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1 **Seletalisib for activated PI3K δ syndromes: open-label Phase 1b and**
2 **extension studies**

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52 **Running title**

53 Seletalisib for activated PI3K δ syndromes

54

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59

60

61 **Abstract**

62 Mutations in two genes can result in activated phosphatidylinositol 3-kinase delta (PI3K δ)
63 syndrome (APDS), a rare immunodeficiency disease with limited therapeutic options.
64 Seletalisib, a potent, selective PI3K δ inhibitor, was evaluated in patients with APDS1 and
65 APDS2. In the Phase 1b study (EudraCT: 2015-002900-10) patients with genetic and clinical
66 confirmation of APDS1 or APDS2 received 15–25 mg/day seletalisib for 12 weeks. Patients
67 could enter an extension study (EudraCT: 2015-005541). Primary endpoints were safety and
68 tolerability, with exploratory efficacy and immunology endpoints. Seven patients (median
69 age 15 years; APDS1 $n=3$; APDS2 $n=4$) received seletalisib; 5 completed the Phase 1b study.
70 Extension study: 4 patients entered, 1 withdrew consent (Week 24), 3 completed ≥ 84 weeks'
71 treatment. In the Phase 1b study, patients had improved: peripheral lymphadenopathy ($n=2$);
72 lung function ($n=1$); thrombocyte counts ($n=1$); chronic enteropathy ($n=1$). Overall, effects
73 were maintained in the extension. In the Phase 1b study, percentages of transitional B cells
74 decreased, naive B cells increased, and senescent CD8 T cells decreased (human cells);
75 effects were generally maintained in the extension. Seletalisib-related adverse events
76 occurred in 4/7 patients (Phase 1b study: hepatic enzyme increased; dizziness; aphthous
77 ulcer, arthralgia, arthritis, increased appetite, increased weight, restlessness, tendon disorder;
78 potential drug-induced liver injury) and 1/4 patients (extension: aphthous ulcer). Serious
79 adverse events occurred in 3/7 patients (Phase 1b study: hospitalization, colitis and potential
80 drug-induced liver injury) and 1/4 (extension: stomatitis). Patients with APDS receiving
81 seletalisib had improvements in variable clinical and immunological features and a favorable
82 risk-benefit profile was maintained for ≤ 96 weeks.

83 **Key points**

84 Seletalisib, a PI3K δ inhibitor, was evaluated in 7 patients with APDS1 and APDS2.

85 Following treatment, patients had improvements in clinical and immunological features.

86 Seletalisib had a favorable risk-benefit profile in a Phase 1b study up to 96 weeks.

87

88

89

90 **Keywords**

91 Human, immunodeficiency diseases, B cells, primary immunodeficiencies, seletalisib,
92 clinical trial, phosphoinositide 3-kinase delta inhibitor, activated PI3K-delta syndrome

93 **Abbreviations used in this article:** AKT, protein kinase B; ALT, alanine

94 aminotransferase; APDS, activated phosphatidylinositol 3-kinase delta syndrome; AST,

95 aspartate aminotransferase; EudraCT, European Clinical Trials Database; HSCT,

96 hematopoietic stem cell transplantation; IGRT, immunoglobulin replacement therapy;

97 mTOR, mammalian target of rapamycin; pAKT^{S473}, AKT phosphorylated at Ser473;

98 PhGADA, Physician's Global Assessment of Disease Activity; PI3K δ , phosphatidylinositol

99 3-kinase delta; pS6, phospho-S6 ribosomal protein; PtGADA, Patient/Caregiver's Global

100 Assessment of Disease Activity; SAE, serious adverse event; SD, standard deviation; TEAE,

101 treatment-emergent adverse event.

102

103 **Introduction**

104 Activated phosphatidylinositol 3-kinase delta (PI3K δ) syndrome (APDS) is a rare genetic
105 form of primary immunodeficiency with diverse clinical manifestations resulting from
106 overactivity of PI3K δ signaling that affects both B and T cells. This subtype of primary
107 immunodeficiency was first described in 2013 (1,2), and currently over 200 cases of APDS
108 have been identified worldwide (3,4). Patients often present with recurrent respiratory
109 infections in infancy or childhood followed by lymphoproliferation, immune dysregulation
110 phenomena – in particular, autoimmune cytopenia and inflammatory bowel disease –
111 bronchiectasis, and recurrent herpes virus infections, plus an increased risk of lymphoma
112 (1,2,4-6). Abnormally high serum IgM and low serum IgG2 and IgA are commonly reported
113 (1,2,7,8), and the B and T cell profile is characterized by high numbers of transitional B cells,
114 low numbers of memory B cells, and high numbers of senescent T cells (1,2,6-8).

115 Two different genetic causes of APDS have been described, resulting from mutations in
116 the *PIK3CD* (APDS1) and *PIK3RI* genes (APDS2) encoding the catalytic p110 δ subunit and
117 the regulatory p85 α subunit of PI3K δ , respectively (1,2,6,8,9). APDS1 and APDS2 share
118 most clinical features, though neurological and developmental manifestations appear to be
119 predominantly associated with APDS2, and bronchiectasis is more frequent in APDS1
120 (3,4,6,7).

121 As there is no approved targeted APDS treatment, current therapy includes antibiotic
122 prophylaxis and immunoglobulin replacement therapy (IGRT) to manage recurrent infections
123 and hypogammaglobulinemia, and steroids and other immunosuppression drugs for immune
124 dysregulation (4,6,7). Treatment options include the mammalian target of rapamycin (mTOR)
125 inhibitor rapamycin, which acts on the PI3K/protein kinase B (AKT)/mTOR signaling
126 pathway (2,6,7,10), and was recently shown to reduce lymphoproliferation in 26 patients,

127 with lower responses in cytopenia and bowel inflammation (4). A case of a young, female
128 patient with APDS2 has suggested that theophylline treatment could reduce
129 lymphoproliferation, improve immunologic abnormalities and reduce infections requiring
130 antibiotics (11). To date, hematopoietic stem cell transplantation (HSCT) is the only
131 definitive curative option. Two series of patients treated with HSCT reported survival rates of
132 9/11 and 7/9 patients, improvements in most clinical symptoms and significant improvements
133 in humoral immunity (12,13). To address the PI3K δ overactivity, several PI3K δ inhibitors are
134 in development for APDS1, but not APDS2, including leniolisib, for which initial results are
135 encouraging (14), and nemiralisib (15).

136 Seletalisib is a potent and selective oral PI3K δ inhibitor with potential for patients with
137 APDS (16-18). We assessed the ability of seletalisib to block PI3K signaling in T cell blast
138 cultures from patients with APDS1 and APDS2. We subsequently conducted this Phase 1b
139 open-label study (European Clinical Trials Database [EudraCT] Number: 2015-002900-10)
140 followed by an extension study (EudraCT Number: 2015-005541) to assess the safety,
141 tolerability, pharmacokinetics and efficacy of seletalisib in patients with APDS1 and APDS2.

142

143 **Materials and Methods**

144 *Translational research*

145 The effect of seletalisib on the expression of AKT phosphorylated at Ser473 (pAKT^{S473}) was
146 determined by flow cytometry in T cell blast cultures generated from two healthy donors
147 (female aged 55 years and unknown blood bank sample), three patients with APDS1 (female
148 aged 8 years and two males aged 15 and 16 years) and three patients with APDS2 (female
149 aged 6 years and two males aged 5 and 22 years). Details are given in the Supplemental
150 Material.

151 *Clinical studies*

152 Study design

153 The Phase 1b, open-label, multicenter, exploratory study aimed to assess the safety,
154 tolerability, pharmacokinetics and efficacy of seletalisib in patients with APDS. Patients were
155 recruited in four centers in France, Germany, Italy and Spain. This study comprised a
156 screening period of up to 19 days, and a 12-week treatment period. Patients who completed
157 the study could enter an extension study. Screening for the extension took place at Week 12
158 of the Phase 1b study, with treatment re-initiated ≤ 14 days thereafter. Details are supplied in
159 Supplemental Table I.

160 Both studies were conducted in accordance with the Declaration of Helsinki and the
161 protocols were approved by the relevant ethics committees. All patients provided written
162 informed consent prior to entry into each study.

163 Patient population

164 Inclusion criteria: patients (≥ 12 years of age) with a confirmed genetic diagnosis of APDS
165 and currently active clinical manifestations related to APDS were eligible. For the extension

166 study, patients must have completed the Phase 1b study and be expected to gain reasonable
167 benefit from seletalisib treatment.

168 Exclusion criteria: treatment with mTOR inhibitors within the previous 6 weeks or with
169 cyclosporine, history of clinically significant gastrointestinal conditions considered
170 incompatible with the study in the previous 12 months (including inflammatory bowel
171 disease, peptic ulcers, or recurrent colitis with rectal bleeding); positive test for human
172 immunodeficiency virus, hepatitis B or C; severe infection during screening; history of
173 allogeneic bone marrow transplantation; known, latent or high risk of tuberculosis infection;
174 high levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline
175 phosphatase or total bilirubin; or history of, or known risk factors for, liver disease. Patients
176 with no clinical manifestations or only advanced bronchiectasis in the previous 12 months,
177 body weight ≤ 20 kg, current or previous lymphoma, low white blood cells, or a low absolute
178 neutrophil count were excluded. Patients with new significant uncontrolled condition or
179 ongoing drug-related serious adverse events (SAE) from the Phase 1b study were excluded
180 from the extension study.

181 Treatment

182 In the Phase 1b study, all patients received oral seletalisib 15–25 mg once daily (based on
183 body weight ≥ 20 – ≤ 35 kg, 15 mg; >35 – ≤ 50 kg, 20 mg; >50 kg, 25 mg). Dose adjustments
184 could be made up to a maximum of 45 mg once daily.

185 In the extension study, patients initially received the same dose as at the end of the Phase
186 1b study. Dose adjustments were permitted.

187 Endpoints

188 In the Phase 1b study, the primary endpoint was safety and tolerability, including incidence
189 and type of adverse events (see Supplemental Table I for definitions). The secondary
190 endpoint was plasma concentration of seletalisib up to 12 weeks.

191 Exploratory efficacy endpoints included changes in clinical features and disease activity.
192 Details of the exploratory efficacy endpoints, and the exploratory immunology and
193 pharmacodynamic endpoints are given in Supplemental Table I.

194 The extension study had the same endpoints as the Phase 1b study, with the exception of
195 responder status as assessed by the investigator. The results for the extension study are
196 reported after the Phase 1b results.

197 Statistical analysis

198 No formal sample size calculation was performed. Descriptive statistics were presented for
199 safety and efficacy data in both studies. Details and definitions of the analysis sets are
200 provided in Supplemental Table I.

201

202 **Results**

203 *Translational data*

204 Seletalisib potently inhibited PI3K signaling, measured by the reduction in the proportion of
205 pAKT⁺ cells among T cell blasts generated from peripheral blood lymphocytes of patients
206 with APDS1 and APDS2 (Fig. 1 and Supplemental Fig. 1). Inhibition occurred both in the
207 absence and presence of T cell activation induced by anti-CD3 stimulation. The ranges of
208 IC₅₀ values were similar for T cell blasts from patients with APDS1 and APDS2. The
209 geometric mean (range) IC₅₀ was: 8 (3–15) nM for APDS1 and 13 (8–20) nM for APDS2 in
210 the absence of anti-CD3 (in healthy donors the pAKT signal was too low to calculate reliable
211 IC₅₀ data). In the presence of anti-CD3, geometric mean (range) IC₅₀ was: 17 (9–42) nM for
212 healthy donors; 21 (7–50) nM for APDS1; and 28 (20–33) nM for APDS2.

213 *Clinical study results*

214 Patient disposition, demographics and baseline characteristics

215 In the Phase 1b study, seven patients received seletalisib, of whom five completed the study.
216 Two patients discontinued due to treatment-emergent adverse events (TEAEs), one after 16
217 days and one after 42 days of treatment.

218 Four patients entered the extension study and received seletalisib. Three patients
219 completed ≥84 weeks of treatment in the extension study; one patient withdrew consent at
220 Week 36 due to personal reasons.

221 Most patients were adolescents; median age was 15 years in the Phase 1b study and 13.5
222 years in the extension study (range 12–24 years for both studies). Three patients had APDS1
223 and four patients had APDS2; two with APDS1 and two with APDS2 entered the extension
224 study. The patients had heterogeneous disease heterogeneous clinical presentations (Table I)

225 and baseline immunological profiles (Table II). Most patients had CD19⁺ B cell lymphopenia
226 and some had low CD4⁺ T cell counts with corresponding high CD8⁺ T cell counts. Most
227 patients had high IgM and low IgA serum levels.

228 Pharmacokinetics

229 Duration of seletalisib exposure for individual patients is given in Supplemental Fig. 2.

230 In the Phase 1b study, geometric mean plasma trough concentrations of seletalisib over
231 time demonstrated that patient exposure to seletalisib was as expected. Plasma concentrations
232 by individual patient are presented in Fig. 2.

233 Efficacy

234 The majority of patients demonstrated an improvement in at least one clinical feature during
235 the Phase 1b study that persisted over time in patients who went on to participate in the
236 extension study. In peripheral lymphadenopathy assessments, two patients had partial
237 remission of lesions by Week 12; two discontinued before Week 12 and could not be
238 assessed. Change from baseline at Week 12 of the sum of the product of the diameters was –
239 67.6% in one patient and –80.6% in another. Among the four patients assessed for
240 mediastinal and/or intra-abdominal lymphadenopathy, all had stable disease. One patient had
241 an improvement in lung function from baseline at Week 12: increased forced expiratory
242 volume in 1 second (0.76 L; 51.4%); decreased forced vital capacity (–0.41 L; –15.4%);
243 increased forced expiratory volume in 1 second/forced vital capacity ratio (0.44 L; 80.0%);
244 and decreased diffusing capacity of the lung for carbon monoxide
245 (–5.83 mL/min/mmHg; –17.0%). One patient experienced normalization of
246 thrombocytopenia and another had normalization in chronic enteropathy.

247 During the extension study, the reduction in lymphoproliferation was maintained in 1/2
248 patients with data available. Lung function remained stable in the three patients assessed and
249 the normalization of thrombocytopenia in the Phase 1b study was maintained. No patients
250 had colitis during the extension study.

251 At the end of the Phase 1b study, 4/7 patients (57.1%) were classified as responders
252 according to the investigator; 1/7 patients (14.3%) remained stable during the study, without
253 any significant benefit, and was judged as a non-responder by the investigator. Two patients
254 could not be assessed since they discontinued the study before Week 12.

255 During the Phase 1b study, seletalisib treatment was associated with a trend for
256 decreased disease activity measured by the Physician's Global Assessment of Disease
257 Activity (PhGADA) and Patient/Caregiver's Global Assessment of Disease Activity
258 (PtGADA), with a mean (SD) change from baseline at Week 12 of -7.6 (21.8) and -10.1
259 (18.5), respectively. Individual patient data indicated that disease activity varied among
260 patients (Fig. 3).

261 No overall trends in PhGADA and PtGADA were observed during the extension study.
262 Disease activity improved from baseline in two patients (decreased PhGADA and PtGADA)
263 at most visits and worsened in two patients (increased PhGADA and PtGADA) at all visits.

264 Immunology

265 At baseline there was an increased percentage of transitional B cells (CD19⁺/CD21⁺CD24⁺⁺)
266 and a decreased percentage of naïve B cells (CD19⁺/CD21⁺⁺). In the Phase 1b study,
267 following treatment with seletalisib, there was a reduction in transitional B cells
268 (CD19⁺/CD21⁺CD24⁺⁺; Fig. 4A) and a corresponding increase in naïve B cells
269 (CD19⁺/CD21⁺⁺; Fig. 4B). No other B cell subpopulations demonstrated clear changes. There
270 were no substantial changes in CD4⁺ or CD8⁺ T cells during the study; however, small

271 reductions in senescent effector T cells (CD3⁺CD8⁺/CD57⁺) (Fig. 4C) and a trend towards a
272 decrease in non-regulatory CD4⁺ (CD4⁺/CD25⁻CD127⁻ [mean: 51.9% at baseline and 37.2%
273 at Week 12]) and CD8⁺ (CD8⁺/CD25⁻CD127⁻ [mean: 79.1% at baseline and 65.4% at Week
274 12]) T cells (data not shown) were observed. Most patients demonstrated a reduction in
275 phospho-S6 ribosomal protein (pS6) expression in unstimulated CD19⁺ B cells (Fig. 4D) and
276 stimulated CD3⁺ T cells (Fig. 4E). In the extension study, these changes were largely
277 sustained; all patients had decreased pS6 in unstimulated CD19⁺ B cells and stimulated CD3⁺
278 T cells from baseline (Fig. 4).

279 In exploratory analyses of sub-populations of immune cells measured centrally, there
280 were no clear or consistent changes in absolute cell numbers of CD19⁺ B cells, transitional B
281 cells as measured by a different combination of markers (CD19⁺CD10⁺CD27⁻), CD4 T cells
282 and naïve T cells in the Phase 1b and extension studies. CD8 effector memory cells
283 (CD3⁺CD8⁺CD45RA⁻CCR7⁻) had no clear or consistent changes in the Phase 1b study but
284 decreased in the extension study (Supplemental Table II).

285 No clear changes were observed in serum immunoglobulins (IgA, IgD, IgE, IgG, or
286 IgM) following treatment with seletalisib in the Phase 1b study (Supplemental Table III).
287 Two patients in the extension study, both with APDS1, had normalization of elevated IgD
288 and IgM, respectively (Supplemental Table III). It should be noted that all patients had
289 current or previous IGRT.

290 Viral DNA was either not detected by polymerase chain reaction or values were at the
291 lower limit of quantification at baseline. No clinically significant (>1 log) changes in Epstein-
292 Barr virus or cytomegalovirus viral load were observed at Week 12, or during the extension
293 study.

294 Safety and tolerability

295 All patients in the Phase 1b study reported TEAEs during the study (Table III). The most
296 common were infections (6/7 patients); these were mild-to-moderate in severity and not
297 considered to be drug-related. The most frequent individual TEAEs were nasopharyngitis,
298 pyrexia, rhinitis, sinusitis, aphthous ulcer and headache (two patients each). No cases of rash,
299 neutropenia or diarrhea were reported, although one patient with pre-existing chronic
300 enteropathy experienced colitis. Drug-related TEAEs were reported by 4/7 patients who had
301 12 events (Table III); most commonly aphthous ulcer (two events) and increased hepatic
302 enzyme (two events). Two patients reported TEAEs leading to discontinuation: one
303 discontinued due to increased hepatic enzyme, which was considered drug related and a
304 potential drug-induced liver injury. This patient had a history of elevated liver enzymes. The
305 second patient discontinued due to a SAE of potential drug-induced liver injury of moderate
306 intensity, and had no history of elevated liver enzymes or liver damage. In total, three patients
307 reported SAEs. The other SAEs were hospitalization (to enable restarting of seletalisib under
308 observation), which was not considered to be seletalisib related; and severe colitis in another
309 patient (as mentioned above), also not considered to be seletalisib related. There were no
310 deaths during the study period.

311 All patients in the extension study experienced TEAEs. The most frequent category was
312 infections (in all four patients), which were mild to moderate in severity and not considered
313 to be seletalisib related. One patient reported a seletalisib-related TEAE of aphthous ulcer
314 (four events; Table III). One patient reported a SAE of severe stomatitis, which was not
315 considered to be seletalisib related, and resolved after treatment; this patient also had
316 episodes of non-serious aphthous ulcer (mild-to-moderate severity, not considered seletalisib
317 related). No patients discontinued due to TEAEs in the extension study, and there were no
318 deaths.

319 No notable clinically relevant abnormalities in hematology, vital signs, and 12-lead
320 electrocardiogram parameters were observed in the Phase 1b study; urinalysis parameters
321 were generally within normal ranges. TEAEs related to abnormal clinical chemistry were
322 reported by four patients: hyperglycemia, drug-induced liver injury, increased hepatic
323 enzyme (two events), and hypertransaminasemia. In the extension study, one patient reported
324 two TEAEs related to abnormal hematology (decreased hemoglobin and increased C-reactive
325 protein) and one TEAE related to vital signs (decreased weight); not considered related to
326 seletalisib and none were clinically significant.

327 **Discussion**

328 This open-label Phase 1b study of seletalisib in patients with APDS1 or APDS2 demonstrated
329 an acceptable safety profile and exploratory analyses demonstrated positive effects on several
330 clinical manifestations of APDS and immune cell dysfunction. Results from the extension
331 study suggested that seletalisib had a favorable risk-benefit profile in the longer term. A
332 broad range of patients with active APDS were enrolled in the study, which resulted in a
333 population with heterogeneous clinical features, and both types of APDS. Target engagement
334 was demonstrated ex vivo by expression of pAKT⁺ in T cell blasts, and in vivo by reductions
335 from baseline in pS6⁺ B and T cells.

336 Exposure to seletalisib was in line with that in studies with healthy volunteers (18). Five
337 of the seven patients in this study tolerated seletalisib treatment during the Phase 1b study. Of
338 the four patients who entered the extension study, three patients tolerated seletalisib for the
339 duration of the study (a further 84 weeks, or 96 weeks overall), and a fourth patient tolerated
340 seletalisib for a further 36 weeks (48 weeks overall) until they withdrew consent due to
341 personal reasons.

342 The most common category of TEAEs in the phase 1b study and its extension was
343 infections, most frequently nasopharyngitis, rhinitis and sinusitis. This was not unexpected as
344 respiratory infections are a frequent symptom of APDS (1,2,5,6). The patient who
345 discontinued the Phase 1b study due to a TEAE of increased hepatic enzymes had high ALT
346 and AST levels at screening and high ALT levels at baseline, together with a history of
347 elevated liver function enzymes that were thought to be related to APDS. The patient who
348 discontinued due to an SAE of potential drug-induced liver injury had no prior history of
349 abnormal liver function tests, and liver enzymes were within the normal range at enrollment,
350 although an underlying APDS-related liver disease was suspected. These TEAEs suggest that

351 monitoring hepatic enzymes is important when treating patients with PI3K δ inhibitors and
352 caution should be considered when prescribing seletalisib in patients with existing liver
353 abnormalities (19). Among 33 patients with APDS, 30% had liver disturbances; elevation of
354 liver transaminases was more frequent in patients with APDS2 and 4/5 liver biopsies
355 suggested nodular regenerative hyperplasia (19). Seletalisib led to clinical improvement in
356 the majority of patients in the Phase 1b study, notably partial remission of peripheral
357 lymphadenopathy ($n=2$) sustained in the extension study in 1/2 patients with data available,
358 improvements in lung function ($n=1$), normalized thrombocytopenia ($n=1$) and normalized
359 gastrointestinal status ($n=1$). There was a trend for reduction in disease activity after 12
360 weeks of seletalisib treatment, principally in PhGADA, and the investigators noted that
361 subjective improvements were also reported by parents and patients in patient quality of life,
362 concentration at school, and quality of sleep in four patients. The number of patients in the
363 study was too small to draw any conclusions about the comparative efficacy of seletalisib in
364 patients with APDS1 versus APDS2.

365 Changes in immune cell sub-populations suggested an effect towards normalization of
366 immune function with seletalisib treatment, especially of B cell maturation, with a decrease
367 in transitional B cells and a corresponding increase in naïve B cells. Changes in transitional B
368 cells, naïve B cells, non-regulatory CD4⁺ and CD8⁺ T cells and senescent CD8⁺ T cells were
369 sustained with long-term seletalisib treatment. Serum immunoglobulins did not show any
370 clear changes in the Phase 1b study; the high baseline IgD of one patient and the high
371 baseline IgM of another patient normalized during the extension study. The potential
372 restoration of IgG production could not be meaningfully assessed because of continued IGRT
373 during the study. Absence of complete restoration of the humoral compartment may have
374 been due to previous damage to the lymph node architecture, which might suggest that early
375 treatment could increase efficacy.

376 Seletalisib inhibition of PI3K signaling was demonstrated by monitoring pAKT^{S473} in T
377 cell blasts derived from peripheral blood of patients with APDS1 and APDS2. In the Phase
378 1b study, pS6⁺CD19⁺ B cells decreased from baseline to Week 12, indicating that seletalisib
379 inhibited PI3K δ ; this decrease was sustained during the extension study.

380 Other PI3K δ inhibitors are in development for treating APDS. Results are available from
381 a small open-label study of leniolisib (14), and an extension study is in progress (20). The
382 leniolisib study population included patients with APDS1 only, and was generally older (aged
383 17–31 years) than that of the current study. Leniolisib doses increased over the 12-week
384 treatment period, while in the current Phase 1b study, most patients had continuous treatment
385 at the same dose, so the two studies may not be wholly comparable. Both studies observed
386 reductions in lymphadenopathy and normalization of immune cell sub-populations.
387 Additional endpoints examined in the current trial suggest that other clinical manifestations
388 of APDS may also respond to seletalisib, such as the patient with marked improvement in
389 respiratory function. Interestingly, efficacy has been noted in an APDS patient treated with
390 theophylline (11), a drug used in severe asthma that appears to inhibit PI3K δ (21). It remains
391 to be seen whether this represents an advantage over treatment with rapamycin (4). A further
392 Phase 2 study in patients with APDS1 has recently been completed using the inhaled PI3K δ
393 inhibitor nemiralisib (15).

394 A preclinical study has suggested that the use of PI3K δ inhibitors may increase genomic
395 instability (22). This effect should be carefully considered, as such inhibitors would likely be
396 administered to APDS patients for years. Regardless of treatment type, patients should be
397 monitored in the long term for development of lymphoma (2,3,6), as patients with APDS
398 have a predisposition for B cell lymphoma (3,4,6,7,23).

399 Limitations of the studies include the small number of patients treated and the open-label
400 study designs. However, as APDS is a very rare, newly described disease, the numbers
401 recruited were in line with feasibility and with other trials in this patient population (14).

402 To conclude, seletalisib demonstrated an acceptable safety profile and had positive
403 effects on several clinical features and disease activity at the expected drug exposure in
404 patients with APDS1 and APDS2. In addition, seletalisib improved several immune cell
405 abnormalities in both APDS1 and APDS2. A favorable risk-benefit profile was maintained in
406 the extension study for up to 84 weeks of treatment. Seletalisib may be an attractive treatment
407 option for this patient population, but results would need to be replicated in confirmatory
408 studies with long-term follow-up. Additionally, it may be used as a bridge treatment prior to
409 HSCT. Given the high unmet need in this serious disease, treatment with seletalisib may
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451

452 **Dating sharing**

453 Due to the small sample size in this trial, Individual Patient Data cannot be adequately
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456 **References**

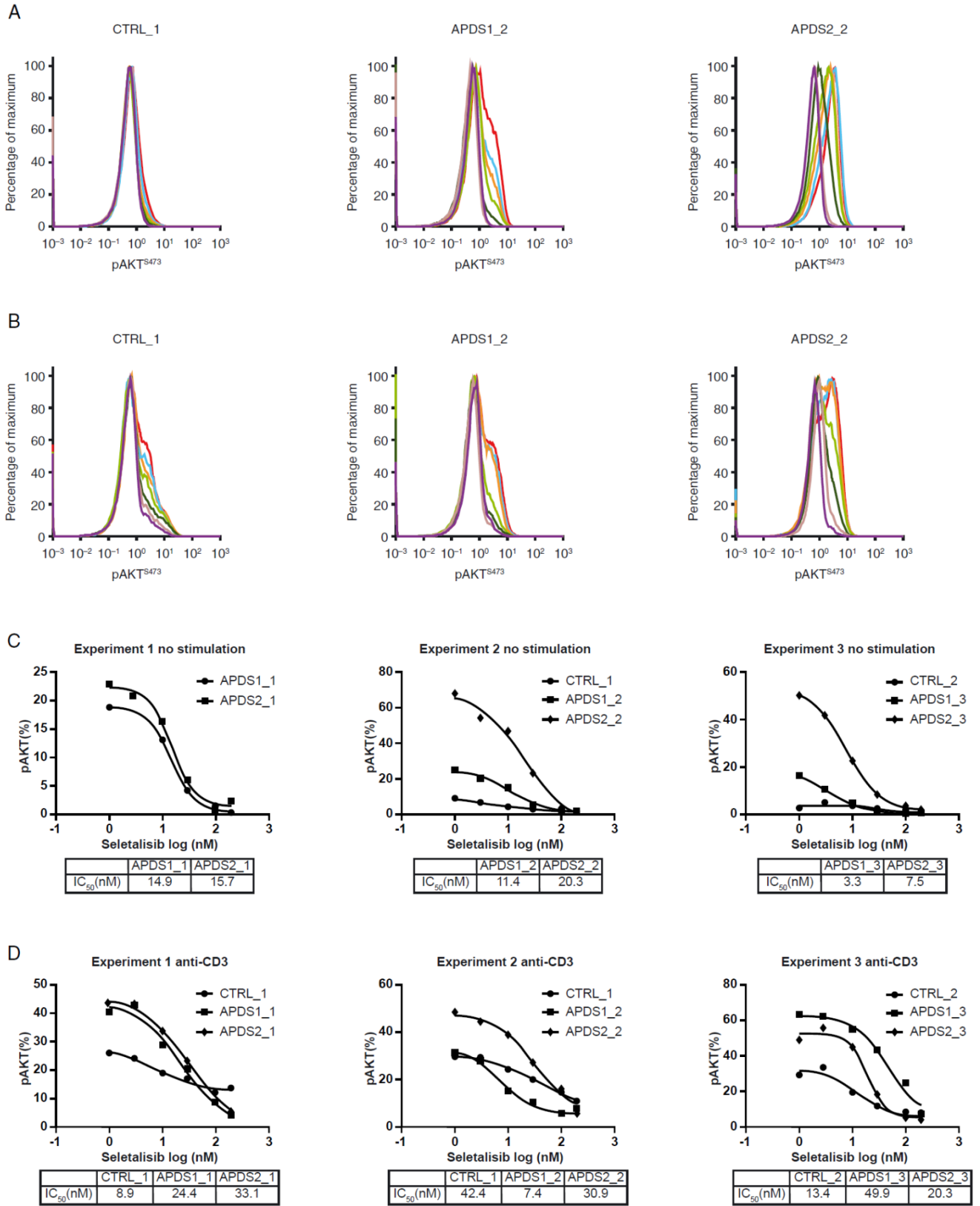
- 457 1. Angulo, I., Vadas, O., Garcon, F., Banham-Hall, E., Plagnol, V., Leahy, T. R.,
458 Baxendale, H., Coulter, T., Curtis, J., Wu, C., Blake-Palmer, K., Perisic, O., Smyth,
459 D., Maes, M., Fiddler, C., Juss, J., Cilliers, D., Markelj, G., Chandra, A., Farmer, G.,
460 Kielkowska, A., Clark, J., Kracker, S., Debre, M., Picard, C., Pellier, I., Jabado, N.,
461 Morris, J. A., Barcenas-Morales, G., Fischer, A., Stephens, L., Hawkins, P., Barrett, J.
462 C., Abinun, M., Clatworthy, M., Durandy, A., Doffinger, R., Chilvers, E. R., Cant, A.
463 J., Kumararatne, D., Okkenhaug, K., Williams, R. L., Condliffe, A. and Nejentsev, S.
464 2013. Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory
465 infection and airway damage. *Science*. 342: 866-871.
- 466 2. Lucas, C. L., Kuehn, H. S., Zhao, F., Niemela, J. E., Deenick, E. K., Palendira, U.,
467 Avery, D. T., Moens, L., Cannons, J. L., Biancalana, M., Stoddard, J., Ouyang, W.,
468 Frucht, D. M., Rao, V. K., Atkinson, T. P., Agharahimi, A., Hussey, A. A., Folio, L.
469 R., Olivier, K. N., Fleisher, T. A., Pittaluga, S., Holland, S. M., Cohen, J. I., Oliveira,
470 J. B., Tangye, S. G., Schwartzberg, P. L., Lenardo, M. J. and Uzel, G. 2014.
471 Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic
472 subunit p110delta result in T cell senescence and human immunodeficiency. *Nat*
473 *Immunol.* 15: 88-97.
- 474 3. Michalovich, D. and Nejentsev, S. 2018. Activated PI3 Kinase Delta Syndrome: From
475 Genetics to Therapy. *Front Immunol.* 9: 369.
- 476 4. Maccari, M. E., Abolhassani, H., Aghamohammadi, A., Aiuti, A., Aleinikova, O.,
477 Bangs, C., Baris, S., Barzaghi, F., Baxendale, H., Buckland, M., Burns, S. O.,
478 Cancrini, C., Cant, A., Cathebras, P., Cavazzana, M., Chandra, A., Conti, F., Coulter,
479 T., Devlin, L. A., Edgar, J. D. M., Faust, S., Fischer, A., Garcia-Prat, M.,
480 Hammarstrom, L., Heeg, M., Jolles, S., Karakoc-Aydiner, E., Kindle, G., Kiykim, A.,
481 Kumararatne, D., Grimbacher, B., Longhurst, H., Mahlaoui, N., Milota, T., Moreira,
482 F., Moshous, D., Mukhina, A., Neth, O., Neven, B., Nieters, A., Olbrich, P., Ozen, A.,
483 Pachlopnik Schmid, J., Picard, C., Prader, S., Rae, W., Reichenbach, J., Rusch, S.,
484 Savic, S., Scarselli, A., Scheible, R., Sediva, A., Sharapova, S. O., Shcherbina, A.,
485 Slatter, M., Soler-Palacin, P., Stanislas, A., Suarez, F., Tucci, F., Uhlmann, A., van
486 Montfrans, J., Warnatz, K., Williams, A. P., Wood, P., Kracker, S., Condliffe, A. M.
487 and Ehl, S. 2018. Disease Evolution and Response to Rapamycin in Activated
488 Phosphoinositide 3-Kinase delta Syndrome: The European Society for
489 Immunodeficiencies-Activated Phosphoinositide 3-Kinase delta Syndrome Registry.
490 *Front Immunol.* 9: 543.
- 491 5. Elgizouli, M., Lowe, D. M., Speckmann, C., Schubert, D., Hulsdunker, J.,
492 Eskandarian, Z., Dudek, A., Schmitt-Graeff, A., Wanders, J., Jorgensen, S. F.,
493 Fevang, B., Salzer, U., Nieters, A., Burns, S. and Grimbacher, B. 2016. Activating
494 PI3Kdelta mutations in a cohort of 669 patients with primary immunodeficiency. *Clin*
495 *Exp Immunol.* 183: 221-229.
- 496 6. Elkaim, E., Neven, B., Bruneau, J., Mitsui-Sekinaka, K., Stanislas, A., Heurtier, L.,
497 Lucas, C. L., Matthews, H., Deau, M. C., Sharapova, S., Curtis, J., Reichenbach, J.,
498 Glastre, C., Parry, D. A., Arumugakani, G., McDermott, E., Kilic, S. S., Yamashita,
499 M., Moshous, D., Lamrini, H., Otremba, B., Gennery, A., Coulter, T., Quinti, I.,

- 500 Stephan, J. L., Lougaris, V., Brodzski, N., Barlogis, V., Asano, T., Galicier, L.,
501 Boutboul, D., Nonoyama, S., Cant, A., Imai, K., Picard, C., Nejentsev, S., Molina, T.
502 J., Lenardo, M., Savic, S., Cavazzana, M., Fischer, A., Durandy, A. and Kracker, S.
503 2016. Clinical and immunologic phenotype associated with activated
504 phosphoinositide 3-kinase delta syndrome 2: A cohort study. *J Allergy Clin Immunol.*
505 138: 210-218.e9.
- 506 7. Coulter, T. I., Chandra, A., Bacon, C. M., Babar, J., Curtis, J., Screaton, N., Goodlad,
507 J. R., Farmer, G., Steele, C. L., Leahy, T. R., Doffinger, R., Baxendale, H.,
508 Bernatoniene, J., Edgar, J. D., Longhurst, H. J., Ehl, S., Speckmann, C., Grimbacher,
509 B., Sediva, A., Milota, T., Faust, S. N., Williams, A. P., Hayman, G., Kucuk, Z. Y.,
510 Hague, R., French, P., Brooker, R., Forsyth, P., Herriot, R., Cancrini, C., Palma, P.,
511 Ariganello, P., Conlon, N., Feighery, C., Gavin, P. J., Jones, A., Imai, K., Ibrahim, M.
512 A., Markelj, G., Abinun, M., Rieux-Laucat, F., Latour, S., Pellier, I., Fischer, A.,
513 Touzot, F., Casanova, J. L., Durandy, A., Burns, S. O., Savic, S., Kumararatne, D. S.,
514 Moshous, D., Kracker, S., Vanhaesebroeck, B., Okkenhaug, K., Picard, C., Nejentsev,
515 S., Condliffe, A. M. and Cant, A. J. 2017. Clinical spectrum and features of activated
516 phosphoinositide 3-kinase delta syndrome: A large patient cohort study. *J Allergy*
517 *Clin Immunol.* 139: 597-606.e4.
- 518 8. Lucas, C. L., Zhang, Y., Venida, A., Wang, Y., Hughes, J., McElwee, J., Butrick, M.,
519 Matthews, H., Price, S., Biancalana, M., Wang, X., Richards, M., Pozos, T., Barlan,
520 I., Ozen, A., Rao, V. K., Su, H. C. and Lenardo, M. J. 2014. Heterozygous splice
521 mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due
522 to dominant activation of PI3K. *J Exp Med.* 211: 2537-2547.
- 523 9. Deau, M. C., Heurtier, L., Frange, P., Suarez, F., Bole-Feysot, C., Nitschke, P.,
524 Cavazzana, M., Picard, C., Durandy, A., Fischer, A. and Kracker, S. 2014. A human
525 immunodeficiency caused by mutations in the PIK3R1 gene. *J Clin Invest.* 124: 3923-
526 3928.
- 527 10. Wang, Y., Wang, W., Liu, L., Hou, J., Ying, W., Hui, X., Zhou, Q., Liu, D., Yao, H.,
528 Sun, J. and Wang, X. 2018. Report of a Chinese Cohort with Activated
529 Phosphoinositide 3-Kinase delta Syndrome. *J Clin Immunol.* 38: 854-863.
- 530 11. Valencic, E., Grasso, A. G., Conversano, E., Lucafo, M., Piscianz, E., Gregori, M.,
531 Conti, F., Cancrini, C. and Tommasini, A. 2018. Theophylline as a precision therapy
532 in a young girl with PIK3R1 immunodeficiency. *J Allergy Clin Immunol Pract.* 6:
533 2165-2167.
- 534 12. Nademi, Z., Slatter, M. A., Dvorak, C. C., Neven, B., Fischer, A., Suarez, F., Booth,
535 C., Rao, K., Laberko, A., Rodina, J., Bertrand, Y., Koltan, S., Debski, R., Flood, T.,
536 Abinun, M., Gennery, A. R., Hambleton, S., Ehl, S. and Cant, A. J. 2017.
537 Hematopoietic stem cell transplant in patients with activated PI3K delta syndrome. *J*
538 *Allergy Clin Immunol.* 139: 1046-1049.
- 539 13. Okano, T., Imai, K., Tsujita, Y., Mitsuiki, N., Yoshida, K., Kamae, C., Honma, K.,
540 Mitsui-Sekinaka, K., Sekinaka, Y., Kato, T., Hanabusa, K., Endo, E., Takashima, T.,
541 Hiroki, H., Yeh, T. W., Tanaka, K., Nagahori, M., Tsuge, I., Bando, Y., Iwasaki, F.,
542 Shikama, Y., Inoue, M., Kimoto, T., Moriguchi, N., Yuza, Y., Kaneko, T., Suzuki, K.,
543 Matsubara, T., Maruo, Y., Kunitsu, T., Waragai, T., Sano, H., Hashimoto, Y., Tasaki,

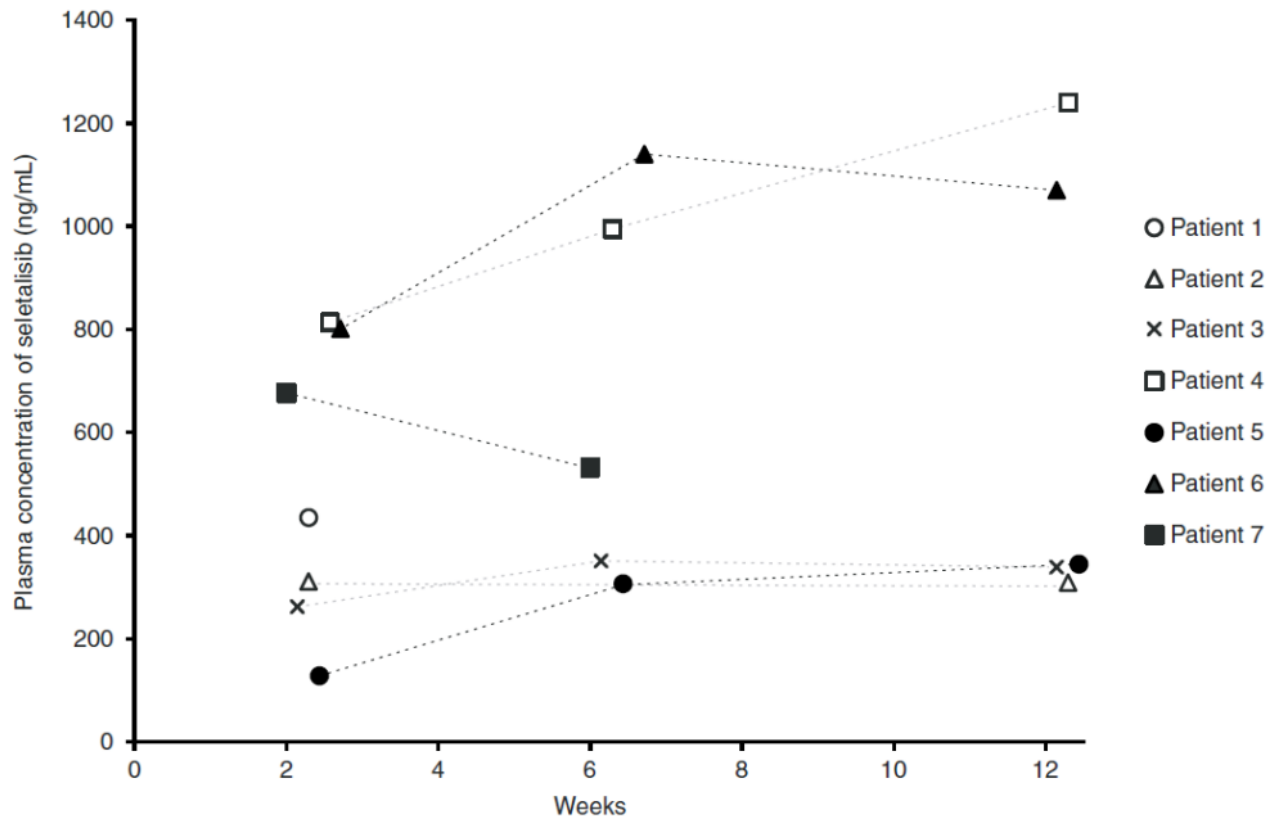
- 544 K., Suzuki, O., Shirakawa, T., Kato, M., Uchiyama, T., Ishimura, M., Tauchi, T.,
545 Yagasaki, H., Jou, S. T., Yu, H. H., Kanegane, H., Kracker, S., Durandy, A., Kojima,
546 D., Muramatsu, H., Wada, T., Inoue, Y., Takada, H., Kojima, S., Ogawa, S., Ohara,
547 O., Nonoyama, S. and Morio, T. 2019. Hematopoietic stem cell transplantation for
548 progressive combined immunodeficiency and lymphoproliferation in patients with
549 activated phosphatidylinositol-3-OH kinase delta syndrome type 1. *J Allergy Clin*
550 *Immunol.* 143: 266-275.
- 551 14. Rao, V. K., Webster, S., Dalm, V., Sediva, A., van Hagen, P. M., Holland, S.,
552 Rosenzweig, S. D., Christ, A. D., Sloth, B., Cabanski, M., Joshi, A. D., de Buck, S.,
553 Doucet, J., Guerini, D., Kalis, C., Pylvaenaenen, I., Soldermann, N., Kashyap, A.,
554 Uzel, G., Lenardo, M. J., Patel, D. D., Lucas, C. L. and Burkhart, C. 2017. Effective
555 "activated PI3Kdelta syndrome"-targeted therapy with the PI3Kdelta inhibitor
556 leniolisib. *Blood.* 130: 2307-2316.
- 557 15. Safety, Pharmacokinetic (PK) and Pharmacodynamic (PD) Study of Repeat Doses of
558 Inhaled GSK2269557 in Patients With APDS/PASLI. 2015. Available from:
559 <https://clinicaltrials.gov/ct2/show/NCT02593539?term=NCT02593539&rank=1>
560 [accessed 20/06/2020].
- 561 16. Allen, R. A., Brookings, D. C., Powell, M. J., Delgado, J., Shuttleworth, L. K.,
562 Merriman, M., Fahy, I. J., Tewari, R., Silva, J. P., Healy, L. J., Davies, G. C. G.,
563 Twomey, B., Cutler, R. M., Kotian, A., Crosby, A., McCluskey, G., Watt, G. F. and
564 Payne, A. 2017. Seletalisib: Characterization of a Novel, Potent, and Selective
565 Inhibitor of PI3Kdelta. *J Pharmacol Exp Ther.* 361: 429-440.
- 566 17. Helmer, E., Nicolas, J. M., Long, J., Roffel, A. F., Jones, E., Chanteux, H., Diaz, N.,
567 Garratt, H. and Bosje, T. 2017. A Dual-Administration Microtracer Technique to
568 Characterize the Absorption, Distribution, Metabolism, and Excretion of [(14)
569 C]Seletalisib (UCB5857) in Healthy Subjects. *J Clin Pharmacol.* 57: 1582-1590.
- 570 18. Helmer, E., Watling, M., Jones, E., Tytgat, D., Jones, M., Allen, R., Payne, A., Koch,
571 A. and Healy, E. 2017. First-in-human studies of seletalisib, an orally bioavailable
572 small-molecule PI3Kdelta inhibitor for the treatment of immune and inflammatory
573 diseases. *Eur J Clin Pharmacol.* 73: 581-591.
- 574 19. Ben-Yakov, G., Kapuria, D., Marko, J., Cho, M. H., Pittaluga, S., Kleiner, D. E., Koh,
575 C., Holland, S., Uzel, G. and Heller, T. 2018. Liver disturbances in activated
576 phosphoinositide 3-kinase delta syndrome. *J Allergy Clin Immunol Pract.* 6: 1763-
577 1765.
- 578 20. Extension to the Study of Efficacy of CDZ173 in Patients With APDS/PASLI. 2016.
579 Available from:
580 [https://clinicaltrials.gov/ct2/show/NCT02859727?term=Extension+to+the+Study+of+](https://clinicaltrials.gov/ct2/show/NCT02859727?term=Extension+to+the+Study+of+Efficacy+of+CDZ173+in+Patients+With+APDS%2FPASLI&rank=1)
581 [Efficacy+of+CDZ173+in+Patients+With+APDS%2FPASLI&rank=1](https://clinicaltrials.gov/ct2/show/NCT02859727?term=Extension+to+the+Study+of+Efficacy+of+CDZ173+in+Patients+With+APDS%2FPASLI&rank=1) [accessed
582 20/06/2020].
- 583 21. Foukas, L. C., Daniele, N., Ktori, C., Anderson, K. E., Jensen, J. and Shepherd, P. R.
584 2002. Direct effects of caffeine and theophylline on p110 delta and other
585 phosphoinositide 3-kinases. Differential effects on lipid kinase and protein kinase
586 activities. *J Biol Chem.* 277: 37124-37130.

- 587 22. Compagno, M., Wang, Q., Pighi, C., Cheong, T. C., Meng, F. L., Poggio, T., Yeap, L.
588 S., Karaca, E., Blasco, R. B., Langellotto, F., Ambrogio, C., Voena, C., Wiestner, A.,
589 Kasar, S. N., Brown, J. R., Sun, J., Wu, C. J., Gostissa, M., Alt, F. W. and Chiarle, R.
590 2017. Phosphatidylinositol 3-kinase delta blockade increases genomic instability in B
591 cells. *Nature*. 542: 489-493.
- 592 23. Durandy, A. and Kracker, S. 2020. Increased activation of PI3 kinase-delta
593 predisposes to B-cell lymphoma. *Blood*. 135: 638-643.
- 594 24. Schatorje, E. J., Gemen, E. F., Driessen, G. J., Leuvenink, J., van Hout, R. W., van
595 der Burg, M. and de Vries, E. 2011. Age-matched reference values for B-lymphocyte
596 subpopulations and CVID classifications in children. *Scand J Immunol*. 74: 502-510.
- 597

598 **FIGURE 1.** Effect of seletalisib on the expression of pAKT^{S473} in T cell blasts.
599 Representative plots showing flow cytometry staining of pAKT^{S473} from (A) healthy donor
600 (CTRL_1), an APDS1 patient (APDS1_2) and an APDS2 patient (APDS2_2) in the absence,
601 and (B) in the presence of T cell activation by anti-CD3 monoclonal antibody, clone OKT3.
602 Doses of seletalisib are 0 nM (red), 1 nM (turquoise), 3 nM (orange), 10 nM (light green), 30
603 nM (dark green), 100 nM (brown), 200 nM (purple). Data from 3 experiments with two
604 different controls and three different APDS1 and APDS2 patients are shown for (C)
605 unstimulated and (D) stimulated T cell blasts. The IC₅₀ values (nM) were calculated as the
606 half-maximal inhibitory concentration by 4-parameter logisitic regression.

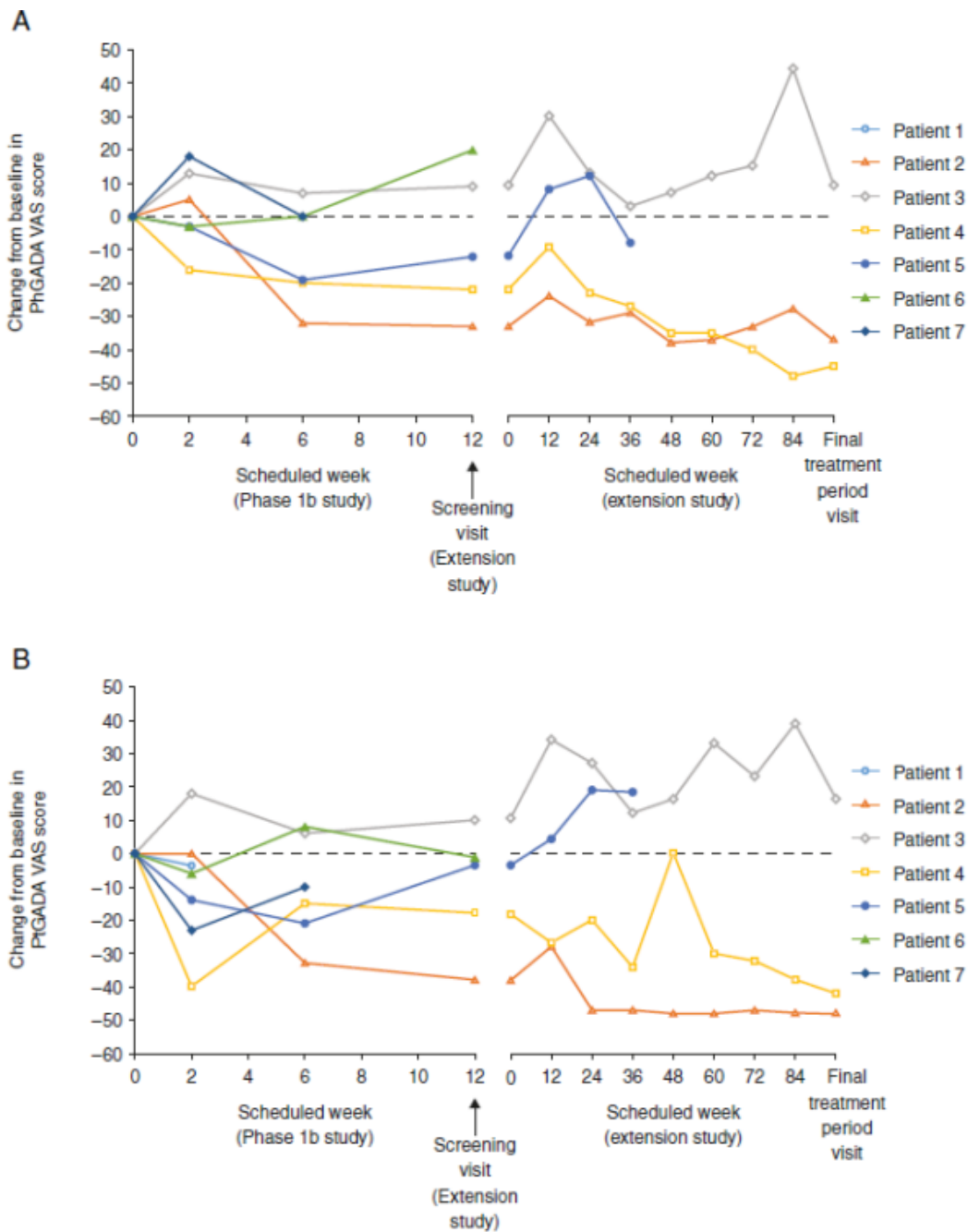


608 **FIGURE 2.** Seletalisib plasma trough concentrations versus time for patients who received
609 seletalisib once daily 15–25 mg based on body weight for 12 weeks. Doses of seletalisib were
610 as follows: Patient 1, 15 mg (stopped seletalisib at Week 2); Patient 2, 25 mg; Patient 3, 20
611 mg; Patient 4, 20 mg, then 15 mg at Week 12; Patient 5, 25 mg; Patient 6, 25 mg before
612 Week 2, then 20 mg to Week 12; Patient 7, 20 mg (stopped seletalisib at Week 6).



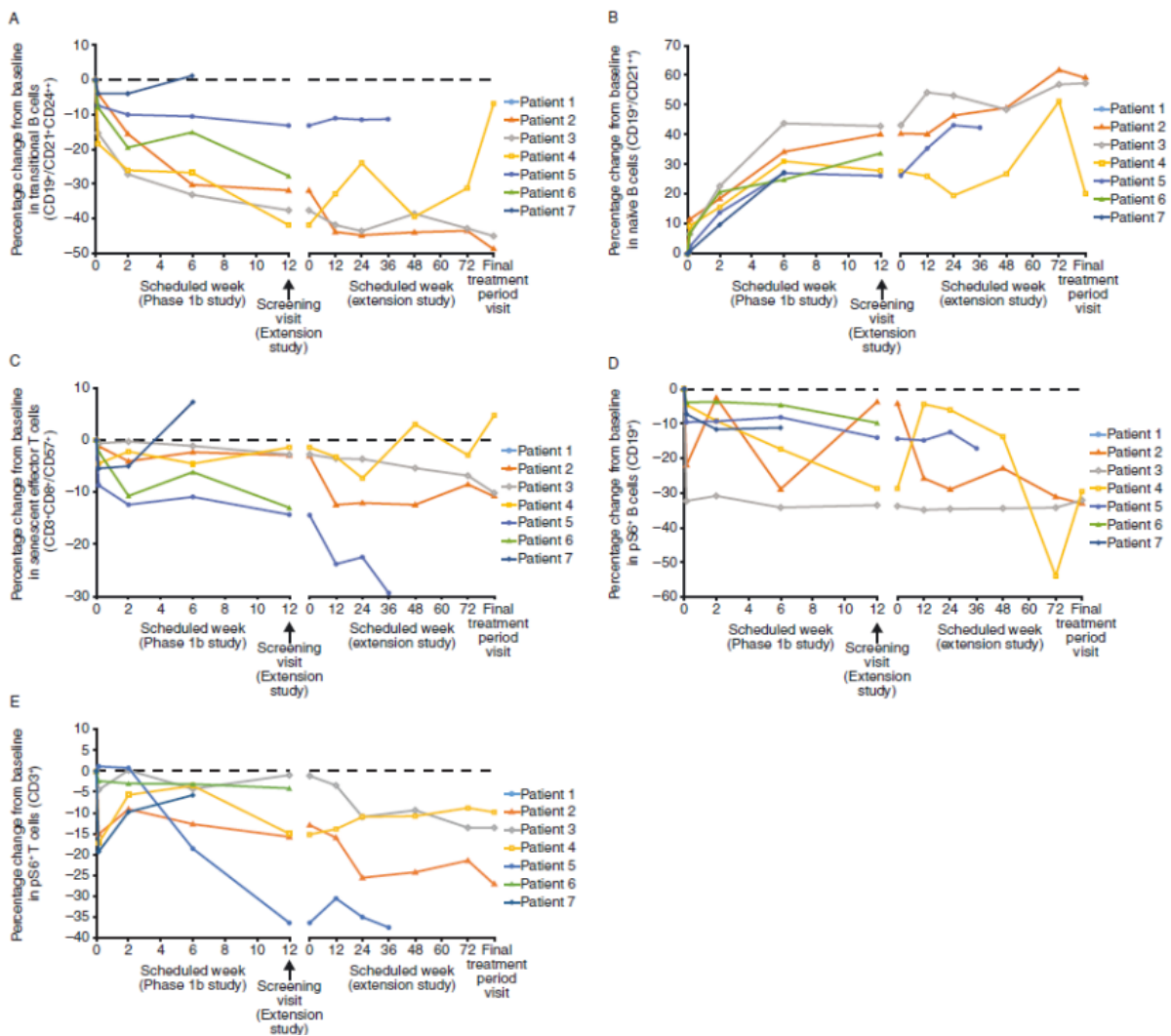
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614 **FIGURE 3.** Changes in disease activity during seletalisib treatment: **(A)** physician’s global
 615 assessment of disease activity (PhGADA) and **(B)** patient/caregiver’s global assessment of
 616 disease activity (PtGADA) (safety set). Patient 1 stopped seletalisib at Week 2; Patient 7
 617 stopped seletalisib at Week 6; Patient 6 did not enter the extension study; and Patient 5
 618 stopped seletalisib at Week 24 of the extension study.



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 620 Reduction in visual analog scale (VAS) indicates improvement in global assessment of
 621 disease activity.

622 **FIGURE 4.** Changes from baseline in immune cell populations during seletalisib treatment:
 623 (A) transitional B cells (CD19⁺/CD21⁺CD24⁺⁺); (B) naïve B cells (CD19⁺/CD21⁺⁺); (C)
 624 senescent effector T cells (CD3⁺CD8⁺/CD57⁺); (D) pS6⁺ B cells (CD19⁺); (E) pS6⁺ T cells
 625 (CD3⁺) (safety set). Patient 1 stopped seletalisib at Week 2 (data not shown); Patient 7
 626 stopped seletalisib at Week 6; Patient 6 did not enter the extension study; and Patient 5
 627 stopped seletalisib at Week 24 of the extension study



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Table I. Patient demographics and baseline characteristics

Patient	Demographics		Disease characteristics		Clinical features, prior and at baseline										Prior/ concomitant treatments		
	Age, years	Sex	Time since APDS diagnosis, years	Disease type (mutation)	Respiratory disorder	Bronchiectasis	Colitis	Thrombocytopenia	Lymphoproliferative disorder	CMV/EBV infection	Chronic enteropathy	Lymphoid hyperplasia of intestine	Failure to thrive	Other clinical features	Antibiotics	IGRT	mTOR inhibitors ^a
1	15	Male	0.9	APDS2 (PIK3R1 ^b)	No	No	No	No	Yes	No	Yes	No	Yes	Melanocytic nevus	Yes	Yes	No
2	15	Male	0.4	APDS2 (PIK3R1 ^b)	Yes	No	Yes	No	Yes ^c	EBV	No	No	No	Splenomegaly, lymphadenopathies, IBD	Yes	Yes	No
3	12	Male	1.6	APDS1 (PIK3CD ^d)	No	Yes	No	No	No	No	No	No	No	Ankle tenderness	Yes	Yes	Yes
4	12	Female	2.2	APDS2 (PIK3R1 ^b)	Yes	Yes	No	No	Yes	EBV	No	No	Yes	Hepato-splenomegaly, lymphadenopathies	Yes	Yes	Yes
5	24	Female	3.5	APDS1 (PIK3CD ^d)	No	No	No	No	No	No	No	No	No	Cholestasis, hemolytic anemia, <i>Herpes zoster</i> , hypothyroidism, portal vein thrombosis, hemangioma, sinusitis	Yes	Yes	Yes
6	17	Male	1.7	APDS2 (PIK3R1 ^b)	No	No	No	No	Yes	CMV	Yes	No	Yes	No	Yes	Yes	No
7	15	Male	3.3	APDS1 (PIK3CD ^d)	No	Yes	Yes	Yes	Yes ^c	CMV	No	Yes	No	Proteinuria, bacterial resistance, digital clubbing, maculopapular rash	Yes	Yes	Yes

633 ^aPrior treatment only; the exclusion criteria did not allow concomitant treatment with mTOR inhibitors. ^bc.1425+1 G>A. ^cAssociated with EBV
634 infection. ^dE1021K. APDS, activated phosphoinositide 3-kinase delta syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; IBD, inflammatory
635 bowel disease; IGRT, immunoglobulin replacement therapy; mTOR, mammalian target of rapamycin.

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Table II. Baseline immunological characteristics

Patient	Lymphocyte counts (x 10 ⁹ /L)	CD19 ⁺ B cells ^a (%) Within the lymphocyte forward scatter/side scatter gate	CD19 ⁺ /CD21 ⁺ CD24 ⁺⁺ transitional B cells (%) Within the B cell CD19 ⁺ gate	CD19 ⁺ /CD21 ⁺⁺ naïve B cells (%) Within the B cell CD19 ⁺ gate	CD3 ⁺ /CD4 ⁺ T cells (%) Within the T cell CD3 ⁺ gate	CD3 ⁺ /CD8 ⁺ T cells (%) Within the T cell CD3 ⁺ gate	CD3 ⁺ CD8 ⁺ /CD57 ⁺ senescent T cells (%) Within the T cell CD3 ⁺ CD8 ⁺ gate	pS6 ⁺ /CD19 ⁺ B cells (%) Within the B cell CD19 ⁺ gate	IgG (g/L)	IgA (g/L)	IgM (g/L)	EBV viral load (copies/mL)
1	5.8 [↑]	ND	ND	ND	ND	ND	ND	ND	3.14 ^b ↓	<0.05↓	<0.05↓	Negative
2	1.2	1.7	51.8	11.5	23.4	54.4	17.8	34.3	6.97 ^b ↓	<0.05↓	3.07 [↑]	<100
3	0.9↓	16.2	47.1	30.5	54.1	31.9	11.2	35.3	14.53 ^b	1.11	1.93	<100
4	1.8	2.1	55.1	7.3	21.5	61.7	60.9	61.6	8.07 ^b	<0.05↓	2.42 [↑]	<100
5	3.3 ^c	3.4	20.0	8.5	57.6	31.4	65.0	19.8	11.52 ^b	0.14↓	17.82 [↑]	<100
6	2.2	1.3	42.6	21.9	20.2	75.4	13.9	12.6	7.55 ^b	<0.05↓	1.51	<100
7	1.2 ^c	4.5	5.3	32.9	19.0	66.2	28.6	16.3	8.65 ^b	<0.05↓	28.2 [↑]	<100

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↓ indicates lower than normal and ↑ indicates higher than normal range (available for lymphocyte counts [normal range 1–4x10⁹/L] and immunoglobulin concentrations only [normal range: IgG 7–16 g/L ; IgA 0.47–2.49 g/L; IgM 0.4–2.3 g/L]).

^aNormal B-lymphocyte range: 7–24% (10–16 years of age) and 4–28% (>16 years of age) (24). ^bUnder Ig replacement therapy. ^cFrom local laboratory blood cell counts – central laboratory blood cell counts were not interpretable due to problems with the samples.

Table III. Incidence of drug-related treatment-emergent adverse events and serious treatment-emergent adverse events during the Phase 1b and the extension studies (safety set)

Patient	Phase 1b study (n = 7)		Extension study (n = 4)	
	Drug-related TEAEs	SAEs	Drug-related TEAEs	SAEs
1	Hepatic enzyme increased (2 events)			
2	Dizziness	Hospitalization		
3	Aphthous ulcer (2 events), arthralgia, arthritis, increased appetite, increased weight, restlessness, tendon disorder		Aphthous ulcer (4 events)	
4				Stomatitis
5				
6		Colitis		
7	Potential drug-induced liver injury ^a	Potential drug-induced liver injury ^a		

^aConsidered related to study drug as assessed by the investigator.

SAE, serious treatment-emergent adverse event; TEAE, treatment-emergent adverse event