

# Continuous Subcutaneous Recombinant Parathyroid Hormone (1-34) Infusion in the management of childhood Hypoparathyroidism associated with Malabsorption

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1 **Continuous Subcutaneous Recombinant Parathyroid Hormone (1-34)**  
2 **Infusion in the management of childhood Hypoparathyroidism associated**  
3 **with Malabsorption.**

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13 **Short Title:** CSPI rhPTH <sup>1-34</sup> therapy in hypoparathyroidism associated with  
14 malabsorption

15

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26 **Keywords:** Hypoparathyroidism, malabsorption, recombinant parathyroid  
27 hormone, teriparatide, continuous subcutaneous infusion.

**Established facts:**

- Hypoparathyroidism associated with malabsorption can be particularly challenging to manage in children due to limited and often erratic intestinal absorption of calcium and vitamin D analogues.
- Conventional treatment in these children is often associated with symptomatic hypocalcaemia and hypo/ hypercalcaemia-related hospital admissions.

**Novel insights:**

- Continuous subcutaneous recombinant parathyroid (rhPTH<sup>1-34</sup>) hormone infusion results in the normalisation and stabilisation of serum calcium and phosphate and therefore is a promising and effective alternative treatment option for children with hypoparathyroidism associated with intestinal malabsorption.

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38 **Abstract:**

39 **Background/ Aims:** Hypoparathyroidism associated with malabsorption can be  
40 particularly challenging to manage due to limited and erratic intestinal  
41 absorption of calcium and vitamin D analogues, resulting in episodes of hypo- or  
42 hypercalcaemia. We evaluated the role of continuous subcutaneous recombinant  
43 parathyroid (rhPTH 1-34) hormone infusion (CSPI) in children with  
44 hypoparathyroidism associated with intestinal malabsorption resistant to  
45 conventional therapy.

46 **Method:** Four patients (8 - 13 years), with symptomatic hypocalcaemia resistant  
47 to conventional therapy were started on CSPI (follow up 3-8 years), in two  
48 paediatric endocrinology units in Europe.

49 **Results:** Serum calcium normalised within 48 hours of commencing treatment in  
50 all 4 patients. An average rhPTH 1-34 dose of 0.4 µg/kg/day resulted in a  
51 substantial reduction in symptomatic hypocalcaemia and hypo/ hypercalcaemia-  
52 related hospital admissions. An increased alkaline phosphatase activity was  
53 noted in the first six months on CSPI, indicating increase in bone turnover. In 2  
54 patients with elevated urinary calcium excretion pre CSPI, this normalised in the  
55 first year on treatment. No significant side effects were noticed in the short or  
56 long term, with patient-reported preference of CSPI over conventional  
57 treatment.

58 **Conclusion:** CSPI is a promising and effective treatment option for managing  
59 hypocalcaemia and hyperphosphatemia in children with hypoparathyroidism  
60 associated with intestinal malabsorption.

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### 63 **1. Introduction:**

64 Hypoparathyroidism is a rare endocrine disorder characterized by low serum  
65 calcium with an inappropriately low or normal serum parathyroid hormone  
66 (PTH) level. [1] In children, it is commonly associated with either defects in  
67 genes involved in parathyroid gland development (*TBX1/22q11.2 del, GCMB*),  
68 function (calcium-sensing receptor *CaSR, GNA11* and *PTH*), or auto-immune  
69 polyglandular syndrome type 1 (*AIRE*). [2, 3]

70 Along with maintaining calcium and phosphate homeostasis through stimulation  
71 of osteoclastic bone resorption, PTH plays a vital role in calcium reabsorption  
72 and phosphate excretion in the renal tubules. PTH also facilitates conversion of  
73 25 hydroxy vitamin D (25OHD) to the active 1,25 dihydroxy vitamin D [1,25  
74 (OH)<sub>2</sub>D] which enhances intestinal calcium and phosphate absorption. [4]

75 Unlike other hormone deficiency states, replacing the missing hormone in  
76 hypoparathyroidism is not routine practice. Instead, conventional therapy with  
77 oral calcium supplements and vitamin D analogues remains the mainstay of  
78 treatment. [5] The role of synthetic subcutaneous PTH injections in the  
79 treatment of hypoparathyroidism was first reported in adults in 1996 [6, 7]  
80 followed by children in 2008. [8] Since then, short [9] and long term studies [10]

81 have demonstrated the efficacy and safety of Continuous Subcutaneous  
82 Recombinant PTH<sup>1-34</sup> Infusion (CSPI) in the management of hypocalcaemia in  
83 children with activating mutations in *CaSR* and with autoimmune  
84 polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

85 Managing hypocalcaemia with conventional therapy can be particularly  
86 challenging in children with hypoparathyroidism associated with intestinal  
87 malabsorption, where calcium and active vitamin D analogue absorption capacity  
88 is both limited and highly variable. Here we report the favourable effects of CSPI  
89 in four children with resistant hypocalcaemia secondary to hypoparathyroidism  
90 associated with malabsorption, managed in two tertiary paediatric  
91 endocrinology units in Europe, Birmingham Children's Hospital, Birmingham,  
92 United Kingdom (patient 1) and Bicêtre Hospital, Paris, France (patient 2-4).

## 93 **2. Subjects and Methods:**

### 94 **2.1. Case Reports:**

95 **Patient 1 (P1):** A 13-year-old boy, born to consanguineous South-Asian parents  
96 was diagnosed with congenital hypoparathyroidism in infancy. He was  
97 subsequently diagnosed with sensory neural hearing loss, developmental delay  
98 and cryptogenic liver disease requiring liver transplant at the age of 2 years. He  
99 developed persistent diarrhoea with hypoalbuminaemia, lymphopaenia,  
100 hypomagnesaemia and recurrent severe hypocalcaemia by the age of 3 years.  
101 Video capsule endoscopy confirmed extensive intestinal lymphangectasia, not  
102 amenable to surgery. Genetic analysis has not identified any significant  
103 abnormalities to date. Despite high doses of alfacalcidol (200ng/kg), oral

104 calcium (300mg/kg/day) and magnesium supplements (15mg/kg/day) his  
105 serum calcium remained between 1.26 and 1.98 mmol/L. High doses of oral  
106 calcium supplements led to worsening diarrhoea. Multiple hospital admissions  
107 with hypocalcaemic seizures or symptomatic refractory hypocalcaemia requiring  
108 i.v. calcium infusions ensued. At the age of 13 years, he was commenced on CSPI  
109 delivered via a Medtronic™ pump and successfully weaned off alfacalcidol,  
110 magnesium and calcium supplements. His serum calcium normalised and  
111 stabilised within 2 days of commencing s.c. rhPTH<sup>1-34</sup>. His calcium homeostasis  
112 is carefully managed with a combination of 2 litres of medium chain triglyceride  
113 (MCT) feeds (calcium 35 mg/kg/day) via gastrostomy in conjunction with rhPTH  
114 <sup>1-34</sup>. He also receives regular oesophageal dilatation secondary to oesophageal  
115 strictures and recently underwent fundoplication due to severe  
116 gastroesophageal reflux. He has remained on CSPI for 3 years.

117 **Patient 2 (P2):** This 13 year old boy born to non-consanguineous Caucasian  
118 parents, first presented at the age of 7 years with hypocalcaemic seizures. He  
119 was diagnosed with and treated for hypoparathyroidism with conventional  
120 therapy. He subsequently developed adrenal insufficiency aged 8.4 years, when a  
121 diagnosis of APECED was confirmed with a compound heterozygous mutation in  
122 *AIRE* gene inherited from parents. He also developed intermittent diarrhoea and  
123 hypercalciuria [urine Calcium: Creatinine ratio (Ca:Cr, in mmol/mmol) 1.3] on a  
124 modest dose of 40ng/kg of alphacalcidol. Despite a short trial on thiazide  
125 diuretics, hypercalciuria persisted with serum calcium of 1.9mmol/L. He  
126 subsequently developed renal cysts. In view of intestinal malabsorption, poor  
127 growth and family history of polycystic kidney disease, he was commenced on

128 CSPI and pancreatic enzyme replacement (pancrelipase) therapy at the age of 9  
129 years, on which he has remained for 6 years. He is otherwise on a normal diet,  
130 his serum calcium stabilised and hypercalciuria resolved subsequently.

131 **Patient 3 (P3) and Patient 4 (P4)** are 15 and 19 year old siblings, born to  
132 consanguineous Senegalese parents, with a diagnosis of APECED (homozygous  
133 *AIRE* gene mutation inherited from both parents) and glucose-6-phosphate  
134 dehydrogenase deficiency. P3 presented at 4 years of age with hypocalcaemic  
135 seizures (serum calcium 1.54 mmol/l). Despite being started on high doses of  
136 alphacalcidol (125ng/kg/day) and oral calcium (85mg/kg/day), he had  
137 recurrent hospital admissions with episodes of hypocalcaemia alternating with  
138 hypercalcaemia and hypercalciuria. These problems persisted on a brief trial of  
139 twice daily subcutaneous injections (40µg) of rhPTH<sup>1-34</sup>. Intestinal  
140 malabsorption was confirmed due to elevated faecal calprotectin and low faecal  
141 elastase levels (**Table 1**). High doses of oral calcium resulted in worsening  
142 diarrhoea and the decision to commence CSPI was made. P4 presented at the age  
143 of 11 years in status epilepticus secondary to hypocalcaemia. Following  
144 normalisation of serum calcium with i.v calcium infusions, he was commenced on  
145 CSPI, for the purpose of consistency in the management of the two siblings. He  
146 subsequently developed diarrhoea and malabsorption was confirmed by  
147 elevated faecal calprotectin and low faecal elastase levels (**Table 1**). Primary  
148 adrenal insufficiency was diagnosed in P3 aged 8 years and P4 at the age of 12  
149 years. Both were commenced on treatment with hydrocortisone and  
150 fludrocortisone as well as on pancrelipase. Both siblings required intermittent  
151 intramuscular vitamin D injections, when adequate serum 25 OHD level was not



152 achieved on monthly oral vitamin D supplements (100,000 IU) alone. To our  
153 knowledge, P3 and 4 were the first reported children to be commenced on CSPI  
154 and P3 has remained on it for the longest duration of 8 years.[10] Here we focus  
155 on the initiation of their PTH therapy and highlight the challenges in managing  
156 resistant hypocalcemia in the context of malabsorption.

157 P4 deceased at the age of 19 years, 6.5 years on CSPI treatment, due to acute  
158 adrenal insufficiency from septic shock secondary to a dental abscess.

## 159 **2.2. CSPI dosing and management:**

160 All patients were commenced on a continuous s.c. infusion of rhPTH<sup>1-34</sup>  
161 (teriparatide, European union trade name Forsteo, 20µg/80µl, Lilly France)  
162 delivered via a Medtronic™ pump. The device was attached to the abdomen or  
163 lower back, and parents trained to fill the pump cartridge with teriparatide and  
164 change the cannula and infusion set every 72 hours. The pump was programmed  
165 to deliver a standard basal rate throughout the day and carers trained to either  
166 increase basal rate in increments of 10-20% during illness or self administer a  
167 bolus following discussion with the medical team. Patient 1 was commenced on  
168 an rhPTH<sup>1-34</sup> dose of 0.16µg/kg/day, currently requiring a higher maintenance  
169 dose of 0.3 µg/kg/day. Patient 2 was on an initial dose of 1µg/kg/day, gradually  
170 weaned down to 0.35µg/kg/day. P3 and P4, the very first patients to have  
171 commenced CSPI were started on a higher initial dose of 2.6µg/kg/day and  
172 weaned down to a maintenance dose of 0.5µg/kg/day in P3 (**Table 2**).[10]

173 As this was not a clinical trial, no ethical approval was required. However as CSPI  
174 was commenced in these patients under exceptional circumstances, a

175 multidisciplinary team of experts approved this decision and individual patient  
176 funding requests were obtained from the respective national bodies. Consent  
177 was obtained from parents of all 4 children prior to commencing CSPI treatment  
178 and informed of the desired effects, potential side effects and uncertainties of  
179 long- term safety of treatment with CSPI in children.

### 180 **3. Results:**

181 Serum calcium normalized in all patients within 36-48 hrs of commencing CSPI.  
182 All patients were successfully weaned off alfacalcidol and only P3 remains on a  
183 reduced dose of oral calcium supplements (40 mg/kg/day). A similar effect was  
184 noted with serum phosphate (**Figure 1**). P2 and P4 had elevated Ca:Cr at the  
185 start of CSPI, which normalized in the first year of treatment (**Figure 1**).

186 Episodes of hypercalcaemia and elevated urinary Ca:Cr in P3-4, 3-6 months into  
187 treatment guided rhPTH<sup>1-34</sup> dose reduction (**Figure 1**).

188 P1, P3-4 had normal renal ultrasound scans with no evidence of nephrocalcinosis  
189 pre CSPI and this continues to remain the case on serial renal ultrasounds (1-3  
190 yearly) on treatment. Grade II nephrocalcinosis was detected in P2 in the first  
191 year of treatment but did not progress on subsequent ultrasound evaluations.  
192 Serum creatinine and estimated GFR remains normal for age in all 4 patients on  
193 CSPI.

194 While P1 receives gastrostomy feeds, P2-3 are on a normal diet. Serum calcium  
195 throughout treatment remained correlated to 1,25(OH)<sub>2</sub>D activity in all patients  
196 (**Figure 2**). The 1,25(OH)<sub>2</sub>D concentrations were also elevated in all patients  
197 during therapy, which in the setting of malabsorption indicates that maximum

198 intestinal calcium absorption capacity is limited. As expected, serum calcium did  
199 not correlate with 25 OHD concentrations.

200 All 4 patients had normal age- and sex- specific ALP activity at start of CSPI. A 60  
201 -180 % increase from baseline in ALP activity was noted at 1 month following  
202 start of treatment, which returned to baseline by 6 months on CSPI (**Figure 3**).

203 Lumbar Spine Bone mineral apparent density (LSBMAD) z score of P1 decreased  
204 from +3.0 pre CSPI to +2.8 and +2.1, 1 and 2 years on CSPI treatment,  
205 respectively. P2-4 only had LS BMAD measured 12-18 months on CSPI with z  
206 scores of -0.5, +1.5 and +1 respectively. There were no fractures reported in any  
207 of the patients on CSPI.

208 A substantial reduction in hypocalcaemia-related hospital admissions were  
209 noted from approximately 5 admissions in the year prior to commencing CSPI, to  
210 2 calcium related admissions in the 1<sup>st</sup> year of treatment (**Table 2**).

211 None of the patients have had to discontinue CSPI and reported preference of  
212 CSPI therapy over conventional treatment due to the perceived improvement in  
213 quality of life. P3 has remained on CSPI treatment for 8 years, with no clinically  
214 significant treatment-related adverse events observed.

215 In our cohort, episodes of hypocalcaemia on CSPI were associated with 1)  
216 mechanical obstruction (catheter blockage or kinking) 2) insufficient vitamin D  
217 supplementation 3) systemic illness, which often requires temporary increase in  
218 basal rhPTH<sup>1-34</sup> infusion rates to avoid hypocalcaemia or 4) insufficient oral  
219 calcium intake/ gastrostomy milk feeds and 5) pubertal growth spurt requiring  
220 temporary higher rhPTH<sup>1-34</sup> doses to maintain normocalcemia. In most instances,

221 these episodes occurred secondary to a combination of the above mentioned  
222 factors. No cannula insertion site reactions or infections were recorded in any of  
223 the four patients.

#### 224 **4. Discussion:**

225 Symptomatic hypocalcaemia associated with under treatment is a common  
226 occurrence with conventional treatment of hypoparathyroidism. Large doses of  
227 oral calcium supplements and alfacalcidol can result in worsening diarrhoea as  
228 observed in P1 and P3. In addition, erratic intestinal calcium absorption can lead  
229 to fluctuating serum calcium and hypercalciuria resulting in nephrocalcinosis.  
230 Here we report our experience demonstrating that this challenging subgroup of  
231 patients responds well to CSPI therapy with normalisation and stabilisation of  
232 serum calcium and phosphate resulting in reduced hospital admissions. The  
233 daily rhPTH<sup>1-34</sup> maintenance dose varied (**Table 2**), likely related to the extent of  
234 malabsorption. CSPI is also the preferred mode of rhPTH<sup>1-34</sup> delivery in these  
235 patients since stabilisation is difficult to achieve with twice daily subcutaneous  
236 injections. The fixed rhPTH<sup>1-34</sup> doses available as injections are often several  
237 times higher than the total daily dose needed during CSPI in these children.

238 From our experience, it is advisable to maintain 25OHD levels above 75 nmol/L  
239 in order to provide adequate substrate for PTH-induced conversion of 25OHD  
240 into active calcitriol (1,25(OH)<sub>2</sub>D). In the setting of malabsorption, it is often  
241 challenging to achieve adequate serum 25OHD by oral supplementation alone.  
242 Therefore, regular intramuscular vitamin D administration should be considered  
243 earlier on in the management of these patients as required in P3-4.

244 A significant increase in alkaline phosphatase activity was noted within the first  
245 month of starting CSPI in our patient cohort, in keeping with the increased bone  
246 turnover associated with rhPTH<sup>1-34</sup> treatment in hypoparathyroidism . This  
247 however returned to pre-treatment levels within 6 months of commencing CSPI.  
248 We recognise the lack of consistent 24-hour urine calcium assessments in our  
249 cohort, as well as the challenges in measuring fasting serum calcium due to  
250 overnight feed requirement in P1.

251 All four patients reported preference of CSPI over conventional treatment due to  
252 the ease of use, fewer episodes of symptomatic hypocalcaemia, and substantial  
253 reduction in hospitalisation perceived as an improvement in quality of life.  
254 Future studies will have to carefully assess quality of life, alongside other  
255 functional outcomes and long-term safety monitoring.

256 Use of conventional treatment remains the mainstay in the treatment of  
257 hypoparathyroidism in children, due to the difficulty in dosing with recombinant  
258 parathyroid hormone and the boxed warning regarding the risk of osteosarcoma  
259 noted in rat toxicology studies [11, 12] but in no other animal models [13, 14]. It  
260 is essential to inform parents/ carers of the possible risks of CSPI treatment. The  
261 safety and efficacy of using rhPTH<sup>1-84</sup> as an alternative treatment option needs to  
262 be further explored. [15, 16]

263 In the absence of other new treatment options on the horizon in children, we  
264 propose CSPI as a promising and effective treatment method for children with  
265 hypoparathyroidism associated with intestinal malabsorption. However, we  
266 recommend careful monitoring of serum calcium daily for the first week, thrice  
267 weekly until serum calcium stabilizes in the normal range, later fortnightly,

268 monthly and 3 monthly or as clinically indicated. To avoid overtreatment urinary  
269 calcium excretion and renal ultrasound should be monitored periodically. Until  
270 further evidence becomes available, we recommend bone density scans, total  
271 body less head and lumbar spine [17] every 2 years. CSPI should be managed in  
272 tertiary rare disease centres with the required expertise. Due to the substantially  
273 higher drug costs and uncertainties of long term adverse events, CSPI is  
274 currently restricted to patients unresponsive and/ or having serious  
275 complications of conventional therapy.

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284

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360 **Table 1: Clinical and biochemical characteristics of the cohort**

361 M = male, APECED – Autoimmune polyendocrinopathy candidiasis ectodermal  
362 dystrophy

| Patient                                | P1  | P2   | P3   | P4   |
|--|---|--|--|--|
| Sex                                    | M   | M  | M  | M  |
| Age at diagnosis                       | 8 m   | 7 y  | 4 y  | 11 y   |
| Diagnosis                              | Congenital hypoparathyroidism, sensory-neural deafness, intestinal lymphangectasia, cryptogenic liver disease | APECED   | APECED   | APECED   |
| Gene mutation                          | No abnormality detected   | Compound Heterozygous <i>AIRE</i> gene mutation (c.415 C>T exon 3 + c.967_979del exon 8) | Homozygous <i>AIRE</i> gene mutation (c.958del exon 8) | Homozygous <i>AIRE</i> gene mutation (c.958del exon 8) |
| Coeliac screen                         | negative  | negative   | negative   | negative   |
| Faecal calprotectin activity (µg/L)*   | -   | 16   | 258  | 62   |
| Faecal elastase (µg/g)**               | > 500   | 408  | 82   | 40   |
| Other investigations for malabsorption | Intestinal biopsy confirmed extensive lymphangectasia   | -  | -  | -  |

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364 \* Normal faecal calprotectin activity < 50 µg/L, \*\*normal faecal elastase level >

365 200 µg/g

366 **Table 2: Dosing, metabolic response and duration of Continuous**

367 **Subcutaneous Recombinant PTH (1-34) Infusion (CSPI)**

| Patient | P1 | P2 | P3 | P4 |
|---------|----|----|----|----|
|---------|----|----|----|----|

|   |      |      |     |     |
|---|------|------|-----|-----|
| Age at start of CSPI (years)  | 13   | 9    | 8   | 11  |
| Initiation dose ( $\mu\text{g}/\text{kg}/\text{day}$ )              | 0.16 | 1    | 2.6 | 2.6 |
| Maintenance dose 1yr on CSPI ( $\mu\text{g}/\text{kg}/\text{day}$ ) | 0.3  | 0.35 | 0.5 | 0.5 |
| Serum calcium normalised post CSPI initiation (days)                | 2    | 2    | 2   | 2   |
| Calcium-related hospital admissions, 1 year pre CSPI                | 8    | 3    | 10  | 1   |
| Calcium-related hospital admissions, 1 year on CSPI                 | 2    | 1    | 6   | 1   |
| Duration of CSPI therapy to date (years)                            | 3    | 6.5  | 8   | 6.5 |

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380 **Figure Legends:**

381 **Figure 1:** Normalisation and maintenance of serum calcium and phosphate  
382 [mean (SD)] and urinary calcium: creatinine ratio in the first two years on CSPI.  
383 Shaded area represents normal reference range. High urinary calcium excretion  
384 in P3 and P4, six months into treatment guided rhPTH<sup>1-34</sup> dose reduction.

385 **Figure 2:** Serial measurements of serum calcium correlate significantly with  
386 rhPTH-driven serum 1,25(OH)<sub>2</sub>D concentrations (estimated R<sup>2</sup> value 0.39, 95%  
387 confidence interval, 0.08-0.68 and two sided p value 0.001 using metacor  
388 package [18]). Normal range for 1,25(OH)<sub>2</sub>D (20-62.5pg/mL) [19]. A similar  
389 correlation with serum 25OHD concentrations was not evident in children on  
390 CSPI.

391 **Figure 3:** Effect of CSPI on serum alkaline phosphatase (ALP) activity. The  
392 transient rise in ALP activity in the first month demonstrates the restoration of  
393 bone turnover followed by normalisation of activity by 6 months on treatment.  
394 Note that the ALP assay used for P1 results in ALP levels approximately twice the  
395 ALP activity of assays used for P2-4. At start of therapy, ALP was within the  
396 normal range in all patients.

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