Buprenorphine pharmacology, safety and clinical application

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History of Buprenorphine

- Developed 1970’s
- Registered as analgesic 1980's
- Clinical research with heroin users
  - Phase II mid 1980’s
  - Phase III randomised trials late 1980’s early 1990’s
- Sublingual tablet (Subutex®) developed mid 1990’s
- Registered for opiate dependence treatment
  - France 1995
  - Australia 2000
- Suboxone tablet 2003
- Suboxone Film 2012
- Approved for opioid addiction treatment in 40 countries
- Depot buprenorphine 2019
Opioid Receptors

• Various receptor subtypes:
  • $\mu$ (mu), $\delta$ (delta), $\kappa$ (kappa) and ORL-1

• Involved in different physiological processes

• $\mu$-opioid receptor mediates:
  • Analgesic effects
  • Euphoria
  • Some side effects:
    • Respiratory depression
    • Sedation
    • Dependence
    • Constipation
What determines opioid effects?

• Receptor affinity
  • How tightly the drug binds to the receptor

• Dissociation
  • How fast the drug leaves the receptor

• Intrinsic activity
  • How much the drug stimulates the receptor
Agonist or antagonist?

• Full agonists – bind to the receptor producing an almost linear increase in physiological effect:
  – Methadone, morphine, heroin

• Partial agonists – bind to the receptor but have less than maximal effect on receptor activation:
  – Buprenorphine

• Antagonists – bind to the receptor but do not produce a biological response; are able to block agonist effects:
  – Naloxone, naltrexone, nalmefene
Understanding Opioid Effects

- Super agonist: fentanyl
- Agonist + partial agonist
- Partial agonist: buprenorphine
- Full agonist: morphine/heroin, hydromorphone
- Antagonist: naltrexone

Positive effect = addictive potential

Negative effect

Potentially lethal dose

Dose
Buprenorphine Pharmacology

• Mu partial agonist, Kappa antagonist
• High Mu receptor affinity and receptor occupancy:
  • Up to 95% at 16mg (Greenwald et al, 2003)
  • Blockade or attenuated effect of additional opioids
• Lower intrinsic activity than full agonists:
  • Favourable safety profile (ceiling effect)
  • Lower street value
  • Lower abuse potential (Walsh et al, 2003)
Pharmacokinetics

- Sublingual tablets
  - high 1st pass metabolism
- Bioavailability: IV > SC > SL > oral
- highly lipophilic
- 2 hepatic pathways: N-dealkylation and glucuronic conjugation
- entero-hepatic cycling
- metabolites predominately excreted in faeces and urine
Buprenorphine Pharmacology
Therapeutic Reality vs Lab. Findings

• Partial Agonism and Ceiling Effect
  • Referred to as ‘Partial efficacy’
  YET
  • Analgesic models Bup > or ~ Morphine
  • Increasing doses increases analgesia
    • Doses up to 11mg (Budd)
  • High and low dependents equally ‘held’
  • Successful high dose transfers
    • 600-900mg Methadone (Gilhooly)
• Ceiling/Plateau observed on side effects
  • Respiratory depression, BP and HR (Walsh, Preston)
    • Bell Shaped Dose Response Curve
Effects of Buprenorphine on $\mu$-opioid receptor availability

MRI

Bup 0 mg

Bup 2 mg

Binding potential (Bmax/Kd)

Bup 16 mg

Bup 32 mg

D Nutt. Personal communication
Subjective effects: blockade/tolerance

Adapted from Bickel et al., 1988
Ceiling effect on respiratory depression

Adapted from Walsh et al., 1994
Pharmacology - effects and benefits

• Slow receptor dissociation:
  • Longer duration of action
  • Milder withdrawal
• Lower physical dependence liability than full agonists
• Limited development of tolerance
• Ceiling effect on respiratory depression
  • Increased safety against overdose
• Relatively slow access to receptors

Sublingually, but NOT orally, active
Naloxone Pharmacology

• Competitive Mu opioid antagonist
• Not orally available (‘inactive’)
• Poor Sublingual availability
• Rapid access to Mu receptors (IV)
  • Precipitates withdrawal in opioid dependents
  • Blocks access of other opioids to receptor
• Relatively quick receptor dissociation
  • Short duration of action(T1/2 life 45mins)
• Mu receptor affinity:-
  • Bup>>>Nx>Methadone>Heroin
Buprenorphine-Nx Pharmacology

• Sublingual Administration:-
  • Nx does NOT compromise absorption
  • Same Buprenorphine plasma levels from Bup and Bup-Nx
  • Buprenorphines’ time of onset and time of peak effect unaltered by Nx
  • Duration of action unaltered by Nx
  • Nx plasma levels undetectable at 8/2mg dose level(Strain 2004)
Clinical Pharmacology: Sublingual Bup-Nx

- Comparison Bup-Nx (4-16mg) with Bup (16mg)
- No effect of Nx on bioavailability, or effects of Bup at 16mg dose level
- Many Nx plasma levels not detected
- Nx bioavailability not measurable
- Subjective and physiological effects similar

(Harris et al 2004)
Clinical Pharmacology: Intravenous Bup-Nx

- Nx gains rapid access to receptors
  - Precipitates withdrawal in opioid dependents

- Nx effects last up to 2 hrs

- Buprenorphine effects evident >1 hr later
Injecting Suboxone

• Precipitates moderate–severe withdrawal syndrome in individuals dependent on full opioid agonists

• Effects of Naloxone are maximized when taken intravenously

• Effects of IV Suboxone are indistinguishable from IV Naloxone alone in individuals dependent on full opioid-agonists

Fudala et al., 1998
Buprenorphine-Nx Combination

4 part Buprenorphine: 1 part Naloxone
The right balance between agonist and antagonist effects

Sublingual: Opiate agonist effect from Buprenorphine
Intravenous: Opiate antagonist effect from Naloxone
<table>
<thead>
<tr>
<th>Drug</th>
<th>Buprenorphine</th>
<th>BupNX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin-dependent</td>
<td>Agonist effect</td>
<td>Antagonist effect</td>
</tr>
<tr>
<td>Non-dependent</td>
<td>Mild agonist effect</td>
<td>Attenuated agonist effect</td>
</tr>
<tr>
<td>Methadone-maintained</td>
<td>Antagonist effect</td>
<td>Antagonist effect</td>
</tr>
<tr>
<td>Buprenorphine or BupNX maintained</td>
<td>Agonist effect</td>
<td>Agonist effect (attenuated)</td>
</tr>
</tbody>
</table>

†assuming some time interval has elapsed since last use of drug
Safety of Bup-Nx

• Well tolerated

• No apparent adverse clinical effects attributable to Naloxone, even during induction

• No safety concerns following administration of 24/6 mg for up to a year

• Naloxone does not appear to interfere with the sublingual absorption of Buprenorphine

• Safety not demonstrated in pregnancy

Mendelson et al., 1996
Buprenorphine-Nx Combination

• Summary:-
  • Efficacy and safety equivalent to that of Buprenorphine alone
  • Discourages IV misuse
  • Reduces street value
  • Reduces diversion potential
Duration of effects

• Onset of action 30 – 60 minutes
• Peak effects: 1 – 4 hours
• Duration of action is dose related
  • low dose : 4 – 12 hrs
  • med dose : ~ 24 hrs
  • high dose : 2 – 3 days
• Steady state equilibrium achieved after 3 days
Side-effects

• Similar to other opioids
• Common in first few days-weeks and then generally subside
• Experience of side-effects variable
  • May experience side-effect to one opioid only
  • may experience similar side-effect with other opioids
• Not all symptoms are necessarily side-effects
  • consider other causes
  • ‘Expectancy’ factors may be important
Common Side-effects

• Headache
• Constipation
• Nausea
• Drowsiness, sedation
• Tiredness, lethargy
• Sleep disturbances
• Sweating
• Reduced libido
Drug Interactions

• Sedatives
  • Additive sedative effects to other sedatives
  • Can result in respiratory depression, heavy sedation, coma and death

• Opioid antagonists

• Opioid agonists

• Precaution with concomitant CYP3A4 inhibitors
  • e.g. protease inhibitors, ketoconazole, nifedipine, and some antiviral medications such as Atazanavir
  • may lead to increased plasma concentrations of buprenorphine
Pharmacological Reality!

• All opioids have abuse potential

• Some abuse of Buprenorphine is to be expected (unauthorised use):
  • Based on the available research, one would predict this to be far less with Bup-NX than Buprenorphine

• Even with this leakage, Buprenorphine is an extremely safe medication and the French data show us that there is safety in the numbers... (Auriacombe)
  • Ratio of deaths/patients is 10x less with Buprenorphine than with Methadone
Opioid withdrawal management
Goals of detoxification

• Reversing neuroadaptation
  • Tolerance and withdrawal
• Promoting uptake of post-detox treatment
• However, completion of withdrawal is difficult for most!
  • Number of different approaches in use globally
  • What works????
  • What are the critical differences?
Opioids: withdrawal management

<table>
<thead>
<tr>
<th>Reviews (N°=7)</th>
<th>Nº Studies</th>
<th>Nº Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone At Tapered Doses For The Management Of Opioid Withdrawal</td>
<td>20</td>
<td>1907</td>
</tr>
<tr>
<td>Buprenorphine For The Management Of Opioid Withdrawal</td>
<td>26</td>
<td>2136</td>
</tr>
<tr>
<td>Alpha2 Adrenergic Agonists For The Management Of Opioid Withdrawal</td>
<td>24</td>
<td>1631</td>
</tr>
<tr>
<td>Opioid Antagonists With Minimal Sedation For Opioid Withdrawal</td>
<td>10</td>
<td>854</td>
</tr>
<tr>
<td>Opioid Antagonists Under Heavy Sedation Or Anaesthesia For Opioid Withdrawal</td>
<td>9*</td>
<td>1109*</td>
</tr>
<tr>
<td>Psychosocial And Pharmacological Treatments Versus Pharmacological Treatments For Opioid Detoxification</td>
<td>9</td>
<td>716</td>
</tr>
<tr>
<td>Inpatient Versus Other Settings For Detoxification For Opioid Dependence</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>96</strong></td>
<td><strong>8118</strong></td>
</tr>
</tbody>
</table>
Methadone and adrenergic agonists are both effective

- 13 studies
- Symptoms emerge earlier and resolve more quickly with clonidine
- Stay in treatment longer with methadone but chances of completion similar
- Adverse effects twice as likely with clonidine c/w methadone
Completion of withdrawal, methadone vs. adrenergic
Buprenorphine vs. Adrenergic agonists

• Buprenorphine:
  • Less severe withdrawal
  • Longer duration of treatment (IP & OP)
  • Greater completion rate (IP & OP)
    • NNT=4 (CI 3-6)

• Adverse effects
  • Limited data
  • Compared to clonidine, buprenorphine associated with fewer adverse effects and fewer premature withdrawals due to adverse effects
Buprenorphine – Withdrawal severity

2.1 Mean peak withdrawal score

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buprenorphine Mean</th>
<th>Buprenorphine SD</th>
<th>Buprenorphine Total</th>
<th>Adrenergic agonist Mean</th>
<th>Adrenergic agonist SD</th>
<th>Adrenergic agonist Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hussain 2015</td>
<td>23.81</td>
<td>4.06</td>
<td>27</td>
<td>22.81</td>
<td>4.92</td>
<td>27</td>
<td>15.0%</td>
<td>0.22 [-0.32, 0.75]</td>
</tr>
<tr>
<td>Linzer's 2002</td>
<td>19.9</td>
<td>11.7</td>
<td>53</td>
<td>29.7</td>
<td>15</td>
<td>56</td>
<td>19.5%</td>
<td>-0.73 [-1.10, -0.35]</td>
</tr>
<tr>
<td>Ngam 1993</td>
<td>16.2</td>
<td>8</td>
<td>22</td>
<td>20.2</td>
<td>9</td>
<td>22</td>
<td>13.4%</td>
<td>-0.46 [-1.06, 0.14]</td>
</tr>
<tr>
<td>O'Connor 1997</td>
<td>22.3</td>
<td>12.3</td>
<td>53</td>
<td>29.9</td>
<td>14.9</td>
<td>55</td>
<td>19.4%</td>
<td>-0.55 [-0.94, -0.14]</td>
</tr>
<tr>
<td>Raasch 2005</td>
<td>14.44</td>
<td>6.97</td>
<td>86</td>
<td>15.78</td>
<td>6.71</td>
<td>80</td>
<td>21.9%</td>
<td>-0.19 [-0.50, 0.11]</td>
</tr>
<tr>
<td>Ziaaddini 2012</td>
<td>15</td>
<td>2.2</td>
<td>14</td>
<td>17</td>
<td>1.6</td>
<td>21</td>
<td>10.6%</td>
<td>-1.05 [-1.73, -0.33]</td>
</tr>
</tbody>
</table>

Total (95% CI) 260

Heterogeneity: Tau² = 0.09; Chi² = 13.41, df = 5 (P = 0.02), I² = 63%
Test for overall effect: Z = 2.79 (P = 0.005)
Completion of Withdrawal: Buprenorphine vs. Adrenergics

### 2.6 Number completing withdrawal treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buprenorphine</th>
<th>Adrenergic agonist</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td><strong>2.6.1 Inpatient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheskin 1994</td>
<td>10</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Collins 2005</td>
<td>27</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>Hussain 2015</td>
<td>27</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Ling 2005</td>
<td>59</td>
<td>77</td>
<td>0</td>
</tr>
<tr>
<td>Nigam 1993</td>
<td>22</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Ponizovsky 2006</td>
<td>90</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>289</td>
<td>250</td>
<td>50.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>235</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.35; Chi² = 77.15, df = 5 (P = 0.00001); I² = 94%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.15 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buprenorphine</th>
<th>Adrenergic agonist</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td><strong>2.6.2 Outpatient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janiri 1994</td>
<td>11</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Ling 2005</td>
<td>46</td>
<td>157</td>
<td>4</td>
</tr>
<tr>
<td>Lintzenis 2002</td>
<td>50</td>
<td>58</td>
<td>32</td>
</tr>
<tr>
<td>Marsch 2005</td>
<td>13</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>O'Connor 1997</td>
<td>43</td>
<td>53</td>
<td>36</td>
</tr>
<tr>
<td>Raistrick 2005</td>
<td>70</td>
<td>107</td>
<td>47</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>406</td>
<td>319</td>
<td>50.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>233</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.07; Chi² = 17.16, df = 5 (P = 0.004); I² = 71%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.79 (P = 0.005)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 605/560 100.0% 1.59 [1.23, 2.06]

Total events 468/258

Heterogeneity: Tau² = 0.16; Chi² = 86.22, df = 11 (P < 0.00001); I² = 87%

Test for overall effect: Z = 3.57 (P = 0.0004)

Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Methadone vs. buprenorphine: duration, severity and completion of withdrawal

• Six studies
• Withdrawal symptoms may resolve more quickly with buprenorphine but severity is same
• No difference in treatment duration or completion rates
• Majority treated with buprenorphine do not experience rebound withdrawal
1.2 Completion of withdrawal treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buprenorphine</th>
<th>Methadone</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bickel 1988</td>
<td>17</td>
<td>14</td>
<td>1.27 [0.85, 1.89]</td>
</tr>
<tr>
<td>Petitjean 2002</td>
<td>17</td>
<td>16</td>
<td>1.01 [0.80, 1.26]</td>
</tr>
<tr>
<td>Seifert 2002</td>
<td>9</td>
<td>5</td>
<td>1.54 [0.71, 3.35]</td>
</tr>
<tr>
<td>Steinmann 2008</td>
<td>9</td>
<td>8</td>
<td>1.13 [0.50, 2.52]</td>
</tr>
<tr>
<td>Wright 2011</td>
<td>74</td>
<td>79</td>
<td>0.98 [0.79, 1.22]</td>
</tr>
</tbody>
</table>

Total (95% CI)      226  231  100.0%  1.04 [0.91, 1.20]

Total events        126  122

Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Inpatient or outpatient?

• Few direct comparisons

• For outpatient need strong motivation, suitable environment and appropriate support

• Inpatient setting most appropriate for those significantly impacted by dependence with limited family support
Criteria for intensive residential settings

• Unstable medical / psychiatric condition
• Polydrug dependence and withdrawal from multiple drugs
• History of medical or psychiatric conditions, or past drug use, uncertain or indicate a need for close monitoring

Criteria for supported residential setting

• Unsupportive home environment, such as with other drug users, or without anyone reliable to supervise and support the patient
• Repeated failure at outpatient withdrawal
## Psychosocial AND Pharmacological Treatments Vs. Pharmacological Treatments Alone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nº Participants</th>
<th>RR</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion Of Treatment</td>
<td>184</td>
<td>1.68</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.11–2.55)</td>
<td></td>
</tr>
<tr>
<td>Use Of Opiate During The Treatment</td>
<td>320</td>
<td>0.82</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.71–0.93)</td>
<td></td>
</tr>
<tr>
<td>Relapsed At Follow Up</td>
<td>208</td>
<td>0.41</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.27–0.62)</td>
<td></td>
</tr>
</tbody>
</table>
Detoxification Conclusions 1

• Relapse common so follow-up treatment and support is important

• Transfer to maintenance is a good outcome if unable to sustain abstinence

• Buprenorphine likely to provide most effective withdrawal amelioration

• Buprenorphine preferred if planning naltrexone Rx post-detoxification
Detoxification Conclusions 2

• Methadone or buprenorphine advantage is ability to extend into maintenance if unable to complete detoxification

• Clonidine (or lofexidine) + symptomatic Rx for those strongly preferring non-opioid treatment
  • Few differences between clonidine and lofexidine
  • Lofexidine may be associated with less hypotension.

• Concomitant psychosocial treatments are effective (completion and compliance)
Buprenorphine maintenance treatment
Objectives of Substitution Maintenance Treatment

- Reduce heroin and other drug use
- Reduce transmission of blood borne viruses
- Reduce mortality
- Improve the general health and well being of patients
- Reduce drug-related crime
Buprenorphine Pharmacology

• High receptor affinity
  • Can result in precipitated withdrawal effects

• Precipitated withdrawal dependant upon:
  • Time of dosing
  • Dose level of other agonist
  • Level of physical dependence
When does a Buprenorphine-precipitated withdrawal occur?

• Generally commences ~30–90 min after 1st dose
• Generally peaks within 90–180 min after 1st dose
• Minor symptoms may continue after 2nd or 3rd dose
• Symptoms may also persist with continued heroin/opioid use
Precipitated withdrawal or not enough Buprenorphine?

Adapted from Lintzeris et al., 2003
Buprenorphine Dose Induction

• Early studies - cautious induction schedules
  • Matched Methadone induction
  • Safety concerns with a new drug
  • Drop outs higher in first 2 weeks
  • Negative impact on retention rates

• Typical induction schedules were
  • 2,4,(6),8mg on consecutive days
  • 7 days to achieve 8mg dose(Italy)
  • 14 days to achieve 16mg dose(Switzerland)
Buprenorphine Dose Induction

• Reasons for drop-outs in first 2 weeks:-
  • Induction too slow
  • First dose too soon after last opioid use
    • Precipitated withdrawal
  • Clear headed feeling
    • Become anxious (uncomfortable with this ‘feel’)
    • Fear of precipitated withdrawal
    • Preference for ‘drugged’ feeling
  • Ease of withdrawal
    • Preference for detoxification
Buprenorphine Dose Induction

- Recommendations:
  - Prepare patient for a ‘different feel’
  - First dose when withdrawal signs evident
  - Higher starting doses
  - More rapid dose escalation
  - Split doses possible

- Induction should be rapid and doses adjusted to clinical need as quickly as possible to reduce withdrawal and craving and prevent early drop-out

- A target dose of 16mg (or more) can be reached within 2-3 days by most patients
Key principles

• first dose of buprenorphine delayed until incipient withdrawal
  • measured by a validated scale e.g. Clinical Opiate Withdrawal Scale (COWS)
  • initiating from short-acting usually not associated with severe precipitated withdrawal.
  • Transfer from slow-release opioid preparations to shorter-acting preparations for several days prior to transfer
Doses should be adjusted

- following review of the patient assessing
  - side effects
  - features of withdrawal (suggesting not enough buprenorphine) or intoxication (suggesting too much buprenorphine or other drug use)
- ongoing cravings
- Other substance use
Alternate day dosing principles

- Doses greater than 16mg associated with increased duration of action
  - little or no increase in degree of opioid effect.
- stabilise on daily dosing before trying alternate-day dosing for two weeks

If successful can then be tried on three-times-a-week regimen
Alternate day dosing practice

• Dose for 48-hour period initially double normal daily dose (to maximum of 32 mg).
• review after first or second 48-hour dose and adjust if needed
• three-times-a-week dosing
  • attempt after two week trial on alt day dosing
  • If 24-hour buprenorphine dose less than 12mg
    • 3-day dose is three times the 24-hour dose
  • If 24-hour dose is 12mg or greater, the 3-day dose should be 32mg
New innovations

• 2 different sustained release products coming to market
  • Indivior Sublocade: monthly
  • Camurus Buvidal: weekly or monthly
How they selected dosing for sublocade for opioid receptor occupancy (µORO) blockade

Mean predicted PK and µORO levels

300 mg dose
- Reaches target of 70% µORO after the first SC injection ($C_{max}$)
- Mean predicted µORO levels were consistently > 70% for subsequent injections

100 mg dose
- Reaches target of 70% µORO at steady-state
- 2 initial doses of 300 mg required to reach effective levels more rapidly