

# Safety of a C1-inhibitor concentrate in pregnant women with hereditary angioedema

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## ABSTRACT

**Background:** Increased estrogen levels during pregnancy can exacerbate hereditary angioedema (HAE), yet disease and treatment ramifications remain poorly studied in pregnant women.

**Objective:** Data from the international Berinert Patient Registry were used to evaluate outcomes of pregnancies exposed to plasma-derived, pasteurized, nanofiltered C1-inhibitor concentrate (pnfC1-INH) during routine HAE management.

**Methods:** This observational registry, conducted between 2010 and 2014 at 30 U.S. and 7 European sites, gathered data on 318 subjects and 15,000 pnfC1-INH infusions. Whenever possible, the subjects who used pnfC1-INH during pregnancy were followed up to term to assess neonatal outcomes and to collect maternal adverse events (AE) that occurred up to 1 month after pnfC1-INH administration.

**Results:** The registry data base included 11 pregnancies in 10 subjects who used pnfC1-INH for HAE attack treatment and/or prophylaxis (>261 doses during pregnancy). Eight pregnancies concluded in the birth of a healthy baby. Of the remaining three pregnancies: one was voluntarily terminated at 9 weeks of gestation; a second ended as a first-trimester spontaneous abortion 1 week after the subject's most recent pnfC1-INH infusion and was considered unrelated to pnfC1-INH treatment; and the third occurred in a subject who exited the registry approximately 2 months before her due date, with no further follow up. As assessed for 30 days after each pnfC1-INH infusion, there were no AEs that were considered related to pnfC1-INH therapy.

**Conclusion:** Administration of pnfC1-INH during pregnancy was generally safe and not associated with any treatment-related AEs. In all registry pregnancies followed up to term, the birth of a healthy baby was reported.

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**H**ereditary angioedema (HAE) is a rare autosomal dominant disorder classified into several subtypes based on the underlying genetic deficit and pathophysiology.<sup>1</sup> A majority of patients with HAE present with low levels of C1-INH and abnormal C1-INH function (HAE-C1-INH type I).<sup>1,2</sup> HAE-C1-INH

type II is less common than type I and is associated with normal or high levels of C1-INH and abnormal C1-INH function.<sup>3</sup> A third and less common variant, HAE with normal C1-INH (previously referred to as type III), presents as recurrent edema without urticaria and has been associated with a factor XII mutation in some, but not all, cases.<sup>4–6</sup> Although HAE-C1-INH types I and II demonstrate no sex predominance, HAE with normal C1-INH primarily, but not exclusively, affects women.<sup>4,7</sup>

Pregnancy has been shown to have variable effects on the clinical course of HAE.<sup>8–11</sup> In some patients, the clinical course of HAE may worsen during pregnancy.<sup>7,9,12</sup> Although results of some studies indicate that the frequency of HAE attacks is highest in the first trimester and generally decreases as pregnancy progresses<sup>9,11,13</sup>, an increase in HAE-attack frequency during the third trimester has also been described.<sup>10</sup> It is important to note that the frequency of attacks during previous pregnancies is not a useful predictor of frequency during subsequent pregnancies.<sup>9,11</sup> Pregnancy-related complications, including premature birth, spontaneous abortion, and cesarean delivery, seem to occur at similar rates among women with HAE compared with the general population.<sup>8,11</sup> Expert guidelines generally

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recommend plasma-derived C1-INH (pdC1-INH) replacement therapy during pregnancy as needed for prophylaxis or acute attacks.<sup>2,9,14,15</sup> Androgens can be useful for routine prophylaxis in HAE; however, their use is generally contraindicated during pregnancy due to potential virilizing effects on female fetuses.<sup>9,14</sup> The product labels for marketed pdC1-INH products state that they should be given to pregnant women only if clearly needed.<sup>16,17</sup>

The Berinert Patient Registry ("Registry") was a large, international registry that collected real-world data on the use of the plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate (pnfC1-INH) Berinert (CSL Behring, King of Prussia, PA) in 318 patients with HAE between 2010 and 2014.<sup>18,19</sup> Within the Registry data set, there were a number of women who were exposed to pnfC1-INH during or around the time of pregnancy. The current report was an observational description of these cases, with the intent that these real-world findings would add to the limited data regarding pnfC1-INH use during pregnancy.

## METHODS

### Study Design and Subjects

The methodology of this international (30 U.S. and 7 European sites) observational registry has previously been described in detail.<sup>18,19</sup> The Registry (NCT01108848) enrolled subjects of any age who were using pnfC1-INH for any reason, regardless of product labeling. Enrollment in the Registry was completely voluntary, and data were gathered by investigators who were the patients' HAE caregivers. The following data were evaluated for this analysis of Registry subjects with documented pregnancies that occurred within the Registry data collection period: pnfC1-INH exposure before and during the pregnancy (number of infusions and doses), obstetrical history, pregnancy outcomes, neonatal findings, and adverse events (AEs). Data that encompassed a 1-month period after each administration of pnfC1-INH were reviewed for AEs. All AEs were to be recorded, regardless of suspected causality to pnfC1-INH administration. Causality was evaluated by the investigator at each study site, who also was the treating physician, as either not related, unlikely related, possibly related, probably related, or related. Serious AEs (SAEs) were those that resulted in death, life-threatening circumstances, required hospitalization, or resulted in persistent or significant disability or incapacity. Signs and symptoms of HAE attacks were not reported as AEs, with the exception of HAE attacks that also met SAE criteria, which were dually reported as SAEs and HAE attacks. The Registry was carried out in accordance with local regulatory requirements that pertain to noninterventional studies. The study protocol and master informed consent form were reviewed

and approved by relevant institutional review boards and independent ethics committees. Informed consent in the context of the Registry refers to subjects' willingness to participate with respect to data collection and was obtained for all the subjects. Subject details and registry data remained confidential, in compliance with International Conference on Harmonization guidelines.

### Pregnancy Outcomes

For Registry purposes, pregnancy was not considered an AE unless an associated complication occurred that met the definition of an AE, resulted in spontaneous abortion or stillbirth, or resulted in a congenital anomaly or birth defect in the fetus; any such complication was reported as an SAE. Whenever possible, a pregnancy that occurred in a subject exposed to pnfC1-INH was followed up to term to assess any potential occurrence of congenital anomalies or birth defects. Follow-up information was recorded, including premature termination and the status of the mother and child after delivery.

### Data Analysis

All data were analyzed descriptively.

## RESULTS

The entire Registry population included 318 subjects with HAE who received a combined total of 15,000 pnfC1-INH infusions. The overall findings for the total Registry population are reported elsewhere.<sup>19</sup> The subjects were predominantly female (65.1%) and white (93.7%), and the mean (standard deviation) age was  $38.8 \pm 17.92$  years. Of 207 female subjects, 113 (54.6%) were characterized as being of child-bearing potential.

### Pregnancies

The Registry data set included 11 pregnancies in 10 subjects who were using pnfC1-INH for on-demand treatment of HAE attacks and/or prophylaxis (Table 1). Collectively, nine subjects received a total of 261 pnfC1-INH doses during pregnancy. For one subject (subject 4), reliable pregnancy dates were not available, thus, the exact number of pnfC1-INH infusions received could not be determined, although this subject was using pnfC1-INH regularly as prophylaxis. Subject age at the time that the pregnancy was first documented ranged from 16 to 40 years. One subject (subject 5) had HAE with normal C1-INH; the remaining subjects had HAE-C1-INH type I. All but one of the subjects who became pregnant during Registry participation (subject 6) were white. Of the 11 pregnancies reported, 8 pregnancies resulted in the births of healthy babies without apparent birth defects or congenital abnormalities. Among the remaining three

Table 1 Summary of pregnancies

| Subject No. | Reason for pnfC1-INH Use       | pnfC1-INH Infusions during Pregnancy, no. (dose)                                                                        | Outcome*                                                                                                                           |
|-------------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| 1           | HAE attacks                    | 3 (1500 IU, 18.1–19.4 IU/kg)                                                                                            | Live birth (vaginal delivery; normal birth weight) at 38 wks; no birth defects or congenital anomalies                             |
| 2           | HAE attacks                    | 4 (500–1000 IU, 9.4–19.2 IU/kg)                                                                                         | Spontaneous abortion during the first trimester                                                                                    |
| 3#          | HAE attacks and/or prophylaxis | 11 (5 HAE attacks, 2700–3000 IU, 20.1–23.1 IU/kg; 6 prophylaxis, 1000 IU, 7.4–7.7 IU/kg)                                | Live birth (cesarean delivery; normal birth weight) at 39 wks; no birth defects or congenital anomalies                            |
| 3#          | HAE attacks and/or prophylaxis | 5 (1 HAE attack, 1000 IU, 7.9 IU/kg; 4 prophylaxis, 1000 IU, 7.9–8.0 IU/kg)                                             | Live birth (cesarean delivery; normal birth weight) at 39 wks; no birth defects or congenital anomalies                            |
| 4           | HAE prophylaxis                | Multiple infusions (2000 IU, 19.5–20 IU/kg)§                                                                            | Unknown                                                                                                                            |
| 5           | HAE attacks and/or prophylaxis | None (exposure before pregnancy)                                                                                        | Elective termination (gestational wk 9)                                                                                            |
| 6           | HAE attacks                    | None (exposure before pregnancy)                                                                                        | Live birth (cesarean delivery; normal birth weight) at 36 wks; no birth defects or congenital anomalies                            |
| 7           | HAE attacks and/or prophylaxis | 10, including prophylaxis on delivery date (9 HAE attacks, 1000 IU, 7.4–13.3 IU/kg; 1 prophylaxis, 1000 IU, 13.3 IU/kg) | Live birth (cesarean delivery; normal birth weight) at 40 wks; no birth defects or congenital anomalies                            |
| 8           | HAE attacks and/or prophylaxis | 149 (149 HAE attacks, 500–1500 IU, 6.7–20 IU/kg)                                                                        | Live birth (cesarean delivery; high birth weight¶), gestational age not reported; no birth defects or congenital anomalies         |
| 9           | HAE attacks                    | 60 (500–1000 IU, 8.1–16.1 IU/kg)                                                                                        | Live birth (delivery route and infant weight not reported), gestational age not reported; no birth defects or congenital anomalies |
| 10          | HAE attacks and/or prophylaxis | 19 (1000–1500 IU, 13.3–23.4 IU/kg)                                                                                      | Live birth (cesarean delivery; normal birth weight), gestational age not reported; no birth defects or congenital anomalies        |

pnfC1-INH = Plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate; HAE = hereditary angioedema.

\*Birth weight categories were based on general International Statistical Classification of Diseases and Related Health Problems (ICD-10) cutoffs for “low” (ICD-10; P07.10; <5.51 lb [2499 g]) and for “high” (ICD-10; P08.0; ≥9.92 lb [4500 g]) birth weights; “normal” in this table reflects birth weights of >5.51 and <9.92 lb [>2499 and <4500 g].

#This subject experienced two separate pregnancies during the Registry.

§Reliable dates of pregnancy were not available for this subject, thus an exact number of pnfC1-INH infusions was not known.

¶Birth weight exceeded the specified cutoff for “normal birth weight” category by 0.04 lb (18.1 g).

pregnancies, one pregnancy ended in spontaneous abortion, one subject was lost to follow up, and one pregnancy was electively terminated. Additional details of these cases are provided.

*Subject 2.* Subject 2, whose obstetrical history included one live birth and a previous miscarriage, ex-

perienced a spontaneous abortion (considered an SAE) during the first trimester of pregnancy, which occurred 1 week after the subject’s most-recent pnfC1-INH infusion (1000 U, 18.8 IU/kg). There was no reported evidence of birth defects or adverse findings during prenatal testing. During pregnancy, the subject received four pnfC1-INH infusions for treatment of HAE

Table 2 AEs reported in the Registry subjects who became pregnant during the Registry data collection period\*

| Subject No. | AEs during Pregnancy                                   | AEs Before or After Pregnancy                                      |
|-------------|--------------------------------------------------------|--------------------------------------------------------------------|
| 1           | None reported                                          | None reported                                                      |
| 2           | 2 Abdominal HAE attacks that required hospitalization# | 7 Abdominal HAE attacks that required hospitalization#             |
| 3           | 2 Abdominal HAE attacks that required hospitalization# | Hypertension, gastroesophageal reflux disease, back muscle spasms  |
| 4           | None reported                                          | Altered mental status; moderate chest pain, noncardiac; narcolepsy |
| 5           | No pnfC1-INH infusions during pregnancy                | None reported                                                      |
| 6           | No pnfC1-INH infusions during pregnancy                | None reported                                                      |
| 7           | None reported                                          | None reported                                                      |
| 8           | Common cold                                            | None reported                                                      |
| 9           | None reported                                          | None reported                                                      |
| 10          | Pneumonia, migraine                                    | Fatigue, abdominal influenza                                       |

Registry = Berinert Patient Registry; AE = adverse event; pnfC1-INH = plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate; HAE = hereditary angioedema.

\*None of the events were considered related to pnfC1-INH.

#Signs and symptoms of HAE attacks were not reported as AEs unless they met criteria for a serious AE (resulting in death, resulting in life-threatening circumstances, requiring hospitalization, or resulting in persistent or significant disability or incapacity).

attacks. Concomitant medications reported for this subject included hydromorphone hydrochloride as needed for pain and ondansetron hydrochloride as needed for vomiting; both medications were recorded early in the first trimester. No concomitant medications were being taken at the time of the spontaneous abortion, and no relevant laboratory testing was performed. This event was considered unrelated to treatment with pnfC1-INH.

**Subject 4.** Subject 4 became pregnant during Registry participation and exited the Registry ~2 months before her due date. She subsequently was lost to follow up. A total of 93 pnfC1-INH infusions for HAE prophylaxis were recorded for this patient within the dates estimated to encompass her pregnancy. No AEs or complications were noted before the point at which the subject exited the Registry.

**Subject 5.** Subject 5 voluntarily terminated a pregnancy at gestational week 9. The subject was exposed to pnfC1-INH before pregnancy (48 infusions during the previous year) but did not receive any infusions of pnfC1-INH during pregnancy. Concomitant medications included icatibant (30 mg subcutaneous), which was used every week at least 1–2 times per week throughout pregnancy. Fetal autopsy was requested, but the results were unavailable, and it was unknown if there were any birth defects or congenital anomalies. The elective termination was classified as a non-SAE.

## AEs

Two subjects did not have any pnfC1-INH infusions during pregnancy (pnfC1-INH exposure was before pregnancy). Among the eight subjects who used pnfC1-INH during pregnancy, four reported eight AEs during pregnancy (Table 2), none of which were considered by the investigator to be related to treatment with pnfC1-INH. Four events reported during pregnancy were abdominal HAE classified by convention as SAEs because they required hospitalization. One subject (subject 2) experienced seven similar events (abdominal HAE attacks that required hospitalization) while not pregnant. The spontaneous abortion was also classified as an SAE but also was not considered to be related to pnfC1-INH. No other SAEs occurred among the subjects who experienced pregnancy during Registry participation.

## Changes in pnfC1-INH Usage Patterns During Pregnancy

Among the seven subjects with reliable pregnancy dates and pnfC1-INH exposure during pregnancy, the mean number of pnfC1-INH infusions increased from 2.1 infusions per month when the subjects were not pregnant to 4.0 infusions per month during pregnancy. This corresponded to an increase in monthly pnfC1-INH dose from 1606 IU (outside of pregnancy) to 2717 IU (during pregnancy) per subject. Most of the additional use was due to on-demand use of pnfC1-INH, which increased from a mean of 2.1 infusions per

month while not pregnant to 3.9 infusions per month while pregnant. No detectable increase in prophylactic use of pnfC1-INH during pregnancy was noted. Only one subject in the current analysis had HAE with normal C1-INH (subject 5). In the 9 months before the onset of pregnancy during which data were available, this subject was administered pnfC1-INH on 22 occasions to treat HAE attacks (range, 0 to 7 administrations per month). During the month before pregnancy onset and throughout the 9-week pregnancy, the subject experienced no HAE attacks that warranted treatment with pnfC1-INH. She experienced six HAE attacks that required pnfC1-INH in the month after elective termination of her pregnancy at 9 weeks.

## DISCUSSION

In this multicenter, observational patient registry of pnfC1-INH conducted in the United States and in Europe, 11 pregnancies were recorded in 10 subjects, 8 of which resulted in the births of healthy babies. One pregnancy resulted in a spontaneous abortion during the first trimester. Such early pregnancy loss is not uncommon,<sup>20</sup> and the risk of miscarriage is higher among women with a previous miscarriage,<sup>21</sup> as was the case for this subject. One pregnancy was terminated electively at 9 weeks of age, and the outcome of one pregnancy was unknown because the subject was lost to follow up. In all the pregnancies followed up to term, the birth of a healthy baby was reported. The safety findings were consistent with results of other studies that reported pregnancy outcomes in patients with HAE who received C1-INH. A prospective, observational study conducted between 1995 and 2007 reported outcomes of 35 pregnancies in 22 women with type I HAE.<sup>10</sup> In this study, pnfC1-INH was used to treat HAE attacks during 11 of the 35 pregnancies and was used as long-term prophylaxis during 18 pregnancies.<sup>10</sup> All the subjects were to receive pnfC1-INH as short-term prophylaxis immediately before delivery. There were no AEs associated with pnfC1-INH treatment before, during, or after pregnancy, and no stillbirths or spontaneous or elective abortions occurred. One premature delivery (at 34 weeks) involved twins. Birth weights ranged between 2.0 and 4.3 kg, and no congenital malformations were observed.<sup>10</sup>

In a long-term retrospective survey of 118 pregnancies in 41 women conducted between 1979 and 2009, pnfC1-INH was used to treat HAE attacks during 12 full-term pregnancies in nine women and as long-term prophylaxis during 2 pregnancies; pnfC1-INH was also used as short-term prophylaxis during delivery in nine patients and in six patients before elective abortion.<sup>11</sup> Of the 118 pregnancies that were followed up, nine spontaneous abortions occurred. We noted that the underlying causes of spontaneous abortions were

considered unrelated to previous treatment with pnfC1-INH. All of the babies born to women treated with pnfC1-INH were full-term and healthy. A retrospective analysis of 16 pregnant women with HAE who received pdC1-INH (Cinryze; Viropharma Inc., Exton, PA) reported that 13 pregnancies resulted in healthy neonates, 1 resulted in a spontaneous abortion, and 1 resulted in a stillborn infant with multiple congenital abnormalities.<sup>22</sup> One subject was lost to follow up. The spontaneous abortion and stillborn were considered unrelated to pdC1-INH treatment. Together, these studies supported the safety of pdC1-INH for treating HAE during pregnancy.

Pregnancy has been reported to have a variable impact on the frequency of HAE attacks among women with type I or type II HAE,<sup>8–10</sup> whereas patients with HAE with normal C1-INH and factor XII mutation often experience a marked exacerbation of HAE during pregnancy.<sup>4,7,12,23</sup> Although the Registry was not purposely designed to evaluate the effects of pregnancy on HAE-attack manifestation and treatment, the findings revealed an increase in monthly pnfC1-INH use during pregnancy in seven subjects with type I HAE-C1-INH, which indicated a greater attack burden in this sample of women.

The number of pregnancies delivered *via* cesarean section reported in the Registry was higher than expected. Of eight live births, the delivery mode was vaginal in one subject, cesarean in six subjects (two in same subject), and undocumented in one subject. Cesarean delivery occurs at similar rates among women with HAE and women without HAE.<sup>8,11</sup> In the United States, Germany, and Switzerland (the three countries of residence for Registry subjects who became pregnant), approximately one-third of live births are delivered *via* cesarean section.<sup>24,25</sup> In previously published studies that involved the use of pnfC1-INH (Berinert) during pregnancy, 10 to 32% of the babies were delivered *via* cesarean section, but the percentage of babies exposed to pnfC1-INH during pregnancy (with the exception of short-term prophylaxis during delivery) who were born *via* cesarean section was not reported.<sup>10,11</sup> Among 16 pregnant women with HAE who received pdC1-INH (Cinryze), 2 of 13 live deliveries (15%) were *via* cesarean section.<sup>21</sup> It is not known why a large proportion of deliveries in the current study occurred *via* cesarean section. It is possible that physicians and patients may have thought that they would be better able to control HAE symptoms by performing a cesarean section and administering pnfC1-INH as a preprocedural intervention than by undergoing spontaneous birth.

This was an observational, noninterventional registry, which presented limitations in terms of nonuniform treatment practices and data collection, that was dependent on what was recorded in medical charts. However, the findings provided a real-world evalua-

tion of treatment strategies and outcomes that was not shaped by the confines of a study protocol. The Registry certainly was not designed to rigorously evaluate the use of pnfC1-INH during pregnancy. The number of pregnancies reported in the Registry was small, yet sizable for a rare disease such as HAE. All but one of the subjects who were pregnant during the Registry were white. Another limitation was that no data were collected on breast-feeding practices or on the HAE status of the infants. In previous studies in which women with HAE received pnfC1-INH during pregnancy, ~45 to 50% of offspring were diagnosed with HAE; this rate was expected based on Mendelian inheritance.<sup>10,11</sup>

## CONCLUSION

Administration of C1-INH during pregnancy in this small group of women treated in real-world settings was generally safe and not associated with any treatment-related AEs. The birth of a healthy baby was reported in all the Registry pregnancies followed up to term. Although these data were by no means definitive, when evaluated in conjunction with previous studies, they added further corroborating reassurance about the safety of pnfC1-INH for women with HAE that required intervention during pregnancy or who become pregnant during treatment.

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