

Comparison of Apotex’s Petition to Apotex’s Expert Declaration (Ex. 1005)¹

Petition Text	Text of Cited Exhibit 1005 Paragraphs										
<p>1. <i>“A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”</i></p> <p>Cowen teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:</p> <table border="1"> <thead> <tr> <th>Claim</th><th>Exemplary Citations</th></tr> </thead> <tbody> <tr> <td>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising</td><td>EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient”); <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same).</td></tr> </tbody> </table>	Claim	Exemplary Citations	1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient ”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087] (“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).	<p>i. <i>“A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”</i></p> <p>108. Cowen teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:</p> <table border="1"> <thead> <tr> <th>Claim</th><th>Exemplary Citations</th></tr> </thead> <tbody> <tr> <td>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering</td><td>EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient”); <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (same).</td></tr> </tbody> </table> <p style="text-align: center;">45</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 49</p> <hr/> <table border="1"> <tbody> <tr> <td></td><td>(“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same).</td></tr> </tbody> </table>	Claim	Exemplary Citations	1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient ”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087] (same).		(“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).
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	(“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).										

¹ Verbatim language between the Petition and the Expert Declaration (Ex. 1005) is highlighted.

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>2. “administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”</p> <p>(a) The use of diazoxide choline would have been obvious</p> <p>The '895 patent explains that diazoxide is “7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide with the empirical formula $C_8H_7ClN_2O_2S$ and a molecular weight of 230.7.” EX1001, 17:1-3, 2:30-33. Cowen discloses the same compound. EX1009, [0007] (“Diazoxide, [has] the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (empirical formula $C_8H_7ClN_2O_2S$)”); EX1005,</p> <p style="text-align: center;">21</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>¶¶110-11. Cowen teaches that diazoxide and other salts are used for the treatment of hyperphagia in a Prader-Willi Syndrome patient. <i>Id.</i>, ¶112; EX1009, [0087].</p>	<p>110. The '895 patent explains that diazoxide is “7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide with the empirical formula $C_8H_7ClN_2O_2S$ and a molecular weight of 230.7.” EX1001, 17:1-3, 2:30-33. As explained above, the structure of the diazoxide was known to the POSA. EX1018; <i>supra</i> at ¶¶70-72.</p> <p>111. Cowen discloses the same compound and also identifies it as diazoxide. EX1009, [0007] (“Diazoxide, [has] the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (empirical formula $C_8H_7ClN_2O_2S$)”).</p> <p>112. As explained above, diazoxide falls within the generic structure of Formula III of Cowen (<i>supra</i> at Section VII(D)), and Cowen teaches that diazoxide and other salts are used for the treatment of hyperphagia in a Prader-Willi Syndrome patient. EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient, a . . . comprising the administration of an effective amount of a KATP channel opener selected from</p>
<p>While Cowen may teach diazoxide (free base) and a limited number of its salts (<i>Id.</i>, [00137]-[00138], [00348]), as Dr. Hollander explains, the POSA would readily recognize diazoxide choline as the preferred compound over diazoxide (free base) and the other salts. EX1005, ¶¶113-15. At the outset, Cowen only specifically claims “diazoxide choline,” immediately drawing the POSA’s attention to this specific compound. <i>Id.</i>; EX1009, Claims 9, 21, 32, 48, 53, 57, 62, 63, & 70.</p>	<p>113. While it is true that Cowen may teach diazoxide (free base) and a limited number of its salts (<i>id.</i>, [00137]-[00138], [00348]), the POSA would readily recognize diazoxide choline as the preferred compound over diazoxide (free base) and the other salts, making its selection obvious. For example, Cowen only specifically claims “diazoxide choline” immediately drawing the POSA’s attention to this specific compound. <i>Id.</i>, Claims 9, 21, 32, 48, 53, 57, 62, 63, & 70.</p>

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<p>Furthermore, Cowen highlights the favorable properties of diazoxide choline over its free base, stating for oral administration it has “significantly greater aqueous solubility over diazoxide free base, rapid conversion to diazoxide base on exposure to an aqueous environment.” <i>Id.</i>, [00750]; EX1005, ¶115. Cowen then solidifies the selection of diazoxide choline by providing detailed examples and formulations that prominently feature this compound. For instance, Cowen includes extensive diazoxide choline pharmaceutical formulation information (EX1009, [0596]-[00603]), details on dissolution studies (<i>id.</i>, [00604]-[00607]), excipient compatibility and stability studies (<i>id.</i>, [00608]-[00615]), and methods for its preparation (<i>id.</i>, [00623]-[000634]). EX1005, ¶115. Moreover, Cowen discusses polymorphic forms (EX1009, [00680]-[00690]) and crystallization of diazoxide choline (<i>id.</i>, [00689]-[00706]). Cowen also provides clinical information for various</p> <p style="text-align: center;">22</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>human disorders using diazoxide choline (<i>id.</i>, [00749]-[00760], [00764], [00766], [00770], [00772], [00778], [00783]-[0084]) and pharmacokinetic data (<i>id.</i>, [00763], [00769]). EX1005, ¶115.</p>	<p>115. Cowen then solidifies the selection of diazoxide choline by providing numerous detailed examples and formulations that prominently feature this compound. For instance, Cowen includes extensive pharmaceutical formulation information using diazoxide choline (<i>id.</i>, [0596]-[00603]), details on dissolution studies (<i>id.</i>, [00604]-[00607]), excipient compatibility and stability studies (<i>id.</i>, [00608]-[00615]), and methods for its preparation (<i>id.</i>, [00623]-[000634]). Moreover, Cowen discusses polymorphic forms (<i>id.</i>, [00680]-</p> <p style="text-align: center;">47</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 51</p> <hr/> <p>[00690]) and crystallization of diazoxide choline (<i>id.</i>, [00689]-[00706]). Cowen also provides clinical information for various human disorders using diazoxide choline (<i>id.</i>, [00749]-[00760], [00764], [00766], [00770], [00772], [00778], [00783]-[0084]) and pharmacokinetic data (<i>id.</i>, [00763], [00769]). These teachings highlight diazoxide choline within Cowen over diazoxide (free base) and any other salt form.</p>

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<p>Thus, a POSA would have been motivated to make a pharmaceutical formulation using diazoxide choline for treating hyperphagia in PWS patients with a reasonable expectation of success from Cowen. <i>Id.</i>, ¶¶109-16.</p>	<p>116. For these reasons, a POSA would have been motivated to make a pharmaceutical formulation using diazoxide choline for treating hyperphagia in PWS patients with a reasonable expectation of success from Cowen.</p>

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<p>Cowen discloses pharmaceutical formulations comprising diazoxide choline. EX1009, [0596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline); EX1005, ¶115. As explained by Dr. Hollander, as a general matter, once-daily administration is always preferable since it increases patient compliance. <i>Id.</i>, ¶117. In any event, Cowen discloses and claims once-daily administration so it would have been an obvious choice for the POSA. EX1009, [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.”), [00766] (“A controlled clinical study was conducted to evaluate the potential for Diazoxide Choline Controlled-Release Tablets administered once daily”), [00411] (formulations of K_{ATP} channel openers selected</p> <p style="text-align: center;">23</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i> from a salt of a compound of Formulae I - VIII administered as a single dose); Claims 31 (“the formulation is administered once per 24 hours.”), 52, 59, 62 & 65; EX1005, ¶118.</p>	<p>117. Cowen discloses pharmaceutical formulations comprising diazoxide choline. <i>Id.</i>, [0596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline). As a general matter, once-daily administration is always preferable since it increases patient compliance.</p> <p>118. In any event, Cowen discloses and claims once-daily administration, so it would have been an obvious choice for the POSA. <i>Id.</i>, [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.”),</p> <p style="text-align: center;">48</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 52</p> <hr/> <p>[00766] (“A controlled clinical study was conducted to evaluate the potential for Diazoxide Choline Controlled-Release Tablets administered once daily”), [00411] (formulations of K_{ATP} channel openers selected from a salt of a compound of Formulae I – VIII administered as a single dose); Claims 31 (“the formulation is administered once per 24 hours.”), 52, 59, 62 & 65.</p>

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<p>Finally, Claim 1 also recites use of “an effective amount” of the diazoxide choline pharmaceutical composition. The ’895 patent provides a definition of an “effective amount.” EX1001, 15:32-36. Cowen discloses an “effective amount” within the meaning of the Claim 1 of the ’895 patent. EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener.”); EX1005, ¶119.</p>	<p>119. Finally, Claim 1 also recites use of “an effective amount” of the diazoxide choline pharmaceutical composition. The ’895 patent provides a definition of an “effective amount.” EX1001, 15:32-36. Cowen discloses an “effective amount” within the meaning of Claim 1 of the ’895 patent. EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener.”).</p>

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<p>The final recitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.” Focusing on the first clause: Cowen explicitly discloses that a pharmaceutical formulation comprising diazoxide choline (a K_{ATP} channel opener) effectively reduces or inhibits hyperphagia. Specifically, Cowen repeatedly references “reduced rates of hyperphagia.” EX1009, [00439], [00442]-[00444]; EX1005, ¶¶120-22. As if that were not enough, Cowen explains its formulations result in “inhibition of hyperphagia” for about 18 hours and 24 hours. EX1009, [0070]-[0071]. Cowen also provides a method to treat “hyperphagia in a Prader-Willi Syndrome patient” (<i>id.</i>, [0087]) and diseases “characterized by . . . hyperphagia” (<i>id.</i>, [0093]). Additionally,</p> <p style="text-align: center;">24</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>Cowen describes formulations administered as a single dose to an “obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.” <i>Id.</i>, [00411]. As explained by Dr. Hollander, these disclosures undeniably teach a reduction/inhibition in hyperphagia. EX1005, ¶¶120-22.</p>	<p>120. The final recitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.” Focusing first on the reduction of hyperphagia portion.</p> <p>121. Cowen explicitly discloses that a pharmaceutical formulation comprising diazoxide choline (a K_{ATP} channel opener) effectively reduces or inhibits hyperphagia. Specifically, Cowen repeatedly references “reduced rates of hyperphagia.” <i>Id.</i>, [00439], [00442]-[00444]. As if that were not enough, Cowen explains its formulations result in an “inhibition of hyperphagia” for</p> <p style="text-align: center;">49</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 53</p> <hr/> <p>about 18 hours and 24 hours. <i>Id.</i>, [0070]-[0071]. Cowen also provides a method to treat “hyperphagia in a Prader-Willi Syndrome patient” (<i>id.</i>, [0087]) and diseases “characterized by . . . hyperphagia” (<i>id.</i>, [0093]).</p> <p>122. Additionally, Cowen describes formulations administered as a single dose to an “obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.” <i>Id.</i>, [00411]. These disclosures undeniably teach a reduction/inhibition in hyperphagia.</p>

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<p>At the outset, a reduction in “one or more food related behaviors in the subject” upon administration of diazoxide choline would have inherently occurred. EX1005, ¶¶123-29. In the context of obviousness, the “mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art.” <i>Persion Pharms. v. Alvogen Malta Oper.</i>, 945 F.3d 1184, 1190 (Fed. Cir. 2019); <i>Par Pharm. v. TWI Pharms., Inc.</i>, 773 F. 3d 1186, 1194-95 (Fed. Cir. 2014) (“inherency may supply a missing claim limitation in an obviousness analysis”). “To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.” <i>Santarus, Inc. v. Par Pharm., Inc.</i>, 694 F.3d 1344, 1354 (Fed. Cir. 2012).</p>	<p>125. At the outset, in my opinion, a reduction in “one or more food related behaviors in the subject” upon administration of diazoxide choline would have inherently occurred. I reach this conclusion for the following reasons.</p>

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<p>As Dr. Hollander explains, administration of diazoxide choline would necessarily result in a reduction in “one or more food related behaviors in the subject” because that is precisely what the chemical does when administered to PWS patients experiencing hyperphagia. EX1005, ¶¶123-29; <i>In re Spada</i>, 911 F.2d 705, 708 (Fed. Cir. 1990); <i>In re Papesch</i>, 315 F.2d 381, 391 (C.C.P.A. 1963) (“From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing.”). To be clear, Apotex is not taking the position that a POSA possessing a compound <i>in the abstract</i> means that all its attendant therapeutic properties would be inherently obvious. Rather, Apotex’s inherency position is that</p> <p style="text-align: center;">26</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>Cowen expressly teaches administering diazoxide choline to the specific patient population that has PWS, which then inhibits or reduces hyperphagia. EX1005, ¶¶123-29. Because hyperphagia and the associated problematic food-related behaviors are linked in these patients, reducing one necessarily reduces the other. <i>Id.</i></p>	<p>126. First, the administration of diazoxide choline would necessarily result in a reduction in “one or more food related behaviors in the subject” because that is precisely what the chemical does when administered to PWS patients experiencing hyperphagia. In the body, an active pharmaceutical will act as it does. Specifically, Cowen expressly teaches administering diazoxide choline to the specific patient population that has PWS, which then inhibits or reduces hyperphagia. Because hyperphagia and the associated problematic food-related behaviors are linked in these patients, reducing one necessarily reduces the other.</p>

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<p>As the '895 patent itself acknowledges (citing to Miller (EX1017)), hyperphagia is associated with problematic food-related behaviors in PWS patients. EX1001, 20:14-22. Critically, the '895 patent describes these behaviors as manifestations of hyperphagia—not independent phenomena. <i>Id.</i> Thus, as Cowen teaches, when diazoxide choline is administered to a PWS patient experiencing hyperphagia and thereby reduces hyperphagia, it necessarily leads to a corresponding reduction in the problematic food-related behaviors. EX1005, ¶¶123-29. Patent Owner can hardly dispute that a POSA following Cowen's express teaching—that administering diazoxide choline to a PWS patient with hyperphagia inhibits or reduces hyperphagia—would then also inherently reduce the problematic food-related behaviors in the patient. This is precisely the outcome that the '895 patent claims would occur. Use of the '185 patent and the work of the inventor to</p>	<p>127. As the '895 patent itself acknowledges (citing to prior art Miller (EX1017)), hyperphagia is associated with problematic food-related behaviors in PWS patients. EX1001, 20:14-22. Here, the patent specification describes</p> <p style="text-align: center;">51</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 55</p> <hr/> <p>these behaviors as manifestations of hyperphagia, not independent phenomena. <i>Id.</i> I discussed Miller (EX1017) above (<i>supra</i> at Section VII(F)) and also discuss further in Ground 3. <i>Infra</i> at Section X.</p> <p>128. Thus, following the teachings of Cowen, when diazoxide choline is administered to a PWS patient experiencing hyperphagia and thereby reducing hyperphagia, it would have necessarily led to a corresponding reduction in the problematic food-related behaviors.</p> <p>129. I have been informed by counsel that to support inherency I may also rely on post-priority date evidence including extrinsic evidence and the work of the inventor and patentee. Following Cowen's express teaching—that administering diazoxide choline to a PWS patient with hyperphagia inhibits or reduces hyperphagia—would then also inherently reduce the problematic food-related behaviors in the patient because this is precisely the outcome that the '895 patent claims would occur.</p>

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<p>In any event, Apotex does not just rely on inherency. “Food related behaviors” within the context of the ’895 patent is taught in Cowen. Turning to Cowen: hyperphagia means “[i]ngestion of a greater than optimal quantity of food.” (EX1009, [00192]). EX1005, ¶¶130-32. And since Cowen teaches that diazoxide choline inhibits or reduces hyperphagia, as explained by Dr. Hollander, the POSA would understand this to mean that the patient would <i>no longer</i> consume “a greater than optimal quantity of food” rather, the patient would consume a more normal (or lesser) amount of food due to the administration of the diazoxide choline. <i>Id.</i> In other words, reducing or inhibiting hyperphagia using diazoxide choline means that the patient will eat a normal quantity of food. <i>Id.</i></p>	<p>130. In any event, I do not just have to rely on inherency in view of the teachings of Cowen. Cowen explains that hyperphagia means “[i]ngestion of a greater than optimal quantity of food.” EX1009, [00192]. And since Cowen teaches that diazoxide choline inhibits or reduces hyperphagia, the POSA would understand this to mean that the patient would reduce its consumption of “a greater than optimal quantity of food”; rather, the patient would consume a</p> <p style="text-align: center;">52</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 56</p> <hr/> <p>reduced or normal amount of food due to the administration of the diazoxide choline. In other words, reducing or inhibiting hyperphagia using diazoxide choline means that the patient will eat a reduced or normal quantity of food.</p>

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<p>To solidify the POSA's understanding that the (problematic) food-related behaviors in PWS patients are reduced in Cowen, Cowen teaches that diazoxide choline "induce[s] weight loss" and can even be the "sole treatment to induce weight loss" (EX1009, [00407], [00415], [00416]). EX1005, ¶¶131-32. The POSA would understand that for diazoxide choline to induce weight loss, especially as a "sole treatment," it must necessarily reduce the (problematic) food-related behaviors described in the '895 patent (<i>e.g.</i>, "PWS patients will eat any food in the line of sight, get up at night to eat."). <i>Id.</i>, ¶131. Furthermore, given the teachings of Cowen, the</p> <p style="text-align: center;">28</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>POSA would have had a reasonable expectation of success of achieving these outcomes. <i>Id.</i></p>	<p>131. The POSA's understanding that the (problematic) food-related behaviors in PWS patients are reduced in Cowen is solidified by its other teachings. Specifically, Cowen teaches that diazoxide choline "induce[s] weight loss" and can even be the "sole treatment to induce weight loss". <i>Id.</i>, [00407], [00415], [00416]. The POSA would understand that for diazoxide choline to induce weight loss, especially as a "sole treatment," it must necessarily reduce the (problematic) food-related behaviors described in the '895 patent (<i>e.g.</i>, "PWS patients will eat any food in the line of sight, get up at night to eat."). Furthermore, given the teachings of Cowen, the POSA would have had a reasonable expectation of success of achieving these outcomes.</p>
<p>Therefore, a reduction in hyperphagia and one or more food-related behaviors would have been obvious to the POSA.</p>	<p>132. Therefore, a reduction in hyperphagia and one or more food-related behaviors would have been obvious to the POSA.</p>
<p>Claims 2 and 3 depend from Claim 1 and recite "wherein the diazoxide choline is administered for at least 10 weeks" (Claim 2) and "wherein the diazoxide choline is administered for one or more years." (Claim 3). These administration periods are taught by Cowen. EX1005, ¶¶133-137.</p>	<p>133. Claims 2 and 3 depend from Claim 1 and recite "wherein the diazoxide choline is administered for at least 10 weeks" (Claim 2) and "wherein the diazoxide choline is administered for one or more years." (Claim 3). These administration periods are taught by Cowen.</p>

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<p>Cowen teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:</p> <p>Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).</p> <p style="text-align: center;">29</p> <hr/> <p><i>Petition for Post-Grant Review of</i> <i>U.S. Patent No. 12,419,895</i> <i>Id.</i>, [00234], [00735]-[00736] (“Formulations of salts of any of the compounds of Formulae I - IV² prepared as described herein can be tested for efficacy in obese humans . . . [s]ubjects are dosed daily for up to 12 months.”); <i>id.</i>, [00741] (“up to 12 months”). EX1005, ¶134. Even if paragraphs [00735]-[00736] may refer to a study dealing with the “[t]reatment of obesity in humans,” as Cowen makes clear, this would include patients suffering from Prader-Willi Syndrome. EX1009, [0093] (“treating diseases characterized by obesity . . . including (a) Prader-Willi Syndrome”). EX1005, ¶135.</p>	<p>134. For example, Cowen teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:</p> <p>Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).</p> <p><i>Id.</i>, [00234], [00735]-[00736] (“Formulations of salts of any of the compounds of Formulae I - IV⁷ prepared as described herein can be tested for efficacy in obese humans . . . [s]ubjects are dosed daily for up to 12 months.”); <i>id.</i>, [00741] (“up to 12 months”). “[U]p to 12 months” is a year.</p> <p>135. Even if paragraphs [00735]-[00736] may refer to a study dealing with the “[t]reatment of obesity in humans,” as Cowen makes clear, this would include patients suffering from Prader-Willi Syndrome. <i>Id.</i>, [0093] (“treating diseases characterized by obesity . . . including (a) Prader-Willi Syndrome”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>The teachings of Cowen necessarily include administering for least 10 weeks and more than a year (<i>i.e.</i>, 52 weeks). <i>Id.</i>, ¶136. Thus, based on Cowen, administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods of Cowen. <i>Id.</i> It is well established that when claimed ranges “overlap or lie inside ranges disclosed by the prior art,” a <i>prima facie</i> case of obviousness exists. <i>In re Wertheim</i>, 541 F.2d 257 (C.C.P.A. 1976); <i>El DuPont de Nemours & Co. v. Synvina Cv</i>, 904 F.3d 996, 1008 (Fed. Cir. 2018) (“The point of our overlapping range cases is that, in the absence of evidence</p> <hr/> <p>² As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA. <i>See, e.g.</i>, EX1005, Sections VII(D) & (E), VIII(A)(ii)(1), IX(A)(ii)(1).</p> <p style="text-align: center;">30</p> <hr/> <p><i>Petition for Post-Grant Review of</i> <i>U.S. Patent No. 12,419,895</i> indicating that there is something special or critical about the claimed range, an overlap suffices to show that the claimed range was disclosed in — and therefore obvious in light of — the prior art.”). Accordingly, the methods of Claims 2-3 would have been obvious.</p>	<p>136. The teachings of Cowen necessarily include administering treatment</p> <hr/> <p>⁷ The generic Formula III in Cowen includes diazoxide. <i>Supra</i> at Section VII(D). As I have explained in this Declaration, use of the choline salt would have been obvious to the POSA.</p> <p style="text-align: center;">54</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 58</p> <hr/> <p>for least 10 weeks and more than a year (<i>i.e.</i>, 52 weeks). Thus, based on Cowen, administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods of Cowen.</p> <p>137. I have been informed that when the claimed ranges overlap or lie inside ranges disclosed by the prior art, a case of obviousness exists. Accordingly, the methods of Claims 2-3 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious. As to the specific recitations of Claims 4-9, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).</p>	<p>138. Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious.</p> <p>139. As to the specific recitations of Claims 4-9, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).</p>
<p>Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2000 mg (Claim 14); and 25 mg to 500 mg (Claim 15).</p>	<p>140. Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2000 mg (Claim 14); and 25 mg to 500 mg (Claim 15).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained above, the “once-daily administration of diazoxide choline” would have been obvious, as would have recited ranges in view of Cowen. Furthermore, Cowen teaches “the salt can be formulated for controlled release following oral administration. Such formulations contain in a single administration</p> <p style="text-align: center;">31</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the K_{ATP} channel openers provided in Formulae I - VIII.” EX1009, [0061], [00380];³ EX1005, ¶141.</p>	<p>141. As explained above, the “once-daily administration of diazoxide choline” would have been obvious. Furthermore, Cowen teaches “the salt can be formulated for controlled release following oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the K_{ATP} channel openers provided in Formulae I - VIII.” EX1009, [0061], [00380].⁸</p>
<p>Thus, Cowen discloses the once-daily administration of diazoxide choline in an amount of 1 mg to 2,000 mg, which overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15). <i>Id.</i>, ¶142; <i>In re Peterson</i>, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (“A <i>prima facie</i> case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.”).</p>	<p>142. Thus, Cowen discloses the once-daily administration of diazoxide choline in an amount of 1 mg to 2,000 mg, which overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
Accordingly, the methods of Claims 4-15 would have been obvious.	143. Accordingly, the methods of Claims 4-15 would have been obvious.
<p>At a high level, Claim 16 covers the well-known method of dose titration of using a starting dose (to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. <i>Supra</i> at VIII.C. (“Methods of Dose Titration Were Well Known”); EX1005, ¶¶75-80. Indeed, as Dr. Hollander explained, using such dose titration to arrive at a maintenance (therapeutic) dose is common practice. <i>Id.</i>, ¶77.</p>	<p>145. At a high level, Claim 16 covers the well-known method of dose titration using a starting dose (to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. <i>Supra</i> at Section VII(C) (“Dose Titration in Clinical Practice Was Well Known as of the Priority Date”). Indeed, using such dose titration to arrive at a maintenance (therapeutic) dose is common practice.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Cowen teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved:</p> <p>In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I - VIII⁴ is reduced using a pharmaceutically acceptable formulation of</p> <p>⁴ As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and of the choline salt would have been obvious to the POSA. <i>See, e.g.</i>, EX1005, Sections VII(D) & (E), VIII(A)(ii)(1), IX(A)(ii)(1).</p> <p>33</p>	<p>146. In any event, Cowen repeatedly teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner until a therapeutic dose is achieved:</p> <p>In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I - VIII⁹ is reduced using a pharmaceutically acceptable formulation of diazoxide or its derivatives that is administered to an subject in need thereof on a daily basis in which the first</p> <p>⁹ The generic Formula III in Cowen includes diazoxide. <i>Supra</i> at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p>57</p>
<p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>diazoxide or its derivatives that is administered to an subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.</p> <p>EX1009, [00478], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [0089], [00481], [00482], [00483], [00489], [00490]; EX1005, ¶146.</p>	<p>APOTEX_EX1005_PGR2026-00034_Page 61</p> <p>dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.</p> <p>EX1009, [00478], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [0089], [00481], [00482], [00483], [00489], [00490].</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As Dr. Hollander explains, Cowen clearly explains that the adverse effects of diazoxide are addressed by using initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose. <i>Id.</i>, ¶147; EX1009, [0089] (“method of reducing the incidence of adverse effects from administration of a KATP channel opener . . . initiating dosing at subtherapeutic levels and in a stepwise manner increasing dose daily until the therapeutic dose is achieved wherein the number of steps is 2 to 10 to reduce the incidence of adverse side effects that occur transiently at the initiation of treatment”), [00448] (“These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of subjects at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved.”), [00478].</p>	<p>147. Cowen clearly explains that the adverse effects of diazoxide are addressed by using an initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose. <i>Id.</i>, [0089] (“method of reducing the incidence of adverse effects from administration of a KATP channel opener . . . initiating dosing at subtherapeutic levels and in a stepwise manner increasing dose daily until the therapeutic dose is achieved wherein the number of steps is 2 to 10 to reduce the incidence of adverse side effects that occur transiently at the initiation of treatment”), [00448] (“These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of subjects at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved”), [00478].</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>In providing a more specific example in the context of obesity, type 1, or type 2 diabetes with a salt of K_{ATP} channel opener to achieve a therapeutic dose (i.e., maintenance dose), Cowen teaches:</p> <p>In accordance with this method, the initial dose is chosen to provide for elevations in supine heart rate that on average are not greater than 5 beats per minute, followed by tolerization and a return to baseline heart rate by the time steady state circulating KATP channel opener levels are reached. This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks. In further embodiments, the method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p>	<p>148. In providing a more specific example in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve a therapeutic dose (i.e., maintenance dose), Cowen teaches:</p> <p>58</p> <p>APOTEX_EX1005_PGR2026-00034_Page 62</p> <hr/> <p>In accordance with this method, the initial dose is chosen to provide for elevations in supine heart rate that on average are not greater than 5 beats per minute, followed by tolerization and a return to baseline heart rate by the time steady state circulating KATP channel opener levels are reached. This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks. In further embodiments, the method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p><i>Id.</i>, [0077]. Thus, as Cowen teaches, the starting dose “preferably between 10 and 200 mg” of diazoxide may be given to the patient daily “for days or a few weeks,” then escalated thereafter. <i>Id.</i>; EX1005, ¶149. The “initial escalating dose” may thereafter be given “for days or a few weeks.” <i>Id.</i>; EX1009, [0077]. The rounds of dose escalation may continue until the therapeutically effective dose is reached. <i>Id.</i> Furthermore, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” <i>Id.</i>, [0089]; EX1005, ¶¶147-49.</p>	<p>149. Thus, as Cowen teaches, the starting dose “preferably between 10 and 200 mg” of diazoxide, may be given to the patient daily “for days or a few weeks,” then escalated thereafter. <i>Id.</i> The “initial escalating dose” may thereafter be given</p> <p style="text-align: center;">59</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 63</p> <hr/> <p>“for days or a few weeks.” <i>Id.</i> The rounds of dose escalation may continue until the therapeutically effective dose is reached. <i>Id.</i> Furthermore, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” <i>Id.</i>, [0089].</p>
<p>Turning to the limitations of Claim 16: as explained above, administration of diazoxide choline would have been obvious to the POSA. <i>Supra</i>, XII.A.2.</p> <p>It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. EX1005, ¶¶150-51. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be subtherapeutic”); EX1005, ¶¶150-51.</p>	<p>150. Turning to the limitations of Claim 16: as explained above with respect to my discussion of Claim 1 and Cowen, administration of diazoxide choline would have been obvious to the POSA.</p> <p>151. It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be subtherapeutic”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen. As Dr. Hollander explains, this recitation has three parts, all of which are taught by Cowen: (1) a titration (escalation) of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached. <i>Id.</i>, ¶¶152-61.</p>	<p>152. As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen.</p> <p>153. This recitation has three parts, all of which are taught by Cowen: (1)</p> <p style="text-align: center;">60</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 64</p> <hr/> <p>a titration (escalation) of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As to the first part, <i>i.e.</i>, the titration, this is taught in Cowen. Once the starting dose (EX1009, [0077]), which is subtherapeutic (<i>id.</i>, [00478]), is given to the patient:</p> <p>[T]he method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p> <p><i>Id.</i>, [0077]. Thus, the POSA would understand that Cowen's "initial escalating dose" is the dose that is titrated up. <i>See also id.</i>, [00478] ("daily dose is subsequently increased stepwise until the therapeutic dose is reached."); EX1005, ¶¶154-55.</p>	<p>154. As to the first part, <i>i.e.</i>, the titration, this is taught in Cowen. Once the starting dose (<i>id.</i>, [0077]), which is subtherapeutic (<i>id.</i>, [00478]), is given to the patient:</p> <p>[T]he method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p> <p><i>Id.</i>, [0077].</p> <p>155. Thus, the POSA would understand that Cowen "initial escalating dose" is the dose that is titrated up. <i>See also id.</i>, [00478] ("daily dose is subsequently increased stepwise until the therapeutic dose is reached.").</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Turning to the second part of this recitation: Claim 16 of the '895 patent recites the titration (dose escalation) occurs “every two weeks to reach a maintenance dose,” whereas Cowen teaches titration “for days or a few weeks.” The claimed titration escalation of “two weeks” falls within the range disclosed in Cowen, <i>i.e.</i>, “for days or a few weeks” and therefore would have been obvious because it is nothing more than routine optimization of a parameter identified in the prior art. <i>Id.</i>, ¶¶156-57; <i>In re Aller</i>, 220 F.2d 454, 456 (C.C.P.A. 1955) (“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”). Moreover, as Dr. Hollander states, it is common for physicians to utilize two weeks as a standard titration interval when titration is needed. EX1005, ¶ 77.</p>	<p>156. Turning the second part of this recitation: Claim 16 of the '895 patent recites the titration (dose escalation) occurs “every two weeks to reach a maintenance dose,” whereas Cowen <i>teaches</i> titration “for days or a few weeks.”</p> <p>61</p> <p>APOTEX_EX1005_PGR2026-00034_Page 65</p> <hr/> <p>The claimed titration escalation of “two weeks” falls within the range disclosed in Cowen, <i>i.e.</i>, “for days or a few weeks,” and therefore would have been obvious because it is nothing more than routine optimization of a parameter identified in the prior art. Moreover, as I explained above, it is common for physicians to utilize two weeks as a standard titration interval when titration is needed. <i>Supra</i> at ¶ 77.</p>
<p>Finally, as Dr. Hollander explains, the third part of this recitation requires a maintenance dose. <i>Id.</i>, ¶¶158-61. This is taught in Cowen: “Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.” EX1009, [0077], [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.”); EX1005, ¶¶158-61.</p>	<p>158. The third part of this recitation <i>requires</i> a maintenance dose. This is taught in Cowen: “Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.” EX1009, [0077], [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on</p> <p>62</p> <p>APOTEX_EX1005_PGR2026-00034_Page 66</p> <hr/> <p>a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>the above discussion: First, any reliance by Patent Owner that Cowen</p> <p>38</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>paragraph [0077] is directed only to the use of diazoxide for treating obesity or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, is misplaced. EX1005, ¶¶159-60. Cowen expressly associates obesity, with “Prader-Willi Syndrome.” EX1009, [0093]. And elsewhere, Cowen makes clear that the use of dose titration to reduce diazoxide’s adverse effects is not confined to the treatment of obesity or type 1 or type 2 diabetes, or for that matter any particular disease state. <i>Id.</i>, [00478], [00448], [0089], [00481], [00482], [00483], [00489], [00490]. The POSA would conclude from the teachings of Cowen that that the dose escalation method successfully used for obesity or type 1 or type 2 diabetes is safe and effective. Thus, a POSA would logically apply this same dose escalation method to any disease state taught in Cowen, including PWS and/or hyperphagia, as referenced at [0087] with a reasonable expectation of success. EX1005, ¶¶159-60.</p>	<p>159. Any suggestion that Cowen paragraph [0077] is directed only to the use of diazoxide for treating <i>obesity</i> or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, and so a POSA would not consider it misplaced. Cowen expressly associates obesity, with “Prader-Willi Syndrome.” <i>Id.</i>, [0093]. And elsewhere, Cowen makes clear that the use of dose titration to reduce diazoxide’s adverse effects is not confined to the treatment of obesity or type 1 or type 2 diabetes, or for that matter any particular disease state. <i>Id.</i>, [00478], [00448], [0089], [00481], [00482], [00483], [00489], [00490].</p> <p>160. The POSA would conclude from the teachings of Cowen that the dose escalation method successfully used for obesity or type 1 or type 2 diabetes is safe and effective. Thus, a POSA would logically apply this same dose escalation method to any disease state taught in Cowen, including PWS and/or hyperphagia, as referenced at [0087] with a reasonable expectation of success.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>regimen,” not only does Cowen disclose to a POSA a multidose regime with a lower starting dose, followed by dose titration until a maintenance dose is reached, <i>it does so with diazoxide choline</i>. EX1009, [0077], [00478]; EX1005, ¶161. For all the above reasons, Claim 16 would have been obvious to a POSA.</p>	<p>161. Thus, not only does Cowen disclose to a POSA a multidose regime with a lower starting dose, followed by dose titration until a maintenance dose is reached, <i>it does so with diazoxide choline</i>. <i>Id.</i>, [0077], [00478]. And as explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen.</p> <p style="text-align: center;">63</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 67</p> <hr/> <p>162. For all the above reasons, Claim 16 would have been obvious to a POSA.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>E. Claims 17-18 (Starting Dose Claims)</p> <p>Claims 17-18 depend from Claim 16. Claim 16 has been addressed above.</p> <p>Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).</p> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>Cowen teaches in the context of its multidose regimen: “This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide.” EX1009, [0077]. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18 establishing a <i>prima facie</i> case of obviousness. EX1005, ¶¶ 163-64; <i>Peterson</i>, 315 F.3d at 1329; <i>Applied Materials, Inc.</i>, 692 F.3d at 1295; <i>Aller</i>, 220 F.2d at 456.</p>	<p>E. Claims 17-18 (Starting Dose Claims)</p> <p>163. Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).</p> <p>164. Cowen teaches in the context of its multidose regimen: “This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide.” EX1009, [0077].</p> <p>And as explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs												
<p>F. Claims 19-25 (Maintenance Dose Claims)</p> <p>Claims 19 and 24-25 depend from Claim 17 (which has been addressed above). Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17's starting doses, and importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 25-100 mg:</p> <p style="text-align: center;">41</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <table border="1"> <tr> <td>Claim 19</td><td>"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"</td></tr> <tr> <td>Claim 24</td><td>"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"</td></tr> <tr> <td>Claim 25</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."</td></tr> </table>	Claim 19	"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"	Claim 24	"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"	Claim 25	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."	<p>F. Claims 19-25 (Maintenance Dose Claims)</p> <p>165. Claims 19 and 24-25 depend from Claim 17 (which has been addressed above).</p> <p>166. Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17's starting doses, and, importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is <i>higher</i> than</p> <p style="text-align: center;">64</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 68</p> <hr/> <p>Claim 17's starting dose of 25-100 mg:</p> <table border="1"> <tr> <td>Claim 19</td><td>"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"</td></tr> <tr> <td>Claim 24</td><td>"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"</td></tr> <tr> <td>Claim 25</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."</td></tr> </table>	Claim 19	"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"	Claim 24	"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"	Claim 25	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."
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<p>Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18's starting doses, and importantly, in each case Claims 20-23 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 50-180 mg:</p> <table> <tr> <td>Claim 20</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"</td></tr> <tr> <td>Claim 21</td><td>"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"</td></tr> <tr> <td>Claim 22</td><td>"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and</td></tr> <tr> <td>Claim 23</td><td>"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."</td></tr> </table>	Claim 20	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"	Claim 21	"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"	Claim 22	"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and	Claim 23	"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."	<p>Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18's starting doses, and, importantly, in each case Claims 20-23 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 50-180 mg:</p> <table> <tr> <td>Claim 20</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"</td></tr> <tr> <td>Claim 21</td><td>"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"</td></tr> <tr> <td>Claim 22</td><td>"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and</td></tr> <tr> <td>Claim 23</td><td>"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."</td></tr> </table>	Claim 20	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"	Claim 21	"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"	Claim 22	"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and	Claim 23	"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."
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Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Cowen teaches a multidose regimen, and, like the Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1005, ¶167; EX1009, [0077] (“The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is</p> <p style="text-align: center;">42</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached”).</p>	<p>167. Cowen teaches a multidose regimen, and, like Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] (“The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on</p> <p style="text-align: center;">65</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 69</p> <hr/> <p>a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached”). And as explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>This only leaves the amounts recited in Claim 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” <i>Id.</i>, [0077]; EX1005, ¶169. Next, it is not limited to a single stepwise increase but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” <i>Id.</i>, ¶170; EX1009, [0077]. And along that same vein, this same teaching to continue dose escalation “until the therapeutically effective dose is reached” teaches the POSA to use routine experimentation. <i>Id.</i>; EX1005, ¶170; EX1013, 52 (“In the dose titration of any patient the objective is, in conceptual terms, to attain and maintain a blood level that exceeds the minimum effective level required for response but does not exceed the minimum toxic (side-effect) level.”). Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” <i>Id.</i>, ¶¶170-72; EX1009, [0089]; <i>Env’t Designs v. Union Oil Co. of Cal.</i>, 713</p>	<p>168. This only leaves the amounts recited in Claims 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points.</p> <p>169. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” <i>Id.</i>, [0077].</p> <p>170. Next, it is not limited to a single stepwise increase, but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” <i>Id.</i> And along that same vein, Cowen teaching that the “rounds of this dose escalation would continue until the therapeutically effective dose is reached” expressly tell the POSA to use routine experimentation. <i>Id.</i> EX1013, 52 (“In the dose titration of any patient the objective is, in conceptual terms, to attain and maintain a blood level that exceeds the minimum effective level required for response but does not exceed the minimum toxic (side-effect) level.”). Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” EX1009, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases.</p>

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<p>With these teachings of Cowen “as a whole” including Cowen teaching of a stepwise increase of “2 to 10” rounds to arrive at a therapeutic dose, using Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener” and increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener” through routine experimentation would have resulted in the POSA arriving at the claimed maintenance amounts. EX1005, ¶172; <i>Aller</i>, 220 F.2d at 456; <i>In re Boesch</i>, 617 F.2d at 276 (“[D]iscovery of an optimum value of a result effective variable . . . is ordinarily within the skill of the art.”):</p> <table><tr><th>Starting Dose</th><th>First Round</th><th>Second Round</th><th>Third Round</th></tr><tr><td>Lower value 10 mg</td><td>35 mg-160 mg</td><td>60 mg-310 mg</td><td>85-460 mg</td></tr><tr><td>Upper value 200 mg</td><td>225 mg-350 mg</td><td>250 mg-500 mg</td><td>275-650 mg</td></tr></table> <p>As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25. EX1005, ¶ 173.</p>	Starting Dose	First Round	Second Round	Third Round	Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg	Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg	<p>172. With this POSA’s knowledge of routine dose titration beginning with Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener”, and then using Cowen’s stepwise increase of “2 to 10” rounds to arrive at a therapeutic (maintenance) dose, increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener”, as taught by the prior art, would have resulted in the POSA arriving the claimed maintenance amounts:</p> <p style="text-align: center;">67</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 71</p> <table><tr><th>Starting Dose</th><th>First Round</th><th>Second Round</th><th>Third Round</th></tr><tr><td>Lower value 10 mg</td><td>35 mg-160 mg</td><td>60 mg-310 mg</td><td>85-460 mg</td></tr><tr><td>Upper value 200 mg</td><td>225 mg-350 mg</td><td>250 mg-500 mg</td><td>275-650 mg</td></tr></table> <p>173. As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25.¹⁰ Determining the therapeutic (maintenance dose) is what a physician would do as part of their routine practice based on factors such patient response, tolerability and the physician’s professional judgement.</p>	Starting Dose	First Round	Second Round	Third Round	Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg	Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg
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<p>Furthermore, the POSA would have known from the teaching of Cowen that these amounts would have been safe and effective for the patient, providing the POSA a reasonable expectation of success: “Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500</p> <p style="text-align: center;">44</p>	<p>174. Furthermore, the POSA would have known from the teaching of Cowen that these amounts would have been safe and effective for the patient providing the POSA a reasonable expectation of success: “Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the K_{ATP} channel openers</p>
<p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>and 2000 mg of the salt of the K_{ATP} channel openers provided in Formulae I - VIII.” EX1009, [0061], [00380]; EX1005, ¶¶173-74.⁵ Therefore, Claims 19-25 would have been obvious.</p>	<p>¹⁰ Claim 19 (100-200 mg); Claim 20 (200-300 mg); Claim 21 (300-500 mg); Claim 22 (500-2000 mg); Claim 23 (100-500 mg); Claim 24 (25-250 mg); Claim 25 (200-300 mg).</p> <p style="text-align: center;">68</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 72</p> <p>provided in Formulae I - VIII.” EX1009, [0061], [00380].¹¹</p> <p>175. Therefore, Claims 19-25 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>G. Claim 26</p> <p>Claim 26 depends from Claim 1 and recites “wherein the pharmaceutical formulation is administered orally.” Cowen discloses pharmaceutical formulations comprising diazoxide choline for oral administration. EX1009, [00369], [00380], [00596]; EX1005, ¶¶176-77. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.</p>	<p>G. Claim 26</p> <p>176. Claim 26 depends from Claim 1 and recites, “wherein the pharmaceutical formulation is administered orally.” Cowen discloses pharmaceutical formulations comprising diazoxide choline for oral administration. EX1009, [00369], [00380], [00596].</p> <p>177. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>A. Claim 1</p> <p>The text of independent Claim 1 is provided as follows:</p> <p>I. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration</p> <hr/> <p>⁵ As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA. <i>See, e.g.</i>, EX1005, Sections VII(D) & (E) and VIII(A).</p> <p>45</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>reduces hyperphagia and one or more food related behaviors in the subject.</p>	<p>A. Claim 1</p> <p>179. The text of independent Claim 1 is provided as follows:</p> <hr/> <p>¹¹ The generic Formula III in Cowen includes diazoxide. <i>Supra</i> at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p>69</p> <p>APOTEX_EX1005_PGR2026-00034_Page 73</p> <hr/> <p>I. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.</p>

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<p>1. “A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”</p> <p>As shown in the chart below (EX1005, ¶180), Cowen and Cotter teach “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:</p> <table border="1"> <thead> <tr> <th>Claim</th><th>Exemplary Citations</th></tr> </thead> <tbody> <tr> <td>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering</td><td> <p>Cowen</p> <p>EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient.”; <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same).)</p> <p>Cotter</p> <p>Title: “METHOD OF TREATING PRADER WILLI SYNDROME AND CONDITIONS ASSOCIATED WITH LOW BASAL METABOLIC RATE OR HYPERPHAGIA”</p> <p>Abstract: “The invention also relates to treating PWS based on the PWS nutritional phase of a patient, to prevent the patient’s PWS nutritional phase from progressing or shift the patient’s PWS nutritional phase back to an earlier phase. The invention further relates to treating PWS, and conditions associated with low basal metabolic rate or hyperphagia.”</p> <p>EX1008, [0002] (“Clinical features of PWS include hypotonia and poor feeding in infancy which almost always requires some type of</p> </td></tr> </tbody> </table> <p>46</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <table border="1"> <tbody> <tr> <td></td><td> <p>assisted feeding for a period of time, followed by hyperphagia as the child ages.”).</p> <p><i>Id.</i>, [0008] (“Also provided herein is a method for treating a disease or condition selected from Prader Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia.”).</p> <p><i>Id.</i>, [0010] (“Surprisingly, the inventor has also discovered that PWS and conditions associated with low basal metabolic rate or hyperphagia can be treated by modulating the dose of KATP channel opener based on a patient’s blood ketone level and/or diet.”).</p> <p><i>Id.</i>, Claim 14 (“A method for treating a disease or condition selected from the group consisting of Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia, comprising administering a K_{ATP} channel opener to a patient in need thereof.”).</p> <p><i>See also id.</i>, [0057] (“inhibit hyperphagia”), [0073].</p> </td></tr> </tbody> </table>	Claim	Exemplary Citations	1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	<p>Cowen</p> <p>EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient.”; <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same).)</p> <p>Cotter</p> <p>Title: “METHOD OF TREATING PRADER WILLI SYNDROME AND CONDITIONS ASSOCIATED WITH LOW BASAL METABOLIC RATE OR HYPERPHAGIA”</p> <p>Abstract: “The invention also relates to treating PWS based on the PWS nutritional phase of a patient, to prevent the patient’s PWS nutritional phase from progressing or shift the patient’s PWS nutritional phase back to an earlier phase. The invention further relates to treating PWS, and conditions associated with low basal metabolic rate or hyperphagia.”</p> <p>EX1008, [0002] (“Clinical features of PWS include hypotonia and poor feeding in infancy which almost always requires some type of</p>		<p>assisted feeding for a period of time, followed by hyperphagia as the child ages.”).</p> <p><i>Id.</i>, [0008] (“Also provided herein is a method for treating a disease or condition selected from Prader Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia.”).</p> <p><i>Id.</i>, [0010] (“Surprisingly, the inventor has also discovered that PWS and conditions associated with low basal metabolic rate or hyperphagia can be treated by modulating the dose of KATP channel opener based on a patient’s blood ketone level and/or diet.”).</p> <p><i>Id.</i>, Claim 14 (“A method for treating a disease or condition selected from the group consisting of Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia, comprising administering a K_{ATP} channel opener to a patient in need thereof.”).</p> <p><i>See also id.</i>, [0057] (“inhibit hyperphagia”), [0073].</p>	<p>180. As shown in the chart below, Cowen and Cotter teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:</p> <table border="1"> <thead> <tr> <th>Claim</th><th>Exemplary Citations</th></tr> </thead> <tbody> <tr> <td>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering</td><td> <p>Cowen</p> <p>EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient.”; <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same).)</p> <p>Cotter</p> <p>Title: “METHOD OF TREATING PRADER WILLI SYNDROME AND CONDITIONS ASSOCIATED WITH LOW BASAL METABOLIC RATE OR HYPERPHAGIA”</p> <p>Abstract: “The invention also relates to treating PWS based on the PWS nutritional phase of a patient, to prevent the patient’s PWS nutritional</p> </td></tr> </tbody> </table> <p>70</p> <p>APOTEX_EX1005_PGR2026-00034_Page 74</p> <hr/> <table border="1"> <tbody> <tr> <td></td><td> <p>phase from progressing or shift the patient’s PWS nutritional phase back to an earlier phase. The invention further relates to treating PWS, and conditions associated with low basal metabolic rate or hyperphagia.”</p> <p>EX1008, [0002] (“Clinical features of PWS include hypotonia and poor feeding in infancy which almost always requires some type of assisted feeding for a period of time, followed by hyperphagia as the child ages.”).</p> <p><i>Id.</i>, [0008] (“Also provided herein is a method for treating a disease or condition selected from Prader Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia.”).</p> <p><i>Id.</i>, [0010] (“Surprisingly, the inventor has also discovered that PWS and conditions associated with low basal metabolic rate or hyperphagia can be treated by modulating the dose of KATP channel opener based on a patient’s blood ketone level and/or diet.”).</p> <p><i>Id.</i>, Claim 14 (“A method for treating a disease or condition selected from the group consisting of Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia, comprising administering a K_{ATP} channel opener to a patient in need thereof.”).</p> <p><i>See also id.</i>, [0057] (“inhibit hyperphagia”), [0073].</p> </td></tr> </tbody> </table>	Claim	Exemplary Citations	1. 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The invention further relates to treating PWS, and conditions associated with low basal metabolic rate or hyperphagia.”</p> <p>EX1008, [0002] (“Clinical features of PWS include hypotonia and poor feeding in infancy which almost always requires some type of assisted feeding for a period of time, followed by hyperphagia as the child ages.”).</p> <p><i>Id.</i>, [0008] (“Also provided herein is a method for treating a disease or condition selected from Prader Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia.”).</p> <p><i>Id.</i>, [0010] (“Surprisingly, the inventor has also discovered that PWS and conditions associated with low basal metabolic rate or hyperphagia can be treated by modulating the dose of KATP channel opener based on a patient’s blood ketone level and/or diet.”).</p> <p><i>Id.</i>, Claim 14 (“A method for treating a disease or condition selected from the group consisting of Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia, comprising administering a K_{ATP} channel opener to a patient in need thereof.”).</p> <p><i>See also id.</i>, [0057] (“inhibit hyperphagia”), [0073].</p>
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	<p>assisted feeding for a period of time, followed by hyperphagia as the child ages.”).</p> <p><i>Id.</i>, [0008] (“Also provided herein is a method for treating a disease or condition selected from Prader Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia.”).</p> <p><i>Id.</i>, [0010] (“Surprisingly, the inventor has also discovered that PWS and conditions associated with low basal metabolic rate or hyperphagia can be treated by modulating the dose of KATP channel opener based on a patient’s blood ketone level and/or diet.”).</p> <p><i>Id.</i>, Claim 14 (“A method for treating a disease or condition selected from the group consisting of Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia, comprising administering a K_{ATP} channel opener to a patient in need thereof.”).</p> <p><i>See also id.</i>, [0057] (“inhibit hyperphagia”), [0073].</p>												
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	<p>phase from progressing or shift the patient’s PWS nutritional phase back to an earlier phase. The invention further relates to treating PWS, and conditions associated with low basal metabolic rate or hyperphagia.”</p> <p>EX1008, [0002] (“Clinical features of PWS include hypotonia and poor feeding in infancy which almost always requires some type of assisted feeding for a period of time, followed by hyperphagia as the child ages.”).</p> <p><i>Id.</i>, [0008] (“Also provided herein is a method for treating a disease or condition selected from Prader Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia.”).</p> <p><i>Id.</i>, [0010] (“Surprisingly, the inventor has also discovered that PWS and conditions associated with low basal metabolic rate or hyperphagia can be treated by modulating the dose of KATP channel opener based on a patient’s blood ketone level and/or diet.”).</p> <p><i>Id.</i>, Claim 14 (“A method for treating a disease or condition selected from the group consisting of Prader-Willi Syndrome, a condition associated with low basal metabolic rate, and a condition associated with hyperphagia, comprising administering a K_{ATP} channel opener to a patient in need thereof.”).</p> <p><i>See also id.</i>, [0057] (“inhibit hyperphagia”), [0073].</p>												

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained in Ground 1, diazoxide choline would have stood out to the POSA from the teachings of Cowen. For example, Cowen expressly discusses the favorable properties of diazoxide choline over the free base. <i>Id.</i>, ¶185; EX1009, [00750]. Cowen then provides numerous examples and formulations highlighting the use of diazoxide choline including: (1) extensive pharmaceutical formulation (<i>id.</i>, at [0596]-[00603]); (2) dissolution studies (<i>id.</i>, [00604]-[00607]); (3) excipient compatibility studies and stability studies (<i>id.</i>, [00608]-[00615]); (4) its preparation, synthesis and characterization (<i>id.</i>, [00623]-[00634], [00680]-[00706]); (5) clinical information for the treatment of different human disorders (<i>id.</i>, [00749]-[00760], [00764], [00766], [00770], [00772], [00778], [00783]-[0084]); and (6) pharmacokinetic data (<i>id.</i>, [00763], [00769]). Cowen also only specifically claims “diazoxide choline” immediately drawing the POSA’s attention to this specific compound. EX1005, ¶¶185-90.</p>	<p>185. As explained in Ground 1, diazoxide choline would have stood out to the POSA from the teachings of Cowen. For example, Cowen expressly discusses the favorable properties of diazoxide choline over the free base. EX1009, [00750]. Cowen then provides numerous examples and formulations highlighting the use of diazoxide choline including: (1) extensive pharmaceutical formulation information using diazoxide choline (<i>id.</i>, at [0596]-[00603]); (2) dissolution studies (<i>id.</i>, [00604]-[00607]); (3) excipient compatibility studies and stability studies (<i>id.</i>, [00608]-[00615]); (4) its preparation, synthesis and characterization (<i>id.</i>, [00623]-[00634], [00680]-[00706]); (5) clinical information for the treatment of different human disorders (<i>id.</i>, [00749]-[00760], [00764], [00766], [00770], [00772], [00778], [00783]-[0084]); and (6) pharmacokinetic data (<i>id.</i>, [00763], [00769]). And importantly, Cowen only specifically claims “diazoxide choline” immediately drawing the POSA’s attention to this specific compound. EX1009, Claims 9, 21, 32, 48, 53, 57, 62, 63, & 70. Simply put, diazoxide choline is the most highlighted active pharmaceutical agent in Cowen.</p> <p style="text-align: center;">73</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 77</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Cotter also teaches generic Formulas I - VIII for the K_{ATP} channel opener, <i>i.e.</i>, the active pharmaceutical ingredient, but significantly, when depicting an actual</p>	<p>187. Cotter teaches generic Formulas I - VIII for the KATP channel opener (EX1008, [0074]), <i>i.e.</i>, the active pharmaceutical ingredient, but significantly, when depicting an actual chemical species, it only depicts diazoxide (free base) which would have immediately drawn the attention of the POSA:</p>
<p>48</p>	<p>74</p>
<p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>chemical species, it only depicts diazoxide (free base) which would have immediately drawn the attention of the POSA:</p>	<p>APOTEX_EX1005_PGR2026-00034_Page 78</p>
<p>[0135] The KATP channel opener may also have the formula 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide (shown below with its tautomer) with the empirical formula C₈H₇ClN₂O₂S and a molecular weight of 230.7.</p> <div data-bbox="348 846 779 971"> <p>The image shows two chemical structures of 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide and its tautomer, separated by the word 'or'. Both structures consist of a benzene ring fused to a six-membered heterocyclic ring containing a sulfur atom double-bonded to two oxygen atoms. The left structure has a methyl group on the nitrogen at position 3 and a chlorine atom at position 7. The right structure is a tautomer with the methyl group on the nitrogen at position 2 and the chlorine atom at position 7.</p> </div> <p>[0136] The KATP channel opener may also be a salt of one of the compounds described by Formulae I-VIII and may have at least one, of the following properties: (1) opening SURx/Kir6.y potassium channels, in which x=1, 2A or 2B and y=1 or 2; (2) binding to the SURx subunit of KATP channels; and (3) inhibiting glucose induced release of insulin following administration of the compound in vivo.</p> <p>EX1008, [0135]-[0136]; EX1005, ¶¶186-87, 99, <i>see also id.</i>, ¶¶70-72 (discussing POSA knowledge of diazoxide and tautomerism).</p>	<p>[0135] The KATP channel opener may also have the formula 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide (shown below with its tautomer) with the empirical formula C₈H₇ClN₂O₂S and a molecular weight of 230.7.</p> <div data-bbox="1241 911 1619 1024"> <p>The image shows two chemical structures of 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide and its tautomer, separated by the word 'or'. Both structures consist of a benzene ring fused to a six-membered heterocyclic ring containing a sulfur atom double-bonded to two oxygen atoms. The left structure has a methyl group on the nitrogen at position 3 and a chlorine atom at position 7. The right structure is a tautomer with the methyl group on the nitrogen at position 2 and the chlorine atom at position 7.</p> </div> <p>[0136] The KATP channel opener may also be a salt of one of the compounds described by Formulae I-VIII and may have at least one, of the following properties: (1) opening SURx/Kir6.y potassium channels, in which x=1, 2A or 2B and y=1 or 2; (2) binding to the SURx subunit of KATP channels; and (3) inhibiting glucose induced release of insulin following administration of the compound in vivo.</p> <p>EX1008, [0135]-[0136]. As explained above, the POSA would have been aware of the structure of diazoxide. EX1018; <i>supra</i> at ¶¶ 70-72, 99-101.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As Cotter explains, Formula III can be the choline salt:</p> <p>The KATP channel opener may also be a structural variant or bioequivalent of a compound defined by Formulae I-</p> <p>50</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>VIII, such as a derivative, salt, prodrug or isomer thereof . . . The KATP channel opener may be a salt of a compound of one of Formulae I-VIII in which the cation is sodium, potassium, choline or hexamethyl hexamethylene diammonium.</p>	<p>III of Cotter includes diazoxide. <i>Supra</i> at Section VII(D). Furthermore, as Cotter explains, Formula III can be the choline salt:</p> <p>75</p> <p>APOTEX_EX1005_PGR2026-00034_Page 79</p> <hr/> <p>The KATP channel opener may also be a structural variant or bioequivalent of a compound defined by Formulae I-VIII, such as a derivative, salt, prodrug or isomer thereof . . . The KATP channel opener may be a salt of a compound of one of Formulae I-VIII in which the cation is sodium, potassium, choline or hexamethyl hexamethylene diammonium.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As shown in Cotter at [0135], the empirical formula of the depicted compound is “C₈H₇ClN₂O₂S”; <i>see also</i> EX1008, [0007] (“Diazoxide, [has] the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (empirical formula C₈H₇ClN₂O₂S)”). As explained in Ground 1, the ’895 patent explains diazoxide (free base) [] and it has the same empirical chemical formula as provided by Cowen and Cotter. EX1001, 2:30-33, 17:1-3; EX1005, ¶¶188, 71-72.</p>	<p>188. As shown in Cotter at [0135], the empirical formula of the depicted compound is “C₈H₇ClN₂O₂S”. <i>See also</i> EX1009, [0007] (“Diazoxide, [has] the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (empirical formula C₈H₇ClN₂O₂S)”). As explained in Ground 1, the ’895 patent explains diazoxide (free base) [] and it has the same empirical chemical formula. EX1001, 2:30-33, 17:1-3; <i>see also</i> EX1018; <i>supra</i> at ¶¶ 70-72, 99-101.</p>
<p>As such, in view of the teachings of Cowen and Cotter, a POSA would have been motivated to select a pharmaceutical formulation comprising diazoxide choline with a reasonable expectation of success. <i>Id.</i>, ¶191.</p>	<p>191. As such, in view of the teachings of Cowen and Cotter, a POSA would have been motivated to select a pharmaceutical formulation comprising diazoxide choline with a reasonable expectation of success.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>(b) “administering to said subject once per day a pharmaceutical formulation comprising an effective amount”</p> <p>Both Cowen and Cotter disclose the claimed pharmaceutical formulations. EX1008, [0142]-[0147] (disclosing pharmaceutical compositions); EX1009, [00380], [00596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline); EX1005, ¶192.</p>	<p>iii. “administering to said subject once per day a pharmaceutical formulation comprising an effective amount”</p> <p>192. Both Cowen and Cotter disclose the claimed pharmaceutical formulations. EX1008, [0142]-[0147] (disclosing pharmaceutical compositions); EX1009, [00380], [00596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline).</p>
<p>Furthermore, as explained by Dr. Hollander, once-daily administration is always preferable since it increases patient compliance, and this is taught in Cowen⁶ and Cotter. <i>Id.</i>, ¶193; EX 1008, [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.”), [00766] (“A controlled clinical study was conducted to evaluate the potential for Diazoxide Choline Controlled-Release Tablets administered once daily”), [00411] (formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII administered as a single dose); EX1008, [0138] (teaching “single administration”), [0141] (“The composition may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per day.”)</p>	<p>193. Furthermore, once-daily administration is always preferable since it increases patient compliance, and this is taught in Cowen and Cotter. EX1009 (Cowen), [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.”), [00766] (“A controlled clinical study was conducted to evaluate the potential for Diazoxide Choline Controlled-Release Tablets administered once daily”), [00411] (formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII¹² administered as a single dose); Claims 31 (“the formulation is administered once per 24 hours.”), 52, 59, 62 & 65; EX1008 (Cotter), [0138] (teaching “single administration”), [0141] (“The composition may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per day.”)</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Finally, the limitation also recites “an effective amount” of the diazoxide choline pharmaceutical composition. EX1005, ¶194. The ’895 patent provides a definition of an “effective amount” (EX1001, 15:32-36). Cowen and Cotter teach the same thing. EX1008, [0140] (“This invention also relates to a method of treatment comprising administering a composition comprising a K_{ATP} channel</p> <hr/> <p>⁶ As mentioned in Ground 1, Cowen also claims once-daily administration. EX1009, Claims 31 (“the formulation is administered once per 24 hours.”), 52, 59, 62 & 65.</p> <p>52</p>	<p>194. Finally, the limitation also recites “an effective amount” of the diazoxide choline pharmaceutical composition. The ’895 patent provides a definition of an “effective amount” (EX1001, 15:32-36). Cowen and Cotter teach</p> <hr/> <p>¹² The generic Formula III in Cowen and Cotter includes diazoxide. <i>Supra</i> at Section VII(D) & (E). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p>77</p> <p>APOTEX_EX1005_PGR2026-00034_Page 81</p>
<hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>opener, which may be a therapeutically effective amount.”); EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener.”); EX1005, ¶194.</p>	<p>the same thing. EX1008, [0140] (“This invention also relates to a method of treatment comprising administering a composition comprising a K_{ATP} channel opener, which may be a therapeutically effective amount.”); EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>3. “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”</p> <p>The remaining limitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.” Both Cowen and Cotter disclose that administering a pharmaceutical formulation diazoxide choline (<i>i.e.</i>, the K_{ATP} channel opener) reduces hyperphagia. EX1005, ¶196; EX1008, [0001] (“The K_{ATP} channel opener dosage for treating PWS or conditions associated with low basal metabolic rate or hyperphagia, such as obesity, may be modulated according to a patient’s blood ketone level or diet.”), [0057] (“The K_{ATP} channel opener may . . . inhibit hyperphagia”); EX1009, [0070] (“pharmaceutical formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII’ wherein administration to an obese, overweight or obesity prone subject results in at least inhibition of hyperphagia for about 18 hours.”), [0071] (“inhibition of hyperphagia for about 24 hours”), [0087] (“[f]urther provided is a</p> <hr/> <p>⁷ As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA. <i>See, e.g.</i>, EX1005, Sections VII(D) & (E), VIII(A)(ii)(1), IX(A)(ii)(1).</p> <p>53</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient,”), [0093] (“method of treating diseases characterized by . . . hyperphagia”), [00411] (“formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII administered as a single dose to an obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.”), [00439] (“(19) reduced rates of hyperphagia”), [00442] (“(26) reduced rates of hyperphagia”), [00443] (“(22) reduced rates of hyperphagia”), [00444] (“(22) reduced rates of hyperphagia”).</p>	<p>iv. “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”</p> <p>195. The remaining limitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”</p> <p>196. Both Cowen and Cotter disclose that administering a pharmaceutical formulation diazoxide choline (<i>i.e.</i>, the K_{ATP} channel opener) reduces hyperphagia. EX1008, [0001] (“The K_{ATP} channel opener dosage for treating PWS or conditions associated with low basal metabolic rate or hyperphagia, such as obesity, may be modulated according to a patient’s blood ketone level or diet.”), [0057] (“The K_{ATP} channel opener may . . . inhibit hyperphagia”); EX1009, [0070] (“pharmaceutical formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII¹³ wherein</p> <hr/> <p>¹³ The generic Formula III in Cowen and Cotter includes diazoxide. <i>Supra</i> at Section VII(D) & (E). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p>78</p> <p>APOTEX_EX1005_PGR2026-00034_Page 82</p> <hr/> <p>administration to an obese, overweight or obesity prone subject results in at least inhibition of hyperphagia for about 18 hours.”), [0071] (“inhibition of hyperphagia for about 24 hours”), [0087] (“[f]urther provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient,”), [0093] (“method of treating diseases characterized by . . . hyperphagia”), [00411] (“formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII administered as a single dose to an obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.”), [00439] (“(19) reduced rates of hyperphagia”), [00442] (“(26) reduced rates of hyperphagia”), [00443] (“(22) reduced rates of hyperphagia”), [00444] (“(22) reduced rates of hyperphagia”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs				
<p>Turning to the limitation of “reduces . . . one or more food related behaviors in the subject”: as explained in Ground 1, the ’895 patent teaches “food related behaviors.” EX1001, 20:14-22. <i>Phillips</i>, 415 F.3d at 1315. As explained above in Ground 1, Cowen teaches this limitation either inherently or expressly (<i>supra</i> at Section XII(A)(4)), but to the extent the PTAB disagrees, then as explained above the POSA would have been aware of Cotter, and given it is in the same field as Cowen using the same API for the treatment of the same disorders, the POSA would have been motivated to combine the references with a reasonable expectation of success. EX1005, ¶¶197-98.</p>	<p>197. Turning to the limitation of “reduces . . . one or more food related behaviors in the subject”: as explained in Ground 1, the ’895 patent explains what it means by “food related behaviors.” EX1001, 20:14-22.</p> <p>198. As explained above in Ground 1, Cowen teaches this limitation either inherently or expressly (<i>supra</i> at Section VIII(A)(v)) but to the extent there is any disagreement over this point, then as explained above the POSA would have been aware of Cotter and given it is in the same field as Cowen using the same API for the treatment of the same disorders, the POSA would have been motivated to combine the references with a reasonable expectation of success.</p>				
<p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>Turning to the teaching of Cotter: Cotter teaches that “the patient may be in PWS nutritional phase 0, 1a, 1b, 2a, 2b, 3, or 4.” EX1008, [0007]; EX1005, ¶¶199-200. Cotter explains that Phase 3 begins at “8 years”¹⁴ and is hyperphagia:</p> <table border="1" data-bbox="287 989 1037 1382"> <tr> <td data-bbox="287 989 562 1036">Phase 3: Hyperphagic, rarely feels full (8 years to adulthood)</td><td data-bbox="562 989 1037 1382"> <ul style="list-style-type: none"> Constantly thinking about food While eating one meal they are already thinking about the next meal Will awaken from sleep early thinking about food Will continue eating if portion size is not limited Rarely (truly) feels full Will steal food or money to pay for food Can eat food from garbage and other unsavory/inedible sources (e.g., dog food, frozen food, crayons, etc.) Typically are not truthful about what they have eaten (i.e. amount and types of food) Will gain considerable amount of weight over a short period of time if not supervised (e.g., some individuals are known to have gained up to 20 pounds in one weekend) Food typically needs to be locked up. Frequently the child will ask the parent to lock the food if the parent has forgotten Will break into neighbors’ houses for food Temper tantrums and “meltdowns” frequently related to food Needs to be placed on a diet that is approximately 50–70% of the RDA to maintain a healthy weight </td></tr> </table>	Phase 3: Hyperphagic, rarely feels full (8 years to adulthood)	<ul style="list-style-type: none"> Constantly thinking about food While eating one meal they are already thinking about the next meal Will awaken from sleep early thinking about food Will continue eating if portion size is not limited Rarely (truly) feels full Will steal food or money to pay for food Can eat food from garbage and other unsavory/inedible sources (e.g., dog food, frozen food, crayons, etc.) Typically are not truthful about what they have eaten (i.e. amount and types of food) Will gain considerable amount of weight over a short period of time if not supervised (e.g., some individuals are known to have gained up to 20 pounds in one weekend) Food typically needs to be locked up. 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Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As the Cotter table above shows, hyperphagia (Phase 3) is characterized by related food behaviors in the subject such as: constantly thinking about food, thinking about the next meal while eating, waking from sleep early thinking about food, stealing food or money to pay for food, eating food from the garbage, and the like. <i>Id.</i>; EX1008, [0007]. This is the same “food related behaviors” discussed in the ’895 patent. EX1001, 20:14-22.</p> <hr/> <p>⁸ The ’895 patent also explains that hyperphagia begins at 8 years old. EX1001, 20:14-22.</p>	<p>200. As the Cotter table above shows, hyperphagia (Phase 3) is characterized by related food behaviors in the subject such as: constantly thinking about food, thinking about the next meal while eating, waking from sleep early thinking about food, stealing food or money to pay for food, eating food from the garbage, and the like. <i>Id.</i> These are the same “food related behaviors” discussed in the ’895 patent. EX1001, 20:14-22.</p> <hr/> <p>¹⁴ The ’895 patent also explains that hyperphagia begins at 8 years old. EX1001, 20:14-22.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Claim 1 of the '895 patent specifically requires that administration of diazoxide choline "reduces . . . [the] one or more food related behaviors in the subject." This is taught by Cotter because Cotter taught that the patient "shifted back" to a pre-hyperphagic phase:</p> <p>Further provided herein is a method for treating Prader-Willi Syndrome which may comprise administering a KATP channel opener to a patient in need thereof. The patient may be in PWS nutritional phase 0, 1a, 1b, 2a, 2b, 3, or 4. The patient's PWS nutritional phase may be prevented from progressing to a later phase. . . The patient's PWS nutritional phase may be shifted back to an earlier PWS nutritional phase. The patient may be in PWS nutritional phase 3 or 4, and the patient's PWS nutritional phase may be shifted back to phase 1a, 1b, 2a, or 2b.</p> <p>EX1008, [0007]. In other words, according to Cotter, if the PWS patient is hyperphagic (<i>i.e.</i>, in Phase 3), administration of K_{ATP} channel opener (which would include a pharmaceutical formulation of diazoxide choline) results in the PWS patient being "shifted back" to an earlier phase, <i>i.e.</i>, "phase 1a, 1b, 2a, or 2b," <i>i.e.</i>, before hyperphagia (Phase 3). EX1005, ¶¶201-02. Therefore, it would have been obvious to a POSA, in view of the teachings of Cowen and Cotter, that administration of a pharmaceutical formulation comprising diazoxide choline results</p> <p style="text-align: center;">56</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i> in the reduction of hyperphagia and one or more food-related behaviors in the subject.</p>	<p>201. Claim 1 of the '895 patent specifically requires that administration of diazoxide choline "reduces . . . [the] one or more food related behaviors in the subject." This is taught by Cotter because Cotter taught that the patient "shifted back" to a pre-hyperphagic phase:</p> <p>Further provided herein is a method for treating Prader-Willi Syndrome which may comprise administering a KATP channel opener to a patient in need thereof. The patient may be in PWS nutritional phase 0, 1a, 1b, 2a, 2b, 3, or 4. The patient's PWS nutritional phase may be prevented from progressing to a later phase. . . The patient's PWS nutritional phase may be shifted back to an earlier PWS nutritional phase. The patient may be in PWS nutritional phase 3 or 4, and the patient's PWS nutritional phase may be shifted back to phase 1a, 1b, 2a, or 2b.</p> <p>EX1008, [0007].</p> <p>202. In other words, according to Cotter, if the PWS patient is hyperphagic (<i>i.e.</i>, in Phase 3), administration of K_{ATP} channel opener (which would include a pharmaceutical formulation of diazoxide choline) results in the PWS patient being "shifted back" to an earlier phase, <i>i.e.</i>, "phase 1a, 1b, 2a, or 2b," <i>i.e.</i>, before hyperphagia (Phase 3).</p> <p>203. Therefore, it would have been obvious to a POSA, in view of the teachings of Cowen and Cotter, that administration of a pharmaceutical</p> <p style="text-align: center;">81</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 85</p> <hr/> <p>formulation comprising diazoxide choline results in the reduction of hyperphagia and one or more food-related behaviors in the subject.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Claims 2 and 3 depend from Claim 1 and recite “wherein the diazoxide choline is administered for at least 10 weeks” (Claim 2) and “wherein the diazoxide choline is administered for one or more years.” (Claim 3). These administration periods are taught by Cowen and Cotter.</p>	<p>204. Claims 2 and 3 depend from Claim 1 and recite “wherein the diazoxide choline is administered for at least 10 weeks” (Claim 2) and “wherein the diazoxide choline is administered for one or more years.” (Claim 3). These administration periods are taught by Cowen and Cotter.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained in Ground 1 Cowen teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:</p> <p>Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).</p> <p><i>Id.</i>, [00234], [00735]-[00736] (“Formulations of salts of any of the compounds of Formulae I - IV⁹ prepared as described herein can be tested for efficacy in obese</p> <hr/> <p>⁹ As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA. <i>See, e.g.</i>, EX1005, Sections VII(D) & (E), VIII(A)(ii)(1), IX(A)(ii)(1).</p> <p>57</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>humans . . . [s]ubjects are dosed daily for up to 12 months.”), [00741] (“up to 12 months”). Even if paragraphs [00735]-[00736] refer to a study dealing with the “[t]reatment of obesity in humans,” as Cowen makes clear, this would include patient suffering from Prader-Willi Syndrome. <i>Id.</i>, [0093] (“treating diseases characterized by obesity . . . including (a) Prader-Willi Syndrome”); EX1005, ¶205. Thus, the teachings of Cowen necessarily include administering for least 10 weeks and more than a year, <i>i.e.</i>, 52 weeks.</p>	<p>205. For example, Cowen, as explained in Ground 1, teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:</p> <p>Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).</p> <p>EX1009, [00234], [00735]-[00736] (“Formulations of salts of any of the compounds of Formulae I - IV¹⁵ prepared as described herein can be tested for efficacy in obese</p> <hr/> <p>¹⁵ In both Cowen and Cotter, generic Formula III includes diazoxide. <i>Supra</i> at Section VII(D). For the reasons explained in this Declaration, use of the choline salt would have been obvious to the POSA.</p> <p>82</p> <p>APOTEX_EX1005_PGR2026-00034_Page 86</p> <hr/> <p>humans . . . [s]ubjects are dosed daily for up to 12 months.”), [00741] (“up to 12 months”). Even if paragraphs [00735]-[00736] refer to a study dealing with the “[t]reatment of obesity in humans,” as Cowen makes clear, this would include patients suffering from Prader-Willi Syndrome. <i>Id.</i>, [0093] (“treating diseases characterized by obesity . . . including (a) Prader-Willi Syndrome”). Thus, the teachings of Cowen necessarily include administering for least 10 weeks and more than a year, <i>i.e.</i>, 52 weeks.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Next, turning to Cotter: Cotter discloses the administration of a pharmaceutical formulation comprising diazoxide being administered to a PWS patient “for a period of 56 weeks.” EX1008, [0150]. That necessarily means that the formulation was administered for least 10 weeks and more than a year, <i>i.e.</i>, 52 weeks EX1005, ¶ 206.</p>	<p>206. Next, turning to Cotter: Cotter discloses the administration of a pharmaceutical formulation comprising diazoxide being administered to a PWS patient “for a period of 56 weeks.” EX1008, [0150]. That necessarily means that the formulation was administered for least 10 weeks and more than a year, <i>i.e.</i>, 52 weeks.</p>
<p>Thus, based on the teachings of Cowen and Cotter, use of diazoxide choline would have been obvious, and administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods taught in Cowen and Cotter establishing obviousness. <i>Peterson</i>, 315 F.3d at 1329; <i>DuPont</i>, 904 F.3d at 1008; EX1005, ¶207. Accordingly, the methods of Claims 2-3 would have been obvious.</p>	<p>207. Thus, based on the teachings of Cowen and Cotter, use of diazoxide choline would have been obvious, and administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods taught in Cowen and Cotter.</p> <p>208. Accordingly, the methods of Claims 2-3 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious. As to the specific recitations of Claims 4-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2,000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).</p>	<p>209. Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious. As to the specific recitations of Claims 4-15, they</p> <p style="text-align: center;">83</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 87</p> <hr style="border: 2px solid black;"/> <p>recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2,000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).</p>
<p>Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2,000 mg (Claim 14); and 25 mg to 500 mg (Claim 15). EX1005, ¶¶209-10.</p>	<p>210. Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2,000 mg (Claim 14); and 25 mg to 500 mg (Claim 15).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained above, the claimed “once-daily administration of diazoxide choline” would have been obvious, as would have recited ranges in view of Cowen and/or Cotter. <i>Id.</i>, ¶211. Cowen teaches “the salt can be formulated for controlled release following oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the KATP channel openers provided in Formulae I -</p> <p>59</p>	<p>211. As explained above, the claimed “once-daily administration of diazoxide choline” would have been obvious, as would have recited ranges in view of Cowen and/or Cotter. Cowen teaches, “the salt can be formulated for controlled release following oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the KATP channel openers provided in</p> <p>84</p> <p>APOTEX_EX1005_PGR2026-00034_Page 88</p>
<p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>VIII.”¹⁰ EX1009, [0061], [00380]. Likewise, Cotter teaches “[t]he dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg.” EX1008, [0138]; EX1005, ¶212.</p>	<p>Formulae I - VIII.”¹⁶ EX1009, [0061], [00380].</p> <p>212. Likewise, Cotter teaches “[t]he dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg.” EX1008, [0138].</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Thus, Cowen and Cotter disclose the once-daily administration of diazoxide choline in an amount of 1 mg to 2,000 mg, which overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15). <i>Peterson</i>, 315 F.3d at 1329; <i>DuPont</i>, 904 F.3d at 1008. Accordingly, the methods of Claims 4-15 would have been obvious. EX1005, ¶¶209-14.</p>	<p>213. Thus, Cowen and Cotter would have rendered obvious a once-daily administration of diazoxide choline in amounts that overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15).</p> <p>214. Accordingly, the methods of Claims 4-15 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>D. Claim 16</p> <p>The text of Claim 16 is provided as follows:</p> <p>16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.</p> <p>¹⁰ As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA. See, e.g., EX1005, Sections VII(D) & (E) and VIII(A).</p> <p>60</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>As explained above Dr. Hollander, at a high level, Claim 16 covers the well-known method and common practice method of dose titration of using a starting dose (presumably to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. <i>Supra</i> at VIII.C. (“Methods of Dose Titration Were Well Known”); EX1005, ¶216.</p>	<p>D. Claim 16</p> <p>215. The text of Claim 16 is provided as follows:</p> <p>16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.</p> <p>216. At a high level, Claim 16 covers the well-known method and</p> <p>¹⁶ Generic Formula III in Cowen and Cotter includes diazoxide. <i>Supra</i> at Section VII(D) & (E). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p>85</p> <p>APOTEX_EX1005_PGR2026-00034_Page 89</p> <hr/> <p>common practice method of dose titration of using a starting dose (to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. <i>Supra</i> at Section VII(C).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained above in Ground 1, Cowen repeatedly teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved. EX1009, [0089], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [00478], [00481]-[00483], [00489]-[00490]. As Dr. Hollander explains, Cowen clearly explains that the adverse effects of diazoxide are addressed by using initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose. EX1005, ¶217.</p>	<p>217. As explained above in Ground 1, Cowen repeatedly teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved. EX1009, [0089], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [00478], [00481]-[00483], [00489]-[00490]. To a POSA, Cowen clearly explains that the adverse effects of diazoxide are addressed by using initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose. <i>Id.</i></p>
<p>Similarly, a POSA would recognize that Cotter also teaches the use of a lower starting dose followed by titration up to a maintenance dose. EX1008, [0149] (“The infant was in PWS nutritional phase 1a transitioning to phase 1b was started at 0.5 mg/kg BID of diazoxide at eight months of age, increasing to 1 mg/kg BID”). These teachings clearly demonstrate the routine nature of dose titration in the prior art. EX1005, ¶218.</p>	<p>218. Similarly, a POSA would recognize that Cotter also teaches the use of a lower starting dose followed by titration up to a maintenance dose. EX1008, [0149] (“The infant was in PWS nutritional phase 1a transitioning to phase 1b was started at 0.5 mg/kg BID of diazoxide at eight months of age, increasing to 1 mg/kg BID”). These teachings clearly demonstrate the routine nature of dose titration in the prior art.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Moreover, Cowen teaches more specific examples in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve a therapeutic dose (<i>i.e.</i>, maintenance dose. EX1009, [0077]). Thus, as Cowen teaches, the starting dose “preferably between 10 and 200 mg” of diazoxide may be given to the patient daily “for days or a few weeks,” then escalated thereafter. <i>Id.</i> The “initial escalating dose” may thereafter be given “for days or a few weeks.” <i>Id.</i> The rounds of dose escalation may continue until the therapeutically effective dose is reached. <i>Id.</i>; EX1005, ¶219.</p>	<p>219. Moreover, Cowen teaches more specific examples in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve</p> <p>86</p> <p>APOTEX_EX1005_PGR2026-00034_Page 90</p> <hr/> <p>a therapeutic dose (<i>i.e.</i>, maintenance dose. EX1009, [0077]). Thus, as Cowen teaches, the starting dose “preferably between 10 and 200 mg” of diazoxide may be given to the patient daily “for days or a few weeks,” then escalated thereafter. <i>Id.</i> The “initial escalating dose” may thereafter be given “for days or a few weeks.” <i>Id.</i> The rounds of dose escalation may continue until the therapeutically effective dose is reached. <i>Id.</i></p>
<p>Turning to the limitations of Claim 16: as explained above, administration of diazoxide choline would have been obvious to the POSA. <i>Supra</i>, XIII.A.2.</p>	<p>220. Turning to the limitations of Claim 16: as explained above with respect to my analysis of Claim 1, the administration of diazoxide choline would have been obvious to the POSA.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be subtherapeutic”); EX1005, ¶¶220-21.</p>	<p>221. It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be subtherapeutic”).</p>
<p>As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen. As Dr. Hollander explains, this recitation has three parts, all of which are taught by Cowen: (1) a titration (escalation) of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached. <i>Id.</i>, ¶¶222-28.</p>	<p>obvious. As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen. This recitation has three parts, all of which are taught by Cowen: (1) a titration (escalation) of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As to the first part, <i>i.e.</i>, the titration, this is taught in Cowen. Once the starting dose (EX1009, [0077]), which is “subtherapeutic” (<i>id.</i>, [00478]), is given to the patient:</p> <p>[T]he method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p>	<p>223. As to the first part, <i>i.e.</i>, the titration, this is taught in Cowen. Once the starting dose (<i>id.</i>, [0077]), which is “subtherapeutic” (<i>id.</i>, [00478]), is given to the patient:</p> <p>[T]he method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p>
<p>Finally, as Dr. Hollander explains, the third part of this recitation requires a maintenance dose. This is taught in Cowen: “Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.” EX1009, [0077], [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.”); EX1005, ¶¶227-28.</p>	<p>226. Furthermore, the teachings of Cowen are not limited to a single step increase at the two-week mark, rather Cowen teaches the claimed “every two weeks to reach a maintenance dose.” As Cowen teaches “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” EX1009, [0077]. Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” <i>Id.</i>, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases. Therefore, titration “every two weeks” until a maintenance dose is reached would have been obvious and nothing more than an exercise in routine experimentation for the POSA to arrive at the maintenance dose.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained in Ground 1, Apotex has already addressed why any contention by Patent Owner that Cowen paragraph [0077] is directed only to the use of diazoxide for treating obesity or type 1 or type 2 diabetes, and not PWS and/or</p> <p style="text-align: center;">64</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i> hyperphagia, is misplaced and explain why the Federal Circuit’s <i>Janssen</i> decision will not save Claim 16 (and any of its dependent claims). <i>Supra</i>, XII.D.</p> <p>For all the above reasons, Claim 16 would have been obvious to a POSA.</p>	<p>228. As explained in Ground 1, I previously addressed why any position suggested that Cowen paragraph [0077] is directed only to the use of diazoxide for treating obesity or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, is misplaced. <i>Supra</i> at ¶¶ 159-61.</p> <p>229. Given it would have been obvious to a POSA to use diazoxide choline, for all the above reasons, Claim 16 would have been obvious to a POSA.</p>
<p>Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).</p>	<p>230. Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Cowen teaches in the context of its multidose regimen: “This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide.” EX1009, [0077]; EX1005, ¶231. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18 establishing a <i>prima facie</i> case of obviousness. <i>Id.</i>; <i>Peterson</i>, 315 F.3d at 1329; <i>Applied Materials, Inc.</i>, 692 F.3d at 1295; <i>Aller</i>, 220 F.2d at 456.</p>	<p>231. As explained above, use of diazoxide choline would have been obvious. Cowen teaches in the context of its multidose regimen: “This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.</p> <p style="text-align: center;">90</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 94</p> <hr style="border: 2px solid black;"/> <p>Preferably, the KATP channel opener is diazoxide.” EX1009, [0077]. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18.</p>
<p>Furthermore, as explained in Ground 1, the Federal Circuit’s <i>Janssen</i> decision will not save Claims 17 and 18. <i>Supra</i>, XII.E. Therefore, Claims 17 and 18 would have been obvious.</p>	<p>232. Therefore, Claims 17 and 18 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs												
<p>Claims 19 and 24-25 depend from Claim 17 (which has been addressed above). Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17's starting doses, and importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 25-100 mg:</p>	<p>233. Claims 19 and 24-25 depend from Claim 17 (which has been addressed above).</p> <p>234. Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17's starting doses, and, importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 25-100 mg:</p>												
<table border="1"> <tr> <td>Claim 19</td><td>"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"</td></tr> <tr> <td>Claim 24</td><td>"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"</td></tr> <tr> <td>Claim 25</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."</td></tr> </table>	Claim 19	"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"	Claim 24	"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"	Claim 25	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."	<table border="1"> <tr> <td>Claim 19</td><td>"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"</td></tr> <tr> <td>Claim 24</td><td>"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"</td></tr> <tr> <td>Claim 25</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."</td></tr> </table>	Claim 19	"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"	Claim 24	"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"	Claim 25	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."
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<p>Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18's starting doses, and importantly, in each case Claims 20-23 include a range of diazoxide choline that is higher than Claim 17's starting dose of 50-180 mg:</p> <table> <tr> <td>Claim 20</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"</td></tr> <tr> <td>Claim 21</td><td>"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"</td></tr> <tr> <td>Claim 22</td><td>"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and</td></tr> <tr> <td>Claim 23</td><td>"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."</td></tr> </table>	Claim 20	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"	Claim 21	"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"	Claim 22	"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and	Claim 23	"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."	<p>235. Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18's starting doses, and, importantly, in each case Claims 20-23 include a range of diazoxide choline that is higher than Claim 17's starting dose of 50-180 mg:</p> <p>91</p> <p>APOTEX_EX1005_PGR2026-00034_Page 95</p> <hr/> <table> <tr> <td>Claim 20</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"</td></tr> <tr> <td>Claim 21</td><td>"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"</td></tr> <tr> <td>Claim 22</td><td>"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and</td></tr> <tr> <td>Claim 23</td><td>"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."</td></tr> </table>	Claim 20	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"	Claim 21	"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"	Claim 22	"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and	Claim 23	"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."
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<p>Cowen teaches a multidose regimen, and, like Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] (“The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached”); EX1005, ¶236.</p>	<p>236. As explained above, use of diazoxide choline would have been obvious. Cowen teaches a multidose regimen, and like Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] (“The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>This only leaves the amounts recited in Claim 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” EX1009, [0077]; EX1005, ¶¶237-38. Next, it is not limited to a single stepwise increase but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” EX1009, [0077]. And along that same vein, this same teaching to continue escalating the “rounds” “until the therapeutically effective dose is reached” tells the POSA to use routine</p>	<p>237. This only leaves the amounts recited in Claims 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points.</p> <p>238. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” <i>Id.</i>, [0077].</p> <p>239. Next, it is not limited to single stepwise increase but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” <i>Id.</i> And along that same vein, Cowen teaching that the “rounds of this dose escalation would continue until the therapeutically effective dose is reached” expressly tell the POSA to use routine experimentation. <i>Id.</i> Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” <i>Id.</i>, [0089]. In other words, Cowen teaches 2 to 10 rounds of increases.</p>
<p style="text-align: center;">67</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>experimentation. <i>Id.</i>; EX1005, ¶239. Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” EX1009, [0089]; EX1005, ¶¶239-40; <i>Env’t Designs</i>, 713 F.2d at 698.</p>	<p style="text-align: center;">92</p> <p style="text-align: right;">APOTEX_EX1005_PGR2026-00034_Page 96</p> <hr/>

Petition Text	Text of Cited Exhibit 1005 Paragraphs																								
<p>With these teachings of Cowen “as a whole” including Cowen’s teaching of stepwise increase “2 to 10” rounds to arrive at a therapeutic dose, using Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener” and increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener” through routine experimentation would have resulted in the POSA arriving at the claimed maintenance amounts. EX1005, ¶240; <i>Aller</i>, 220 F.2d at 456; <i>Boesch</i>, 617 F.2d at 276:</p> <table><tr><th>Starting Dose</th><th>First Round</th><th>Second Round</th><th>Third Round</th></tr><tr><td>Lower value 10 mg</td><td>35 mg-160 mg</td><td>60 mg-310 mg</td><td>85-460 mg</td></tr><tr><td>Upper value 200 mg</td><td>225 mg-350 mg</td><td>250 mg-500 mg</td><td>275-650 mg</td></tr></table>	Starting Dose	First Round	Second Round	Third Round	Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg	Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg	<p>240. With the POSA’s knowledge of routine dose titration, beginning with Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener”, and then using Cowen’s stepwise increases of “2 to 10” rounds to arrive at a therapeutic (maintenance) dose, increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener” as taught by the prior art would have resulted in the POSA arriving at the claimed maintenance amounts:</p> <table><tr><th>Starting Dose</th><th>First Round</th><th>Second Round</th><th>Third Round</th></tr><tr><td>Lower value 10 mg</td><td>35 mg-160 mg</td><td>60 mg-310 mg</td><td>85-460 mg</td></tr><tr><td>Upper value 200 mg</td><td>225 mg-350 mg</td><td>250 mg-500 mg</td><td>275-650 mg</td></tr></table>	Starting Dose	First Round	Second Round	Third Round	Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg	Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg
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<p>As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25. EX1005, ¶¶241-42. Furthermore, the POSA would have known from the teaching of Cowen or Cotter that these amounts would have been safe and effective for the patient, providing the POSA a reasonable expectation of success: “Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500</p>	<p>241. As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25. Determining the therapeutic (maintenance dose) is what a physician would do as</p> <p style="text-align: center;">93 APOTEX_EX1005_PGR2026-00034_Page 97</p>
<p style="text-align: center;">68</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>mg or between 500 and 2,000 mg of the salt of the K_{ATP} channel openers provided in Formulae I - VIII.” <i>Id.</i>; EX1009, [0061], [00380]¹¹; EX1008, [0138] (“[t]he dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg.”). Therefore, Claims 19-25 would have been obvious.</p>	<p>part of their routine practice based on factors such patient response, tolerability and the physician’s professional judgement.</p> <p>242. Furthermore, the POSA would have known from the teaching of Cowen or Cotter that these amounts would have been safe and effective for the patient, providing the POSA a reasonable expectation of success: “Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2,000 mg of the salt of the K_{ATP} channel openers provided in Formulae I - VIII.” EX1009, [0061], [00380]¹⁷; EX1008, [0138] (“[t]he dose of the K_{ATP} channel opener may be at least 1, 5, 10, 15, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, or 2000 mg.”).</p> <p>243. Therefore, Claims 19-25 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>G. Claim 26</p> <p>Claim 26 depends from Claim 1 and recites “wherein the pharmaceutical formulation is administered orally.” Cowen and Cotter disclose pharmaceutical formulations comprising diazoxide choline for oral administration. EX1008, [0141]-[0142]; EX1009, [00369], [00380], [00596]; EX1005, ¶¶244-45. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.</p>	<p>244. Claim 26 depends from Claim 1 and recites, “wherein the pharmaceutical formulation is administered orally.” Cowen and Cotter disclose pharmaceutical formulations comprising diazoxide choline for oral</p> <hr/> <p>¹⁷ Generic Formula III in Cowen includes diazoxide. <i>Supra</i> at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p style="text-align: center;">94</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 98</p> <hr/> <p>administration. EX1008, [0141]-[0142]; EX1009, [00369], [00380], [00596].</p> <p>245. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>A. Claim 1</p> <p>The text of independent Claim 1 is provided as follows:</p> <p>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a</p> <hr/> <p>¹¹ As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA.</p> <p>EX1005, Sections VII(D) & (E), VIII(A)(ii)(1), IX(A)(ii)(1), X(A)(ii).</p> <p>69</p>	<p>A. Claim 1</p> <p>247. The text of independent Claim 1 is provided as follows:</p> <p>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.</p> <hr/> <p>¹⁷ Generic Formula III in Cowen includes diazoxide. <i>Supra</i> at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p>94</p>
<hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>pharmaceutical formulation comprising an effective amount of diazoxide choline, wherein administration reduces hyperphagia and one or more food related behaviors in the subject.</p>	

Petition Text	Text of Cited Exhibit 1005 Paragraphs										
<p>1. <i>“A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”</i></p> <p>As explained in Ground 1 (EX1005, ¶248), Cowen teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:</p> <table> <tr> <th>Claim</th><th>Exemplary Citations</th></tr> <tr> <td>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering</td><td>EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient.”); <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same).</td></tr> </table>	Claim	Exemplary Citations	1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient .”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087] (“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).	<p>i. <i>“A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising”</i></p> <p>248. As explained in Ground 1, Cowen teaches “a method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS)”:</p> <table> <tr> <th>Claim</th><th>Exemplary Citations</th></tr> <tr> <td></td><td>95 APOTEX_EX1005_PGR2026-00034_Page 99</td></tr> </table> <hr/> <table> <tr> <td>1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering</td><td>EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient.”); <i>see also id.</i>, [0093] (“Prader-Willi Syndrome”); <i>id.</i>, [00413] (same); <i>id.</i>, [00449] (same); <i>id.</i>, [0069] (“inhibition of hyperphagia”); <i>id.</i>, [0070] (same); <i>id.</i>, [0071] (same); <i>id.</i>, [0087] (“hyperphagia”); <i>id.</i>, [0093] (same); <i>id.</i>, [0093] (same).</td></tr> </table>	Claim	Exemplary Citations		95 APOTEX_EX1005_PGR2026-00034_Page 99	1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient .”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087] (“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).
Claim	Exemplary Citations										
1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient .”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087] (“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).										
Claim	Exemplary Citations										
	95 APOTEX_EX1005_PGR2026-00034_Page 99										
1. A method of treating hyperphagia in a subject having Prader-Willi Syndrome (PWS), the method comprising administering	EX1009, [0087] (“Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient .”); <i>see also id.</i> , [0093] (“Prader-Willi Syndrome”); <i>id.</i> , [00413] (same); <i>id.</i> , [00449] (same); <i>id.</i> , [0069] (“inhibition of hyperphagia”); <i>id.</i> , [0070] (same); <i>id.</i> , [0071] (same); <i>id.</i> , [0087] (“hyperphagia”); <i>id.</i> , [0093] (same); <i>id.</i> , [0093] (same).										

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>2. “administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”</p> <p>(a) The use of diazoxide choline would have been obvious</p> <p>The '895 patent explains that diazoxide is “7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide with the empirical formula $C_8H_7ClN_2O_2S$ and a molecular weight of 230.7.” EX1001, 17:1-3, 2:30-33. Cowen discloses the same compound also identified as diazoxide. EX1009, [0007]. Furthermore, Cowen</p> <p>70</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>teaches the use of diazoxide and other salts for the treatment of hyperphagia in a Prader-Willi Syndrome patient. <i>Id.</i>, [0087]; EX1005, ¶249.</p>	<p>ii. “administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”</p> <p>1) The use of diazoxide choline would have been obvious</p> <p>249. The '895 patent explains that diazoxide is “7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide with the empirical formula $C_8H_7ClN_2O_2S$ and a molecular weight of 230.7.” EX1001, 17:1-3, 2:30-33. Cowen discloses the same compound also identified as diazoxide. EX1009, [0007]. Furthermore, the structure of diazoxide was well known to the POSA. EX1018; <i>supra</i> at ¶¶ 70-72. Cowen also teaches the use of diazoxide and other salts for the treatment of hyperphagia in a Prader-Willi Syndrome patient. EX1009, [0087].</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>(b) “administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”</p> <p>Cowen discloses pharmaceutical formulations comprising diazoxide choline.</p> <p>EX1009, [0596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline). As explained by Dr. Hollander, once-daily administration is always preferable since it increases patient compliance, and it is disclosed and claimed in Cowen. <i>Id.</i>, [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.”), [00411] (formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII administered as a single dose), [00766] (“A controlled clinical study was conducted</p>	<p>iii. “administering to said subject once per day a pharmaceutical formulation comprising an effective amount of diazoxide choline,”</p> <p>252. Cowen discloses pharmaceutical formulations comprising diazoxide choline. <i>Id.</i>, [0596]-[00603] (providing extensive pharmaceutical formulation information using diazoxide choline).</p> <p>253. Once-daily administration is always preferable since it increases</p>
<p>71</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>to evaluate the potential for Diazoxide Choline Controlled-Release Tablets administered once daily”); Claims 31 (“the formulation is administered once per 24 hours.”), 52, 59, 62 & 65; EX1005, ¶¶252-53.</p>	<p>97</p> <p>APOTEX_EX1005_PGR2026-00034_Page 101</p> <hr/> <p>patient compliance, and it is disclosed and claimed in Cowen. <i>Id.</i>, [0087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a K_{ATP} channel opener . . . In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.”), [00411] (formulations of KATP channel openers selected from a salt of a compound of Formulae I - VIII¹⁸ administered as a single dose), [00766] (“A controlled clinical study was conducted to evaluate the potential for Diazoxide Choline Controlled-Release Tablets administered once daily”); Claims 31 (“the formulation is administered once per 24 hours.”), 52, 59, 62 & 65.</p>

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<p>Finally, Claim 1 also recites use of “an effective amount” of the diazoxide choline pharmaceutical composition. The '895 patent provides a definition of an “effective amount.” EX1001, 15:32-36. Cowen discloses an “effective amount” within the meaning of the Claim 1 of the '895 patent. EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener.”); EX1005, ¶254.</p>	<p>254. Finally, Claim 1 also recites use of “an effective amount” of the diazoxide choline pharmaceutical composition. The '895 patent provides a definition of an “effective amount.” EX1001, 15:32-36. Cowen discloses an “effective amount” within the meaning of Claim 1 of the '895 patent. EX1009, [00087] (treating “hyperphagia in a Prader-Willi Syndrome patient, comprising the administration of an effective amount of a KATP channel opener.”).</p>

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<p>The remaining limitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.” Cowen explicitly discloses that a pharmaceutical formulation comprising diazoxide choline (<i>i.e.</i>, a K_{ATP} channel opener) reduces hyperphagia. For instance, Cowen teaches methods to treat obesity or hyperphagia in a Prader-Willi Syndrome patient through administration of a K_{ATP} channel opener. EX1009, [0087]. Furthermore, Cowen provides that such formulations result in inhibition of hyperphagia for about 18 or 24 hours. <i>Id.</i>, [0068], [0070]-[0071], [00411]. This reduction in hyperphagia is a consistent therapeutic outcome highlighted by Cowen. <i>Id.</i>, [00439] (“(19) reduced rates of hyperphagia”), [00442] (“(26) reduced rates of hyperphagia”), [00443]</p>	<p>255. The remaining limitation of Claim 1 is “wherein administration reduces hyperphagia and one or more food related behaviors in the subject.”</p> <p>256. Cowen explicitly discloses that a pharmaceutical formulation comprising diazoxide choline (<i>i.e.</i>, a K_{ATP} channel opener) reduces hyperphagia. For instance, Cowen teaches methods to treat obesity or hyperphagia in a Prader-Willi Syndrome patient through administration of a K_{ATP} channel opener. <i>Id.</i>, [0087].</p> <p>257. Furthermore, Cowen provides that such formulations result in inhibition of hyperphagia for about 18 or 24 hours. <i>Id.</i>, [0068], [0070]-[0071], [00411]. This reduction in hyperphagia is a consistent therapeutic outcome highlighted by Cowen. <i>Id.</i>, [00439] (“(19) reduced rates of hyperphagia”), [00442] (“(26) reduced rates of hyperphagia”), [00443] (“(22) reduced rates of hyperphagia”), [00444] (“(22) reduced rates of hyperphagia”).</p>
<p style="text-align: center;">72</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>“(22) reduced rates of hyperphagia”), [00444] (“(22) reduced rates of hyperphagia”); EX1005, ¶¶256-57.</p>	

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Turning to the limitation of “reduces . . . one or more food related behaviors in the subject”: as explained in Ground 1, the ’895 patent defines “food related behaviors.” EX1001, 20:14-22. <i>Phillips</i>, 415 F.3d at 1315. As explained above in Ground 1, Cowen teaches this limitation either inherently or expressly (<i>supra</i> at Section XII(A)(4)) but to the extent the PTAB disagrees, a POSA would have been aware of the teachings of Miller which would have rendered the limitation obvious. EX1005, ¶258.</p>	<p>258. Turning to the limitation of “reduces . . . one or more food related behaviors in the subject”: as explained in Ground 1, the ’895 patent explains what is meant by “food related behaviors.” EX1001, 20:14-22. As explained above in Ground 1, Cowen teaches this limitation either inherently or expressly (<i>supra</i> at Section VII(A)(v)) but to the extent there is disagreement on this point, a POSA would have been aware of the teachings of Miller which would have rendered the limitation obvious.</p>
<p>Miller, entitled “Nutritional Phases in Prader–Willi Syndrome,” provides a review of PWS. EX1017, 1. A POSA would have been motivated to combine the teachings of Cowen and Miller, with a reasonable expectation of success. Cowen discloses methods of inhibiting and reducing hyperphagia in a PWS patient using diazoxide choline preparations, and Miller provides additional details on the manifestations of hyperphagia in a PWS patient, thus informing a POSA what it means to inhibit or reduce hyperphagia using the diazoxide choline preparations taught in Cowen. EX1005, ¶259.</p>	<p>259. Miller, entitled “Nutritional Phases in Prader–Willi Syndrome,” provides a review of PWS. EX1017, 1. A POSA would have been motivated to combine the teachings of Cowen and Miller, with a reasonable expectation of success. Cowen discloses methods of inhibiting and reducing hyperphagia in a PWS patient using diazoxide choline preparations, and Miller provides additional details on the manifestations of hyperphagia in a PWS patient, thus informing a POSA what it means to inhibit or reduce hyperphagia using the diazoxide choline preparations taught in Cowen. EX1017, Table 1.</p>

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<p>Miller teaches that “Phase 3 is characterized by hyperphagia, typically accompanied by food-seeking and lack of satiety (median age of onset: 8 years; quartiles 5–13 years).” EX1017, Abstract, 5. Miller Table 1 provides various clinical</p> <p>73</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>manifestations of hyperphagia. <i>Id.</i>, Table 1. The table in Miller provides the same “food related behaviors” discussed in the ’895 patent. EX1001 at 20:14-22; EX1005, ¶260.</p>	<p>260. Miller teaches that “Phase 3 is characterized by hyperphagia, typically accompanied by food-seeking and lack of satiety (median age of onset: 8 years; quartiles 5–13 years).” <i>Id.</i>, Abstract, 5. Miller Table 1 provides various clinical manifestations of hyperphagia. <i>Id.</i>, Table 1. The table in Miller provides the same “food related behaviors” discussed in the ’895 patent. EX1001 at 20:14-22.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Accordingly, if a PWS patient is hyperphagic (<i>i.e.</i>, in Phase 3), administration of a K_{ATP} channel opener, such as a pharmaceutical formulation of diazoxide choline, results in the reduction or inhibition of hyperphagia. EX1009, [0087]. That inhibition or reduction of hyperphagia necessarily means that the food-related behaviors discussed in Miller will be reduced. As Miller explains, if a patient is introduced to an intervention method, Phase 3 tends to be less severe. EX1017, 8 (“As a result, when phase 3 begins it is often less severe in those families who have implemented early intervention measures versus what has been traditionally described in the literature”). A POSA would consider Cowen’s diazoxide choline an intervention method, and, based on the teachings of Cowen regarding a reduction/inhibition of hyperphagia, the POSA would reasonably expect a corresponding reduction in the food-related behaviors described in Miller. EX1005, ¶¶261-63.</p>	<p>261. Accordingly, if a PWS patient is hyperphagic (<i>i.e.</i>, in Phase 3), administration of a K_{ATP} channel opener, such as a pharmaceutical formulation of diazoxide choline, results in the reduction or inhibition of hyperphagia. EX1009, [0087].</p> <p>262. That inhibition or reduction of hyperphagia necessarily means that the food-related behaviors discussed in Miller will be reduced or inhibited. As</p> <p style="text-align: center;">100 APOTEX_EX1005_PGR2026-00034_Page 104</p> <hr/> <p>Miller explains, if a patient is introduced to an intervention method, Phase 3 tends to be less severe. EX1017, 8 (“As a result, when phase 3 begins it is often less severe in those families who have implemented early intervention measures versus what has been traditionally described in the literature”).</p> <p>263. A POSA would consider Cowen’s diazoxide choline an intervention method and, based on the teachings of Cowen regarding a reduction/inhibition of hyperphagia, the POSA would reasonably expect a corresponding reduction in the food-related behaviors described in Miller.</p>

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<p>Therefore, it would have been obvious to a POSA, in view of the teachings of Cowen and Miller, that administration of a pharmaceutical formulation comprising diazoxide choline results in the reduction of hyperphagia which, in turn, causes the reduction of one or more food-related behaviors in the subject. <i>Id.</i>, ¶264.</p> <p style="text-align: center;">74</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>Accordingly, it would have been obvious to a POSA to achieve the method of treating hyperphagia in a patient having PWS, as recited in Claim 1.</p>	<p>264. Therefore, it would have been obvious to a POSA, in view of the teachings of Cowen and Miller, that administration of a pharmaceutical formulation comprising diazoxide choline results in the reduction of hyperphagia which, in turn, causes the reduction of one or more food-related behaviors in the subject. Accordingly, it would have been obvious to a POSA to achieve the method of treating hyperphagia in a patient having PWS as recited in Claim 1.</p>
<p>Claims 2 and 3 depend from Claim 1 and recite “wherein the diazoxide choline is administered for at least 10 weeks” (Claim 2) and “wherein the diazoxide choline is administered for one or more years.” (Claim 3). These administration periods are taught by Cowen.</p>	<p>265. Claims 2 and 3 depend from Claim 1 and recite, “wherein the diazoxide choline is administered for at least 10 weeks” (Claim 2) and “wherein the diazoxide choline is administered for one or more years.” (Claim 3). These administration periods are taught by Cowen.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Cowen teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:</p> <p>Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).</p> <p><i>Id.</i>, [00234], [00736] (“Formulations of salts of any of the compounds of Formulae I - IV¹² prepared as described herein can be tested for efficacy in obese humans . . . [s]ubjects are dosed daily for up to 12 months.”), [00741] (“up to 12 months”).</p>	<p>obvious in light of Cowen. Cowen teaches “prolonged administration” (EX1009, Abstract) with specific administration periods ranging from at least 7 days to 12 months:</p> <p>Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).</p> <p>EX1009, [00234], [00736] (“Formulations of salts of any of the compounds of Formulae I - IV¹⁹ prepared as described herein can be tested for efficacy in obese humans . . . [s]ubjects are dosed daily for up to 12 months.”), [00741] (“up to 12 months”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>¹² As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA. See, e.g., EX1005, Sections VII(D) & (E), VIII(A)(ii)(1), IX(A)(ii)(1), X(A)(ii).</p> <p style="text-align: center;">75</p> <hr style="border: 2px solid black; margin: 10px 0;"/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>Based on the teachings of Cowen, use of diazoxide choline would have been obvious, and administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods disclosed in Cowen. It is well established that when claimed ranges “overlap or lie inside ranges disclosed by the prior art,” a <i>prima facie</i> case of obviousness exists. <i>Peterson</i>, 315 F.3d at 1329; <i>DuPont</i>, 904 F.3d at 1008. Accordingly, Claims 2-3 would have been obvious. EX1005, ¶¶265-67.</p>	<p>267. Based on the teachings of Cowen, use of diazoxide choline would have been obvious, and administration “for at least 10 weeks” (Claim 2) or “for one or more years” would have overlapped with the administration periods disclosed in Cowen. Accordingly, Claims 2-3 would have been obvious.</p> <p style="text-align: center;">C. Claims 4-15</p> <p>¹⁹ Generic Formula III in Cowen includes diazoxide. <i>Supra</i> at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p>
<p>Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious. As to the specific recitations of Claims 4-9, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2,000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).</p>	<p>268. Claims 4-15 depend from Claim 1. As explained above, Claim 1 would have been obvious. As to the specific recitations of Claims 4-9, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 4), 50 mg to 180 mg (Claim 5), 50 mg to 275 mg (Claim 6), 300 mg to 500 mg (Claim 7), 500 mg to 2,000 mg (Claim 8); and 25 mg to 500 mg (Claim 9).</p>

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<p>Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2,000 mg (Claim 14); and 25 mg to 500 mg (Claim 15). EX1005, ¶¶268-69.</p>	<p>269. Turning to Claims 10-15, these claims depend from Claim 3. As explained above, Claim 3 would have been obvious. As to the specific recitations of Claims 10-15, they recite various ranges of the obvious “once-daily administration of diazoxide choline,” <i>i.e.</i>, 25 to 100 mg (Claim 10), 50 mg to 180 mg (Claim 11), 50 mg to 275 mg (Claim 12), 300 mg to 500 mg (Claim 13), 500 mg to 2,000 mg (Claim 14); and 25 mg to 500 mg (Claim 15).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained above, the “once-daily administration of diazoxide choline” would have been obvious, as would have recited ranges in view of Cowen. Cowen teaches “the salt can be formulated for controlled release following oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the KATP channel openers provided in Formulae I - VIII.”¹³ EX1009, [0061], [00380].</p> <p>Thus, Cowen discloses the once-daily administration of diazoxide choline in an amount of 1 mg to 2000 mg, which overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15). <i>Peterson</i>, 315 F.3d at 1329; <i>DuPont</i>, 904 F.3d at 1008. Accordingly, Claims 4-15 would have been obvious. EX1005, ¶¶270-271.</p>	<p>270. As explained above, the “once-daily administration of diazoxide choline” would have been obvious, as would have recited ranges in view of Cowen. Cowen teaches that “the salt can be formulated for controlled release following oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the KATP channel openers provided in Formulae</p> <p style="text-align: center;">103</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 107</p> <hr/> <p>I - VIII.”²⁰ EX1009, [0061], [00380].</p> <p>271. Thus, Cowen discloses the once-daily administration of diazoxide choline in an amount of 1 mg to 2000 mg, which overlaps with the claimed ranges of 25 to 100 mg (Claims 4 and 10), 50 mg to 180 mg (Claims 5 and 11), 50 mg to 275 mg (Claims 6 and 12), 300 mg to 500 mg (Claims 7 and 13), 500 mg to 2,000 mg (Claims 8 and 14); and 25 mg to 500 mg (Claims 9 and 15).</p> <p>272. Accordingly, Claims 4-15 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>The text of Claim 16 is provided as follows:</p> <p>_____</p> <p>¹³ As explained by Dr. Hollander, generic Formula III of Cowen and/or Cotter contain diazoxide and use of its choline salt would have been obvious to the POSA. See, e.g., EX1005, Sections VII(D) & (E), VIII(A)(ii)(1), IX(A)(ii)(1), X(A)(ii).</p> <p style="text-align: center;">77</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.</p>	<p>²⁰ Generic Formula III in Cowen includes diazoxide. <i>Supra</i> at Section VII(D). As explained in this Declaration, use of the diazoxide choline salt would have been obvious to the POSA.</p> <p style="text-align: center;">104</p> <p>273. The text of Claim 16 is provided as follows:</p> <p>16. The method of claim 1, wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline and then titrated every two weeks to reach a maintenance dose of diazoxide choline.</p>
<p>As explained above by Dr. Hollander, at a high level, Claim 16 covers the well-known method of dose titration of using a starting dose (presumably to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. <i>Supra</i>, VIII.C. (“Methods of Dose Titration Were Well Known”); EX1005, ¶274. Indeed, as Dr. Hollander explained, using such dose titration to arrive at a maintenance (therapeutic) dose is common practice. <i>Id.</i></p>	<p>274. At a high level, Claim 16 covers the well-known method of dose titration using a starting dose (to address adverse patient side effects) followed by dose titration every two weeks to reach another level referred to as a maintenance dose. <i>Supra</i> at Section VII(C). (“Dose Titration in Clinical Practice Was Well Known as of the Priority Date”). Using such dose titration to arrive at a maintenance (therapeutic) dose is common practice.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained above in Ground 1, Cowen teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved. EX1009, [00478], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [0089], [00481]-[00483], [00489]-[00490]. As Dr. Hollander explains, Cowen clearly explains that the adverse effects of diazoxide are addressed by using initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose. EX1005, ¶275.</p>	<p>275. As explained above in Ground 1, Cowen repeatedly teaches, for various disease states, that in order to reduce the adverse side effects known to occur with diazoxide, patients can be initiated at subtherapeutic doses and titrated up in a stepwise manner, until a therapeutic dose is achieved. EX1009, [00478], [00448] (providing examples of adverse effects that can be reduced using titration to therapeutic dose), [0089], [00481]-[00483], [00489]-[00490]. Cowen clearly explains that the adverse effects of diazoxide are addressed by using an initiation or starting dose and then increasing the dose to a maintenance (therapeutic) dose.</p>
<p>Moreover, Cowen teaches more specific examples in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve a therapeutic dose (<i>i.e.</i>, maintenance dose). EX1009, [0077]. Thus, as Cowen teaches, the starting dose “preferably between 10 and 200 mg” of diazoxide may be given to the patient daily “for days or a few weeks,” then escalated thereafter. <i>Id.</i> The “initial escalating dose” may thereafter be given “for days or a few weeks.” <i>Id.</i> The rounds of dose escalation may continue until the therapeutically effective dose is reached. <i>Id.</i>; EX1005, ¶276.</p>	<p>276. Moreover, Cowen teaches more specific examples in the context of obesity or type 1 or type 2 diabetes with a salt of K_{ATP} channel opener to achieve a therapeutic dose (<i>i.e.</i>, maintenance dose). <i>Id.</i>, [0077]. Thus, as Cowen teaches, the starting dose of “preferably between 10 and 200 mg” of diazoxide may be given to the patient daily “for days or a few weeks,” then escalated thereafter. <i>Id.</i> The “initial escalating dose” may thereafter be given “for days or a few weeks.” <i>Id.</i> The rounds of dose escalation may continue until the therapeutically effective dose is reached. <i>Id.</i></p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>1. “wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline”</p> <p>Turning to the limitations of Claim 16: as explained above, administration of diazoxide choline would have been obvious to the POSA. <i>Supra</i>, XIV.A.2.</p>	<p>i. “wherein the administration of diazoxide choline is initiated at a starting dose of diazoxide choline”</p> <p>277. Turning to the limitations of Claim 16: as explained above with</p> <p style="text-align: center;">105</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 109</p> <hr/> <p>respect to my analysis of Claim 1, the administration of diazoxide choline would have been obvious to the POSA.</p>
<p>It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches that a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be subtherapeutic”); EX1005, ¶278.</p>	<p>278. It would have been obvious to the POSA to “initiate[] at a starting dose of diazoxide choline” based on the teachings of Cowen. For example, Cowen teaches a “starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks.” EX1009, [0077], [00478] (“in which the first dose is known to be subtherapeutic”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>2. <i>“and then titrated every two weeks to reach a maintenance dose of diazoxide choline”</i></p> <p>79</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen. As Dr. Hollander explains, this recitation has three parts, all of which are taught by Cowen: (1) a titration of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached. EX1005, ¶279.</p>	<p>ii. <i>“and then titrated every two weeks to reach a maintenance dose of diazoxide choline”</i></p> <p>279. As to “then titrat[ing] every two weeks to reach a maintenance dose of diazoxide choline,” this is also taught by Cowen. This recitation has three parts, all of which are taught by Cowen: (1) a titration of the medication; (2) this titration occurs every two weeks and continues until (3) maintenance dose is reached.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As to the first part, <i>i.e.</i>, the titration, this is taught in Cowen. Once the starting dose (EX1009, [0077]), which is “subtherapeutic” (<i>id.</i>, [00478]), is given to the patient:</p> <p>[T]he method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p>	<p>280. As to the first part, <i>i.e.</i>, the titration, this is taught in Cowen. Once the starting dose (<i>id.</i>, [0077]), which is “subtherapeutic” (<i>id.</i>, [00478]), is given to the patient:</p> <p>[T]he method includes escalating the dose which is administered when after supine heart rates return to</p> <p>106</p> <p>APOTEX_EX1005_PGR2026-00034_Page 110</p> <hr/> <p>baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.</p>
<p><i>Id.</i>, [0077]. Thus, the POSA would understand that Cowen’s “initial escalating dose” is the dose that is titrated up. <i>See also id.</i>, [00478] (“daily dose is subsequently increased stepwise until the therapeutic dose is reached.”); EX1005, ¶¶280-81.</p>	<p><i>Id.</i>, [0077].</p> <p>281. Thus, the POSA would understand that Cowen’s “initial escalating dose” is the dose that is titrated up. <i>See also id.</i>, [00478] (“daily dose is subsequently increased stepwise until the therapeutic dose is reached.”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Turning to the second part of this recitation: Claim 16 of the '895 patent recites the titration (dose escalation) occurs "every two weeks to reach a maintenance dose," whereas Cowen teaches titration "for days or a few weeks." The claimed titration escalation of "two weeks" falls within the range disclosed in Cowen, <i>i.e.</i>, "for days or a few weeks" and therefore would have been obvious because it is nothing more than routine optimization of a parameter identified in the prior art. <i>Aller</i>, 220 F.2d at 456; <i>Applied Materials, Inc.</i>, 692 F.3d at 1295; EX1005, ¶¶ 282-83. Moreover, as Dr. Hollander states, it is common for physicians to utilize two weeks as a standard titration interval when titration is needed. EX1005, ¶77.</p>	<p>282. Turning to the second part of this recitation: Claim 16 of the '895 patent recites that the titration (dose escalation) occurs "every two weeks to reach a maintenance dose," whereas Cowen teaches titration "for days or a few weeks." The claimed titration escalation of "two weeks" falls within the range disclosed in Cowen, <i>i.e.</i>, "for days or a few weeks" and therefore would have been obvious because it is nothing more than routine optimization of a parameter identified in the prior art. Moreover, as I explained above, it is common for physicians to utilize two weeks as a standard titration interval when titration is needed. <i>Supra</i> at ¶ 77.</p>
<p>Finally, as Dr. Hollander explains, the third part of this recitation requires a maintenance dose. This is taught in Cowen: "Further rounds of this dose escalation would continue until the therapeutically effective dose is reached." EX1009, [0077], [00478] ("diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached."); EX1005, ¶284.</p>	<p>284. Finally, the third part of this recitation requires a maintenance dose. This is taught in Cowen: "Further rounds of this dose escalation would continue until the therapeutically effective dose is reached." <i>Id.</i>; <i>see also id.</i>, [00478] ("diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.").</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As explained in Ground 1, Apotex has already addressed why any contention by Patent Owner that Cowen paragraph [0077] is directed only to the use of diazoxide for treating obesity or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, is misplaced and explains why the Federal Circuit’s <i>Janssen</i> decision</p> <p style="text-align: center;">81</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>will not save Claim 16 (and any of its dependent claims). <i>Supra</i>, XII.D; EX1005, ¶285.</p> <p>For all the above reasons, Claim 16 would have been obvious to a POSA.</p>	<p>285. As explained in Ground 1, I have already addressed why any position that Cowen paragraph [0077] is directed only to the use of diazoxide for treating obesity or type 1 or type 2 diabetes, and not PWS and/or hyperphagia, is misplaced. <i>Supra</i> at ¶¶159-61.</p> <p>286. Given it would have been obvious to use diazoxide choline, for all</p> <p style="text-align: center;">108</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 112</p> <hr/> <p>the above reasons, Claim 16 would have been obvious to a POSA.</p>
<p>E. Claims 17-18 (Starting Dose Claims)</p> <p>Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).</p>	<p>E. Claims 17-18 (Starting Dose Claims)</p> <p>287. Claims 17-18 depend from Claim 16. Claim 16 has been addressed above. Claims 17-18 recite “that the starting dose of diazoxide choline is between 25-100 mg” (Claim 17) and “the starting dose of diazoxide choline is between 50-180 mg” (Claim 18).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Cowen teaches in the context of its multidose regimen: “This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide.” EX1009, [0077]. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18 establishing a <i>prima facie</i> case of obviousness. <i>Peterson</i>, 315 F.3d at 1329; <i>Applied Materials, Inc.</i>, 692 F.3d at 1295; <i>Aller</i>, 220 F.2d at 456; EX1005, ¶288.</p> <p>Furthermore, as explained in Ground 1, the Federal Circuit’s <i>Janssen</i> decision will not save Claims 17 and 18. <i>Supra</i>, XII.E. Therefore, Claims 17 and 18 would have been obvious.</p>	<p>288. As explained above, use of diazoxide choline would have been obvious in light of the teachings of Cowen and Cowen teaches in the context of its multidose regimen: “This starting dose is preferably between 10 and 200 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the KATP channel opener is diazoxide.” EX1009, [0077]. The starting doses taught by Cowen overlap with the claimed starting doses of Claims 17 and 18.</p> <p>289. Therefore, Claims 17 and 18 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs												
<p>F. Claims 19-25 (Maintenance Dose Claims)</p> <p>82</p> <hr/> <p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>Claims 19 and 24-25 depend from Claim 17 (which has been addressed above). Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17's starting doses, and importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 25-100 mg:</p> <table> <tr> <td>Claim 19</td><td>"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"</td></tr> <tr> <td>Claim 24</td><td>"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"</td></tr> <tr> <td>Claim 25</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."</td></tr> </table>	Claim 19	"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"	Claim 24	"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"	Claim 25	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."	<p>F. Claims 19-25 (Maintenance Dose Claims)</p> <p>1. Claims 19 and 24-25 depend from Claim 17 (which has been addressed above). Claims 19 and 24-25 are then directed to the subsequent maintenance dose from Claim 17's starting doses, and, importantly, in each case Claims 19 and 24-25 include a range of diazoxide choline that is higher than Claim 17's starting dose of 25-100 mg:</p> <p>109</p> <p>APOTEX_EX1005_PGR2026-00034_Page 113</p> <hr/> <table> <tr> <td>Claim 19</td><td>"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"</td></tr> <tr> <td>Claim 24</td><td>"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"</td></tr> <tr> <td>Claim 25</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."</td></tr> </table>	Claim 19	"wherein the maintenance dose of diazoxide choline is between 100-200 mg of diazoxide choline"	Claim 24	"wherein the maintenance dose of diazoxide choline is between 25-250 mg of diazoxide choline"	Claim 25	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline."
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Petition Text	Text of Cited Exhibit 1005 Paragraphs																
<p>Claims 20-23 depend from Claim 18 (which has been addressed above).</p> <p>Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18's starting doses, and, importantly, in each case, Claims 20-23 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 50-180 mg:</p> <table> <tr> <td>Claim 20</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"</td></tr> <tr> <td>Claim 21</td><td>"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"</td></tr> <tr> <td>Claim 22</td><td>"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and</td></tr> <tr> <td>Claim 23</td><td>"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."</td></tr> </table>	Claim 20	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"	Claim 21	"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"	Claim 22	"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and	Claim 23	"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."	<p>290. Claims 20-23 depend from Claim 18 (which has been addressed above). Claims 20-23 are then directed to the subsequent maintenance dose from Claim 18's starting doses, and, importantly, in each case Claims 20-23 include a range of diazoxide choline that is <i>higher</i> than Claim 17's starting dose of 50-180 mg:</p> <table> <tr> <td>Claim 20</td><td>"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"</td></tr> <tr> <td>Claim 21</td><td>"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"</td></tr> <tr> <td>Claim 22</td><td>"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and</td></tr> <tr> <td>Claim 23</td><td>"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."</td></tr> </table>	Claim 20	"wherein the maintenance dose of diazoxide choline is between 200-300 mg of diazoxide choline"	Claim 21	"wherein the maintenance dose of diazoxide choline is between 300-500 mg of diazoxide choline"	Claim 22	"wherein the maintenance dose of diazoxide choline is between 500-2000 mg of diazoxide choline"; and	Claim 23	"wherein the maintenance dose of diazoxide choline is between 100-500 mg of diazoxide choline."
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Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>Cowen teaches a multidose regimen, and like the Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] (“The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached”); EX1005, ¶291.</p>	<p>291. Cowen teaches a multidose regimen, and like Claims 19-25, Cowen teaches the maintenance dose will be higher than the starting dose when using diazoxide choline. EX1009, [0077] (“The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of KATP channel opener . . . Further rounds of this dose escalation would continue until the therapeutically effective dose is reached.”), [00478] (“diazoxide or its derivatives that is administered to a subject in need thereof on</p> <p style="text-align: center;">110</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 114</p> <hr/> <p>a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached”).</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>This only leaves the amounts recited in Claims 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” EX1009, [0077]. Next, it is not limited to single stepwise increases but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” <i>Id.</i> And along that same vein, Cowen teaching that the “rounds of this dose escalation would continue until the therapeutically effective dose is reached” expressly tells the POSA to use routine</p>	<p>292. This only leaves the amounts recited in Claims 19-25 of the '895 patent. And in this regard, Cowen teaches the POSA some important points.</p> <p>293. First, the dose may be escalated (titrated up) in increments of “preferentially 25 to 150 mg of KATP channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide.” <i>Id.</i>, [0077].</p> <p>294. Next, it is not limited to a single stepwise increase but “[f]urther rounds of this dose escalation would continue until the therapeutically effective dose is reached.” <i>Id.</i> And, along that same vein, Cowen teaching that the “rounds of this dose escalation would continue until the therapeutically effective dose is reached” expressly tell the POSA to use routine experimentation. <i>Id.</i> Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” <i>Id.</i>, [0089]. In other words, Cowen teaches</p>
<p style="text-align: center;">84</p> <hr/> <p><i>Petition for Post-Grant Review of</i> <i>U.S. Patent No. 12,419,895</i> experimentation. <i>Id.</i> Elsewhere, Cowen would have taught the POSA that “the number of steps is 2 to 10 to reduce the incidence of adverse side effects.” <i>Id.</i>, [0089]; EX1005, ¶¶292-94; <i>Env’t Designs</i>, 713 F.2d at 698.</p>	<p>2 to 10 rounds of increases.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs																								
<p>With these teachings of Cowen “as a whole” including Cowen teaching of stepwise increase “2 to 10” rounds to arrive at a therapeutic dose, using Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener” and increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener” through routine experimentation would have resulted in the POSA arriving at the claimed maintenance amounts. EX1005, ¶295; <i>Aller</i>, 220 F.2d at 456; <i>Boesch</i>, 617 F.2d at 276:</p> <table><tr><th>Starting Dose</th><th>First Round</th><th>Second Round</th><th>Third Round</th></tr><tr><td>Lower value 10 mg</td><td>35 mg-160 mg</td><td>60 mg-310 mg</td><td>85-460 mg</td></tr><tr><td>Upper value 200 mg</td><td>225 mg-350 mg</td><td>250 mg-500 mg</td><td>275-650 mg</td></tr></table>	Starting Dose	First Round	Second Round	Third Round	Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg	Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg	<p>295. With the POSA’s knowledge of routine dose titration, beginning with Cowen’s starting dose of “between 10 and 200 mg of KATP channel opener”, and then using Cowen’s stepwise increases of “2 to 10” rounds to arrive at a therapeutic (maintenance) dose, increasing the medication by two rounds in escalation increments of “25 to 150 mg of KATP channel opener” as taught by</p> <p>111</p> <p>APOTEX_EX1005_PGR2026-00034_Page 115</p> <hr/> <p>the prior art would have resulted in the POSA arriving the claimed maintenance amounts:</p> <table><tr><th>Starting Dose</th><th>First Round</th><th>Second Round</th><th>Third Round</th></tr><tr><td>Lower value 10 mg</td><td>35 mg-160 mg</td><td>60 mg-310 mg</td><td>85-460 mg</td></tr><tr><td>Upper value 200 mg</td><td>225 mg-350 mg</td><td>250 mg-500 mg</td><td>275-650 mg</td></tr></table>	Starting Dose	First Round	Second Round	Third Round	Lower value 10 mg	35 mg-160 mg	60 mg-310 mg	85-460 mg	Upper value 200 mg	225 mg-350 mg	250 mg-500 mg	275-650 mg
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Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25. Furthermore, the POSA would have known from the teaching of Cowen that these amounts would have been safe and effective for the patient providing the POSA a reasonable expectation of success: "Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500</p> <p style="text-align: center;">85</p>	<p>296. As the chart above shows, two rounds would have resulted in a range of 60 mg to 500 mg of diazoxide choline; three rounds would have resulted in the range of 85 mg to 650 mg, which are the claimed ranges recited in Claims 19-25. Determining the therapeutic (maintenance dose) is what a physician would do as part of their routine practice based on factors such patient response, tolerability and the physician's professional judgement.</p> <p>297. Furthermore, the POSA would have known from the teaching of Cowen that these amounts would have been safe and effective for the patient, providing the POSA a reasonable expectation of success: "Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the K_{ATP} channel openers</p>
<p><i>Petition for Post-Grant Review of U.S. Patent No. 12,419,895</i></p> <p>and 2000 mg of the salt of the K_{ATP} channel openers provided in Formulae I - VIII." EX1009, [0061], [00380]; EX1005, ¶¶296-97.¹⁴ Therefore, Claims 19-25 would have been obvious.</p>	<p style="text-align: center;">112</p> <p style="text-align: center;">APOTEX_EX1005_PGR2026-00034_Page 116</p> <p>provided in Formulae I - VIII." EX1009, [0061], [00380].²¹ Therefore, Claims 19-25 would have been obvious.</p>

Petition Text	Text of Cited Exhibit 1005 Paragraphs
<p>G. Claim 26</p> <p>Claim 26 depends from Claim 1 and recites “wherein the pharmaceutical formulation is administered orally.” Cowen discloses pharmaceutical formulations comprising diazoxide choline for oral administration. EX1009, [00369], [00380], [00596]; EX1005, ¶¶298-99. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.</p>	<p>G. Claim 26</p> <p>298. Claim 26 depends from Claim 1 and recites “wherein the pharmaceutical formulation is administered orally.” Cowen discloses pharmaceutical formulations comprising diazoxide choline for oral administration. <i>Id.</i>, [00369], [00380], [00596].</p> <p>299. Accordingly, it would have been obvious for a POSA to administer the claimed pharmaceutical formulation orally, with a reasonable expectation of success.</p>