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PROMPT: A prospective study to assess efficacy and safety of metyrapone in endogenous Cushing's syndrome

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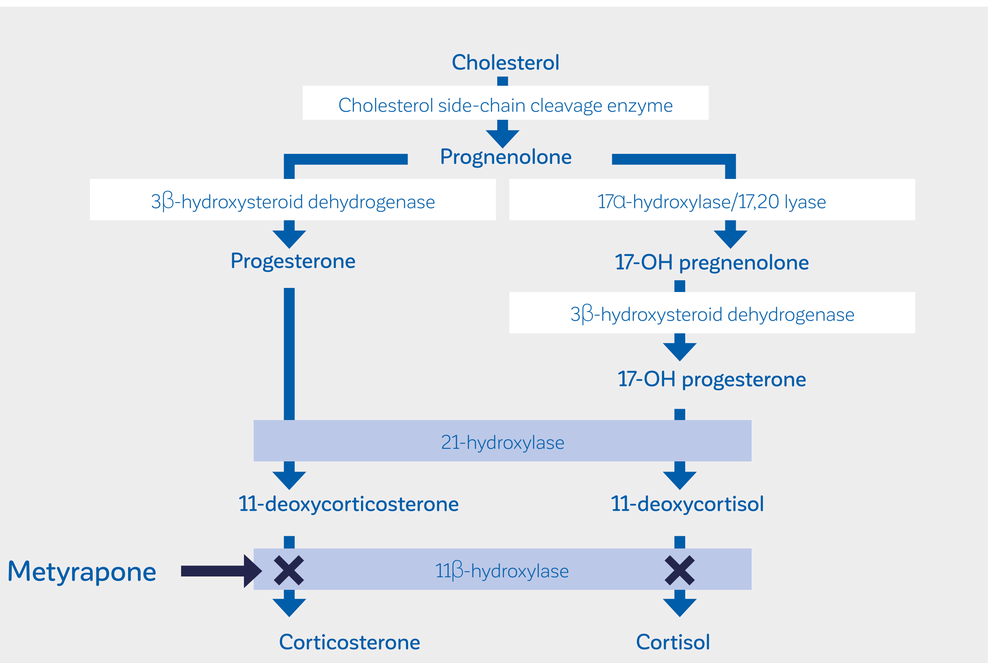
INTRODUCTION

- Metyrapone blocks cortisol production by inhibiting 11β-hydroxylation of 11-deoxycortisol, the last step of cortisol synthesis (**Figure 1**).[1]
- Based on observational retrospective studies published over more than 50 years, metyrapone is approved for the treatment of endogenous Cushing's syndrome (CS) in 15 European countries.[2]
- PROMPT is the first prospective study to document the safety and efficacy of metyrapone using modern assay techniques.

Figure 1: Mode of action of metyrapone



Adapted from: Kulstad EB, et al. *West J Emerg Med.* 2010;11(2):161–172. Creative Commons (CC BY-NC 4.0)

METHODS

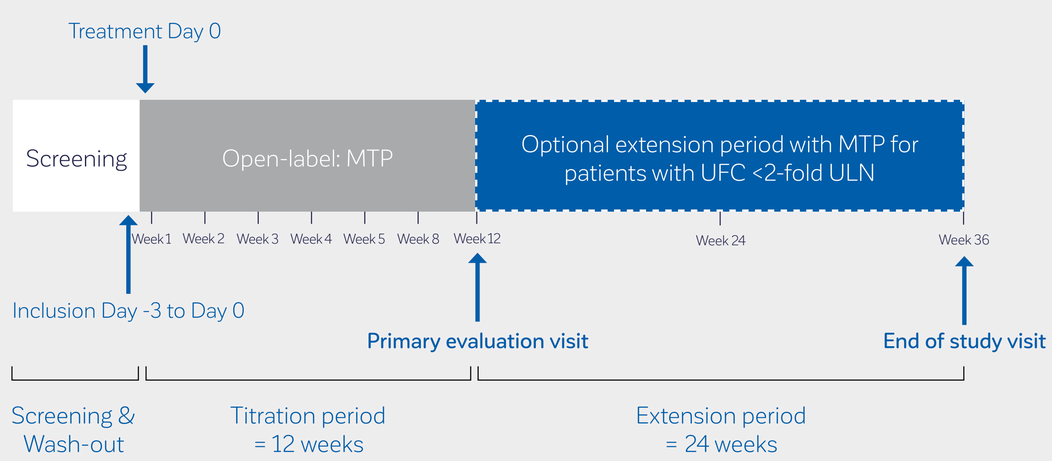
Patients

- Adult patients with a new diagnosis of endogenous CS of any etiology (except advanced adrenal carcinoma) or recurrent or persistent Cushing's disease (CD) after transsphenoidal surgery (TSS), were eligible if three baseline urinary free cortisol (UFC) values measured over 24 hours were at least 50% above the upper limit of normal (ULN=165 nmol/24h).

Study design (Figure 2)

- The international European Phase III/IV PROMPT study commenced in 2015 (ClinicalTrial.gov registry: NCT02297945).
- This single arm, open-label, multicenter trial is ongoing in seven countries:
  - Belgium, Germany, Hungary, Italy, Poland, Spain, Turkey

Figure 2: Study design



MTP: metyrapone; UFC: urinary free cortisol; ULN: upper limit of normal

- Metyrapone given three or four times daily was individually titrated based on cortisol levels in urine and serum over 12 weeks to achieve normal urine and serum cortisol levels according to a titration scheme (**Figure 2**).
- After 12 weeks, patients whose mean value of 3 UFCs (mUFC) was less than twice the ULN, continued to receive metyrapone for another 24 weeks (**Figure 2**).
- Cortisol was measured in a central laboratory by liquid chromatography tandem–mass spectrometry (LC-MS/MS) method. This assay is used to avoid cross-reactivity of 11-deoxycortisol in cortisol immunoassays.

Table 1: Metyrapone titration scheme

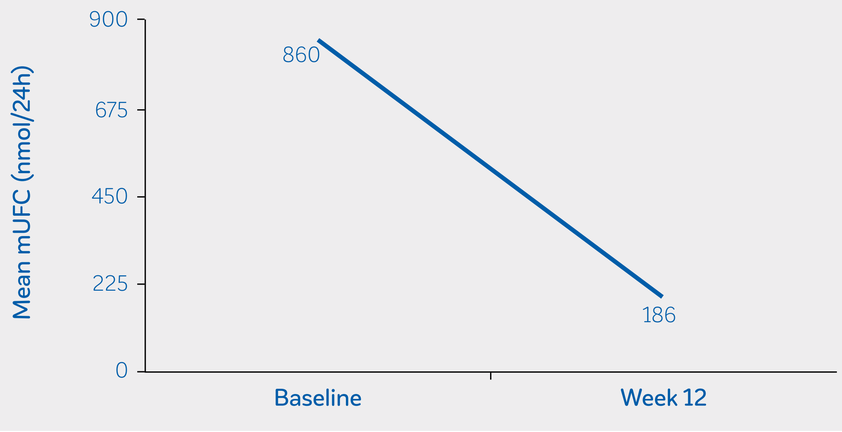
Baseline UFC	Initial MTP dose	MTP dose change		
		UFC > ULN (165 nmol/24h) Or Morning serum cortisol >330 nmol/L	Serum cortisol <193 nmol/L Or Signs/symptoms of adrenal insufficiency	UFC ≤ ULN (165 nmol/24h) Or 193 nmol/L ≤serum cortisol ≤330 nmol/L
Moderate CS Baseline UFC ≤ 5 x ULN	750 mg/day	↑250–500 mg/day	↑250–500 mg/day	Optimal dose reached
Severe CS Baseline UFC > 5 x ULN	1500 mg/day	↑500–1000 mg/day	↑500–1000 mg/day	Optimal dose reached

CS: Cushing's syndrome; MTP: metyrapone; UFC: urinary free cortisol; ULN: upper limit of normal

ENDPOINTS

- The primary endpoint is to assess the efficacy of metyrapone to normalize mUFC after 12 weeks of treatment.
- Secondary endpoints are:
  - Assessment of the efficacy of metyrapone to normalize serum and salivary cortisol after 12 weeks and UFC after 24 weeks;
  - Assessment of changes in clinical symptoms of CS, systolic and diastolic blood pressure, and quality of life (CushingQoL and Tübingen CD QoL inventory);
  - Assessment of safety and tolerability, including adverse events (AEs) and Ferriman-Gallwey score of hirsutism in women;
  - Assessment of impact of metyrapone blockade on circulating lipids, glucose, adrenocorticotropic hormone (ACTH), 11-deoxycortisol, deoxycorticosterone, renin/renin activity, androstenedione, dehydroepiandrosterone sulfate and total testosterone levels;
  - Estimation of time to 50% reduction of UFC, eucortisolemia, clinical and biochemical improvements.
- Exploratory endpoints include factors predicting success and response relationships.

Figure 3: Mean mUFC at baseline and at Week 12 in the initial 28 patients



mUFC: mean urinary free cortisol

STATUS

- The study commenced in 2015 and is ongoing.
- By April 2018, 35 patients were included: 24 women and 11 men, with a mean age of 45 years old (range: 21–73).
- A total of 32 patients had CD and 21 patients had previously undergone TSS (range: 1–3).
- Nine patients discontinued the study at/or after the primary objective endpoint (Week 12) owing to: inefficacy (n=3), mUFC >2 x ULN despite improvement by 70% (n=1), hirsutism (n=1), serious AEs (n=1; severe hypotension, cellulitis, venous thrombosis and renal insufficiency) and decision to undergo TSS despite control with metyrapone (n=3).
- The mean of the mUFC values in the first 28 patients treated over 12 weeks decreased from 860 nmol/24h at baseline to 186 nmol/24h at Week 12 (**Figure 3**).

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1. HRA Pharma UK & Ireland Ltd. Metopirone® (metyrapone) capsules 250mg. Summary of Product Characteristics. December 2016. https://www.medicines.org.uk/emc/product/4092 (Accessed: April 2018)
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