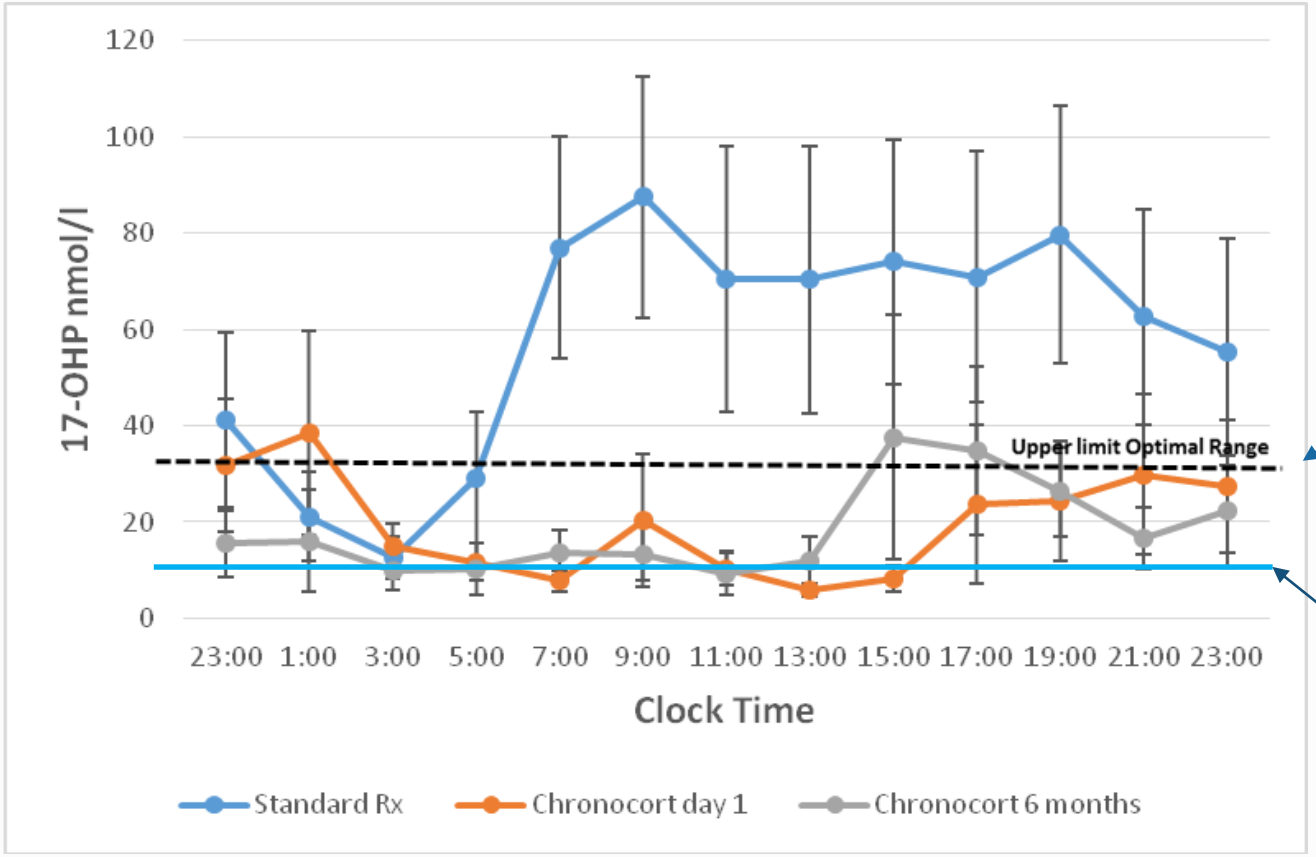
- Control of morning 17-OHP
  94% of patients vs 31% on standard treatment in Phase II trial



$410m market opportunity (Europe and US)

Source: Debono et al. JCEM (2009); Mallappa et al JCEM (2014) & company data on file; BID, twice daily; TID, thrice daily

Chronocort Phase 2 Overview



UPPER LIMIT OPTIMAL RANGE
36.4 nmol/l

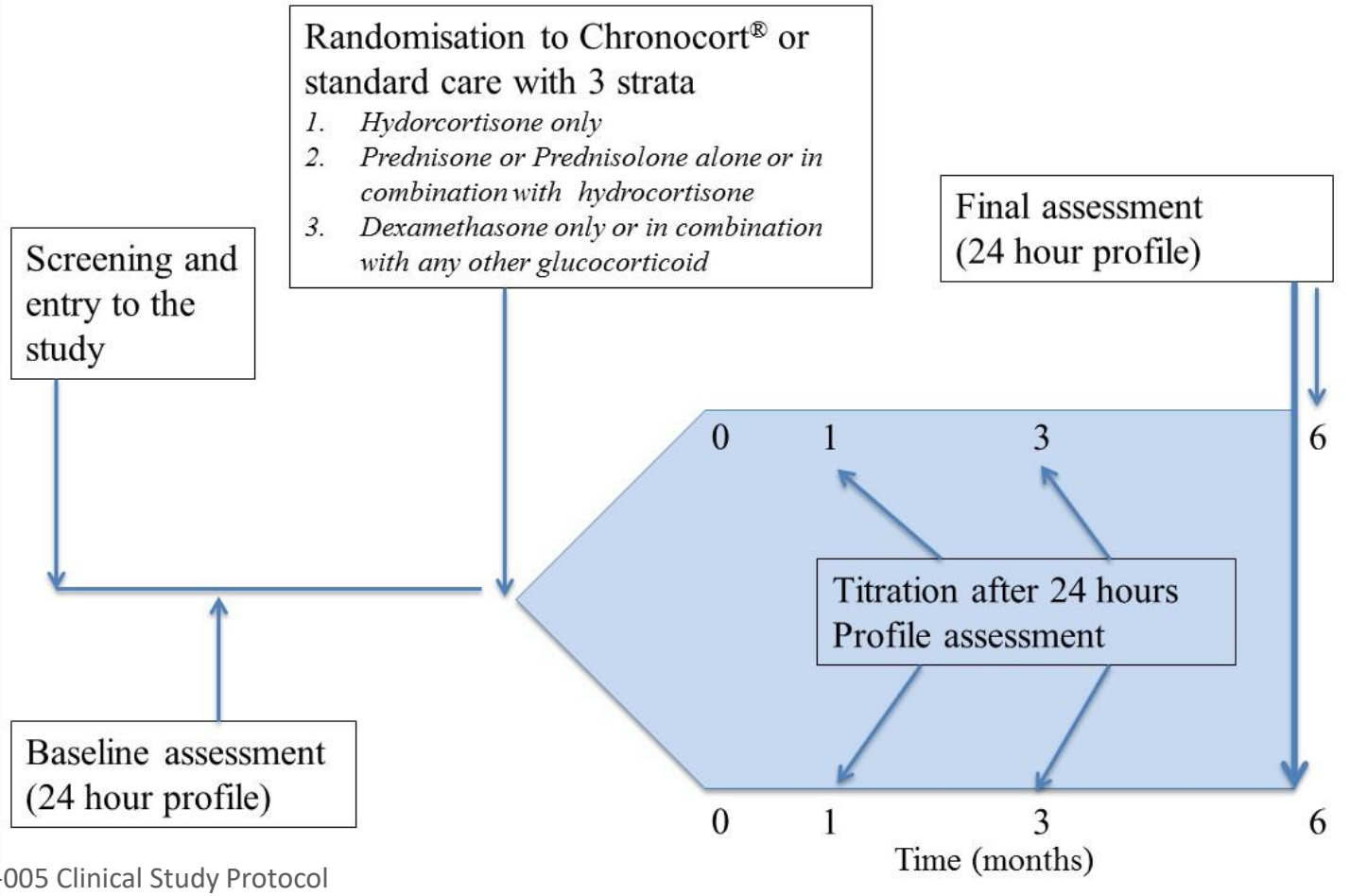
UPPER LIMIT REFERENCE RANGE
8.6nmol/l
Female

Source: Mallappa et al JCEM (2015)

No titration of SoC (baseline); Chronocort titrated at 0, 2 and 4 months

Pivotal Phase 3 Study in CAH:

- Largest and most detailed interventional study ever carried out in CAH; 122 patients enrolled across 11 specialist centres and 7 countries



Source: DIUR-005 Clinical Study Protocol

Phase 3: Overview

Primary Endpoint:

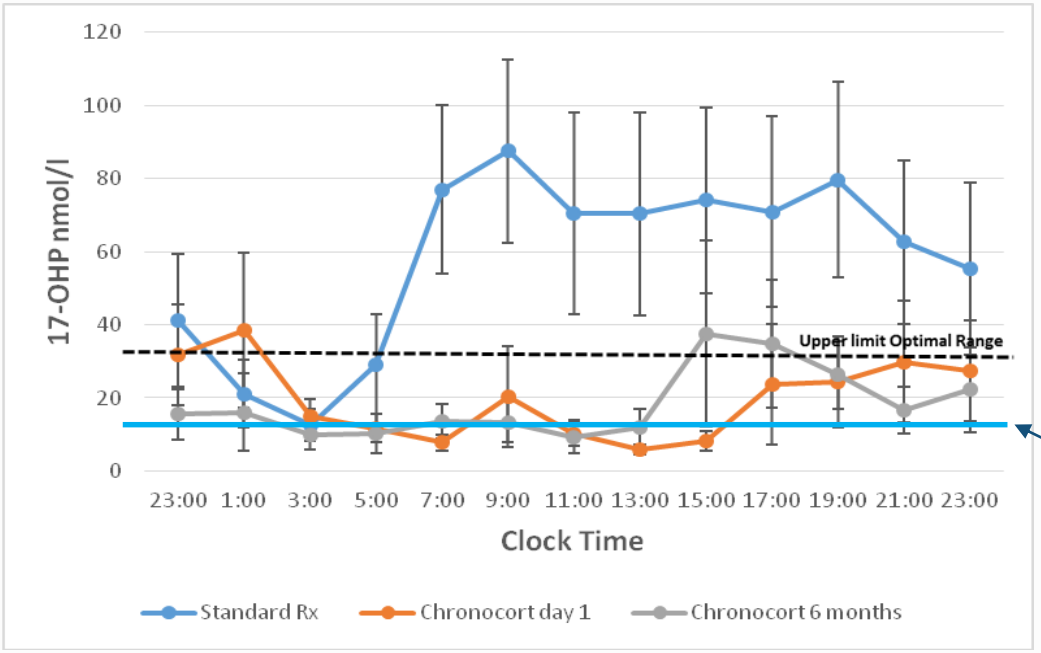
The change from baseline to 24 weeks in the natural logarithm of the mean of the 24-hour standard deviation score (SDS) profile of 17-OHP.

NOT MET

However:

- **Highly effective titration regime- not possible in clinical care**
- **Chronocort® achieves significantly better control of 17-OHP in the period 0700-1500**
- **Significantly lower overall 17-OHP over 24 hours (AUC)**
- **17-OHP less variable on Chronocort® over 24hrs**
- **Androgen control (both 17-OHP and A4) achieved on a lower dose of steroid**
- **More episodes of unexpected therapeutic benefit seen with Chronocort®**
- **Fewer sick day rules with Chronocort®**
- **No adrenal crises with Chronocort®**
- **Other AEs & secondary endpoints comparable between the arms**

Chronocort Phase 2 Reminder



UPPER LIMIT REFERENCE RANGE

Baseline above optimal range

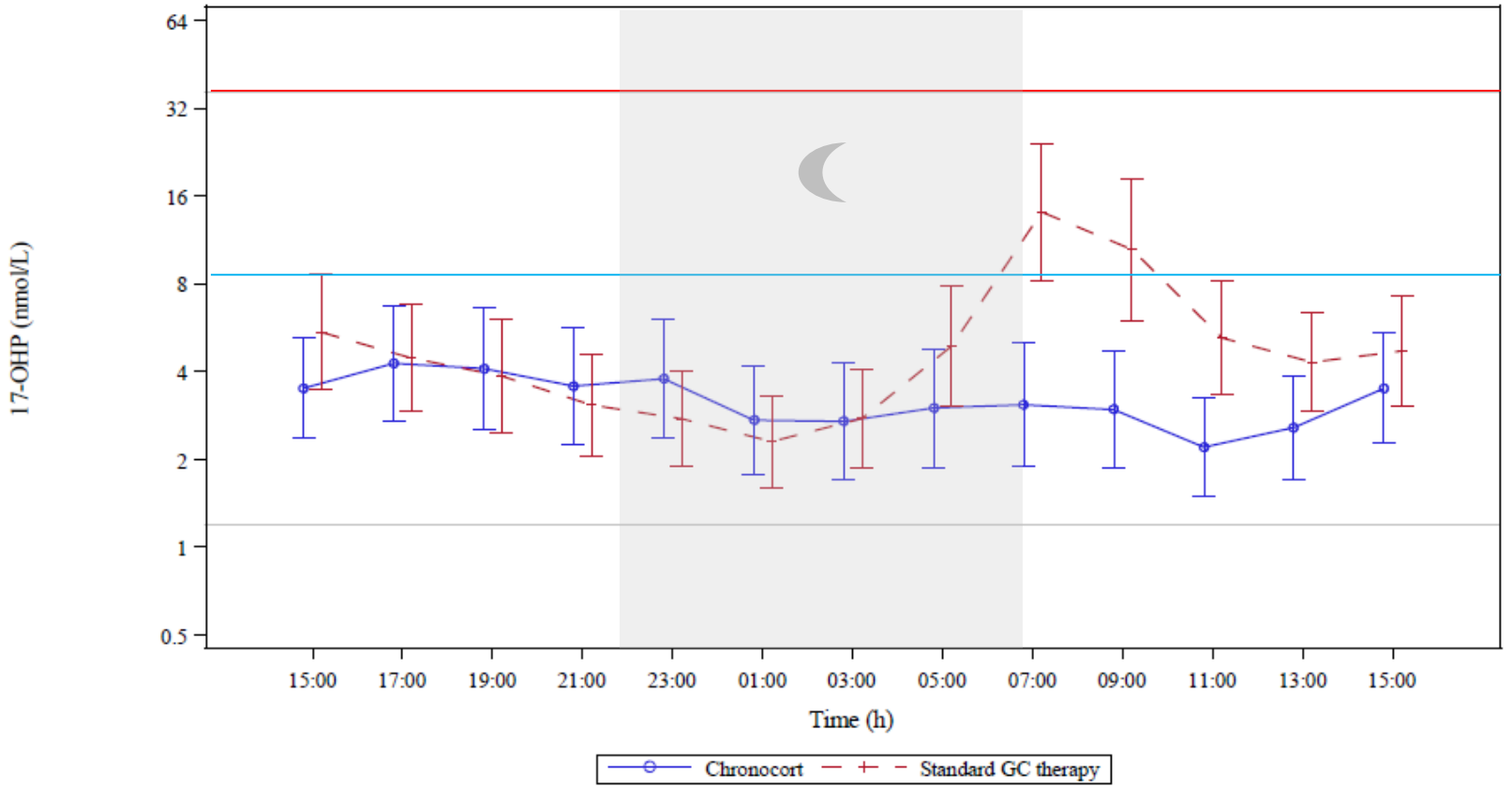
On Chronocort levels below optimal range

Source: Mallappa et al JCEM (2015)

No titration of SoC (baseline); Chronocort titrated at 0, 2 and 4 months

Androgen (17-OHP) Profile Phase 3

Protocol Number: DIUR-005 Page 1 of 1
Final Outputs, Database Lock Date: 14 September 2018
Figure 14.2.1.4.3 Geometric mean +/- 95% CI for 17-OHP (nmol/L) week 24 profile by treatment group (Efficacy evaluable analysis set)



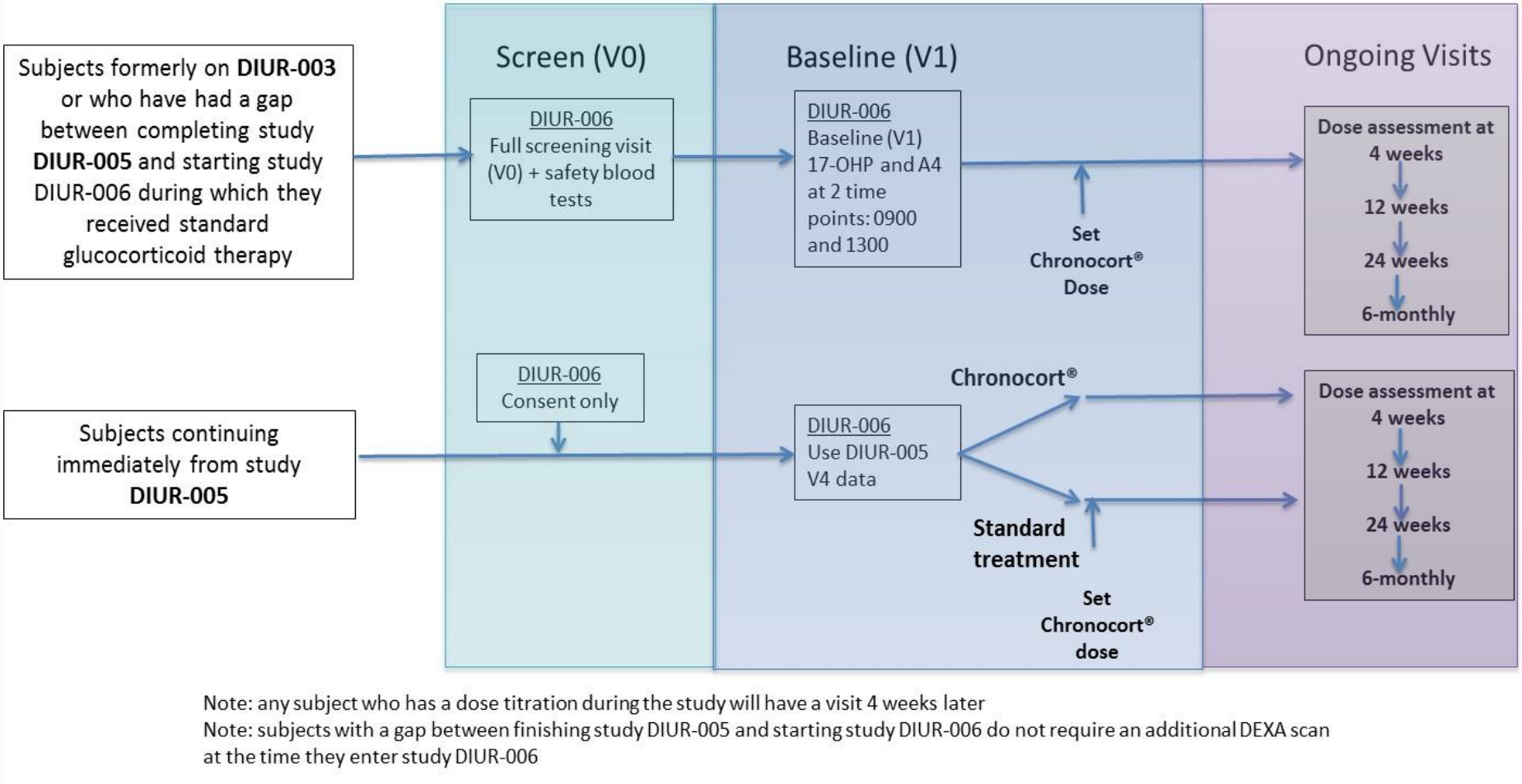
Number of evaluable subjects, n													
Chronocort	53	53	53	53	53	53	53	53	53	53	53	53	53
Standard GC therapy	52	52	52	52	52	52	52	52	52	52	52	52	52

OPTIMAL RANGE

REFERENCE RANGE

Source: Diurnal Data

Safety Extension Study (DIUR-006)



Note: any subject who has a dose titration during the study will have a visit 4 weeks later
Note: subjects with a gap between finishing study DIUR-005 and starting study DIUR-006 do not require an additional DEXA scan at the time they enter study DIUR-006

Source: DIUR-006 Clinical Study Protocol

DIUR-006: Interim Analysis

- 91 patients enrolled on study at end of enrolment
  - Clinicians report that patients want to continue on Chronocort & seeing beneficial effects
  - Monitoring regime suitable for normal clinical care
- DIUR-006 interim analysis (data cut Mar-18)
  - Complete data on 53 patients for 6 months treatment; 19 patients for 12 months treatment; 7 patients for 18 months treatment; 3 patients have been on Chronocort for 24 months
- Androgen control (17OHP & A4) maintained over the period
- Further steroid dose reductions over period
- Weight/BMI maintained
- Metabolic parameters unchanged - reassuring
- Study scheduled to run until Feb-2020

Summary & Next Steps

- Submitted Scientific Advice Request to EMA on 7th Dec-18
- The Scientific Advice package includes further analysis of the DIUR-005 and DIUR-006 interim data
- The Company has asked questions of the EMA around the suitability of the data package as the basis for Chronocort® registration in Europe, achieving orphan drug status for CAH and the applicability to other diseases of cortisol deficiency
- Meeting with the EMA anticipated towards the end of Q1, 2019 with advice available towards the beginning of Q2, 2019

Q&A