處方資訊重點

這些重點並不包括所有安全有效地使用 BEYFORTUS™ 所需的資訊。請參閱BEYFORTUS的完整處方資訊。

BEYFORTUS™(nirsevimab-alip)注射劑，這項肌肉注射首次於 2023 年獲得美國核准使用。

近期主要變更

警告和注意事項 (5.1) 02/2024

適應症和用法

BEYFORTUS是一種呼吸道融合病毒 (RSV) F蛋白導向的融合抑制劑，適用於以下群體，預防因感染RSV所引起的下呼吸道疾病：

- 正值或進入第一個RSV季節時出生的新生兒和嬰兒。(1)
- 在第二個RSV季節仍易患嚴重RSV疾病的24個月以下兒童。(1)

劑量和用藥方法

採用肌肉注射方式給藥。(2.1)

建議劑量：

在正值或進入第一個 RSV 季節時出生的新生兒和嬰兒：

- 如果體重小於5公斤，給藥50毫克。(2.1)
- 如果體重大於或等於5公斤，給藥100毫克。(2.1)

在第二個RSV季節仍然容易患病的兒童：

- 200毫克 (2x100毫克注射劑)。(2.1)

定性及定量組成

注射劑：

- 採用單劑量預充填注射器，每支50毫克/0.5毫升。(3)
- 採用單劑量預充填注射器，每支 100毫克/毫升。(3)

禁忌症

對nirsevimab-alip或其賦形劑有嚴重過敏或全身性過敏反應史的嬰兒和兒童禁用BEYFORTUS。(4)

警告和注意事項

- 包括全身性過敏的過敏反應：BEYFORTUS使用後曾通報過出現嚴重過敏反應。這些反應包括蕁麻疹、呼吸困難、發紺和/或肌肉張力低下。並觀察到與人類免疫球蛋白G1 (IgG1) 單株抗體相關的全身性過敏。如果出現全身性過敏或其他臨床上顯著過敏反應的徵兆和症狀，請立即採取適當的治療。(5.1)

不良反應

最常見的不良反應包括皮疹 (0.9%) 和注射部位不良反應 (0.3%)。(6.1)

如需通報可疑的不良反應，請致電 1-855-239-3678 聯絡 Sanofi，或致電1-800-FDA-1088 聯絡 FDA，或瀏覽網站 www.fda.gov/medwatch.

在特定族群的使用

BEYFORTUS在24個月以上兒童中的安全性和有效性尚未確定。(8.4)

患者諮詢資訊和美國食品藥物管理局 (FDA) 核准的患者標籤見 17

修訂日期：2024年8月

完整的處方資訊：內容*

*未列出完整處方資訊中省略的部分或小節。

完整的處方資訊

1 適應症和用法

BEYFORTUS 適用於以下群體中預防因感染RSV而導致的下呼吸道疾病：

- 正值或進入第一個RSV季節時出生的新生兒和嬰兒。
- 在第二個RSV好發季節仍易罹患嚴重 RSV疾病的24個月以下兒童。

2 劑量和用藥方法

2.1 建議劑量

新生兒和嬰兒：第一個RSV好發季節

正值第一個RSV好發季節時出生的新生兒和嬰兒，自出生時起開始注射BEYFORTUS。對於在RSV好發季節之外出生的新生兒和嬰兒，因考慮BEYFORTUS可提供的保護力持續時間，建議在RSV季節開始之前給嬰兒注射一次BEYFORTUS*[請參閱臨床藥理學(12.2)]*。對於正值或進入第一個RSV季節時出生的新生兒和嬰兒，BEYFORTUS的建議劑量參照體重 (見表 1)，以單劑量肌肉注射(IM)的方式給藥。

表1 第一個RSV好發季節-BEYFORTUS的建議劑量

用藥時的體重	建議劑量
低於 5 公斤	50 毫克，肌肉注射
5 公斤及以上	100 毫克，肌肉注射

在第二個RSV好發季節，仍有高風險罹患嚴重RSV疾病的兒童

對於在第二個 RSV 好發季節仍有高風險罹患嚴重 RSV 疾病的 24 個月以下兒童，無論體重，請參考下方表2中的建議劑量。

表2 第二個RSV好發季節仍有高風險罹患嚴重RSV疾病的兒童-BEYFORTUS的建議劑量

給藥時兒童的年齡	建議劑量
24個月以下*	200毫克，以兩次肌肉注射方式給藥 (2 x 100毫克)

* 無論體重

第一個和第二個RSV好發季節，接受心肺體外循環進行心臟手術的兒童

對於接受心肺體外循環進行心臟手術的兒童，建議在術後兒童情況穩定時盡快給予額外的BEYFORTUS劑量，以確保有足夠的nirsevimab-alip血清濃度。按照建議劑量，肌肉注射BEYFORTUS。

在第一個RSV好發季節：

- 如果手術是在接受BEYFORTUS後的90天內進行，額外劑量應根據接受額外劑量時的體重來決定。按體重給藥請參考表 1。
- 如果接受BEYFORTUS後超過90天，無論體重如何，額外劑量應為50毫克。

第二個RSV好發季節：

- 如果手術是在接受BEYFORTUS後的90天內進行，無論體重如何，額外劑量應為200毫克。
- 如果接受BEYFORTUS 後超過90天，無論體重如何，額外劑量應為100毫克。

2.2 給藥說明

BEYFORTUS必須由醫療人員給藥。

在溶液和容器允許的情況下，給藥前應目視檢查注射藥物是否有顆粒物質和變色。BEYFORTUS是一種透明至乳白色、無色至黃色的溶液。如果液體混濁、變色，或含有大顆粒或外來顆粒物，請勿注射。

如果BEYFORTUS預充填注射器掉落或損壞，藥品外盒的安全封條已損壞，或過了有效期，請勿使用。

本產品分為 50 毫克和 100 毫克預充填注射器。檢查 BEYFORTUS 藥品外盒和預充填注射器上的標籤，確保使用正確的 50 毫克或 100 毫克產品

同時注射兒童疫苗和免疫球蛋白產品

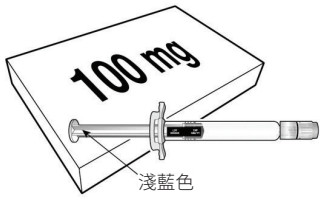
本產品可與兒童疫苗同時注射*[見臨床藥理學(12.3)]*。當與疫苗同時注射時，應使用不同的注射器注射在不同的部位。請勿將本產品與任何疫苗或藥物混合在同一注射器或小瓶中。

目前尚無本產品與其他免疫球蛋白產品同時使用的相關資訊。在同一季節已經接受過本產品的嬰兒不應使用Palivizumab。一旦使用Palivizumb進行預防治療後，該如何使用本產品替代Palivizumb，目前尚無相關資料。本產品可以在第二個RSV好發季節之前或期間給予24個月以下，仍易感染嚴重RSV疾病且在第一個RSV好發季節接受過Palivizumab 的兒童使用*[見不良反應 (6.1) 及臨床研究 (14.3)]*。

單劑量預充填注射器的給藥說明

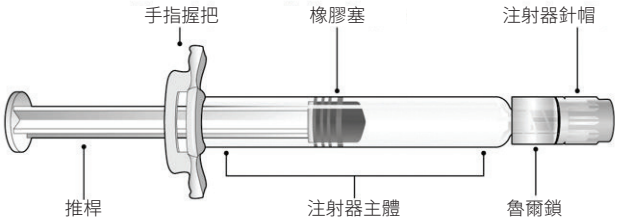
預充填BEYFORTUS 50 毫克（50 毫克/0.5 毫升）帶有紫色推桿的注射器。

預充填BEYFORTUS 100 毫克（100毫克/毫升）帶有淺藍色推桿的注射器。



參考圖 1，預充填注射器組件。

圖 1 Luer Lock射器組件



步驟 1:用一隻手握住 Luer Lock（避免握住推桿或注射器主體），用另一隻手逆時針擰開注射器針帽。

步驟 2:將 Luer Lock 針頭連接到預充注射器上，將針頭順時針輕輕擰到預充注射器上，直到感覺到有輕微的阻力。

步驟 3:用一隻手握住注射器主體，另一隻手小心地將針帽直接拉開。拆卸針帽時，請勿握住推桿，否則橡膠塞可能會移動。請勿觸摸針頭或讓針頭接觸到任何表面。請勿重複裝針頭或將其從注射器中拔出來。

步驟 4:將 BEYFORTUS 預充填注射器中的全部內容物透過肌肉注射法注入到體內，注射部位最好在大腿的前外側。臀部肌肉不應作為注射部位，因為有損傷坐骨神經的風險。

步驟 5:將注射器丟入針具回收桶中。

如果需要分兩次注射，請在不同的注射部位重複步驟 1-5。

3 定性及定量組成

BEYFORTUS是一種透明至乳白色，無色至黃色的溶液，有以下兩種規格：

- **注射劑**：採用單劑量預充填注射器，每支 50毫克/0.5毫升。
- 注射劑：採用單劑量預充填注射器，每支100毫克/毫升。

4 禁忌症

對nirsevimab-alip或其賦形劑有嚴重過敏或全身性過敏反應史的嬰兒和兒童禁用BEYFORTUS*[見警告和注意事項 (5.1) 以及簡介 (11)]*。

5 警告和注意事項

5.1 包括全身性過敏的過敏反應

BEYFORTUS使用後曾通報過出現嚴重過敏反應。這些反應包括蕁麻疹、呼吸困難、發紺和/或肌肉張力低下。並觀察到與人類免疫球蛋白G1（IgG1）單株抗體相關的全身性過敏。如果出現全身性過敏或其他臨床上顯著過敏反應的徵兆和症狀，請立即採取適當的治療。

5.2 用於患有顯著的臨床出血性疾病患者

與任何其他肌肉注射劑一樣，對於患有血小板減少症、凝血功能障礙或正在接受抗凝血藥物治療的嬰兒和兒童，應謹慎使用BEYFORTUS。

6 不良反應

6.1 臨床試驗經驗

由於臨床試驗是在各種不同的條件下進行的，在一種藥物的臨床試驗中觀察到的不良反應率並不能直接與另一種藥物的臨床試驗中的不良反應率進行比較，也可能無法反映實際狀況中觀察到的不良反應率。

在2期和3期臨床試驗（試驗03、04和05）中，共有3,224例兒科受試者按建議劑量接受了BEYFORTUS，包括2,119例出生時胎齡在35週或以上的嬰兒，以及1,105例出生時胎齡不足35週的嬰兒。在試驗05中，共有247例患有早產兒慢性肺部疾病(CLD)或血液動力學上顯著之先天性心臟疾病 (CHD) 的任何胎齡的嬰兒按照建議劑量接種BEYFORTUS。

進入第一個RSV好發季節的新生兒和嬰兒（試驗 03和試驗04）

試驗03是一項在胎齡大於或等於29週且小於35週的早產嬰兒中進行的隨機、雙盲、安慰劑對照試驗。受試者以2:1的比例，透過肌肉注射，隨機接受BEYFORTUS(N=968)或安慰劑 (N=479)。 所有隨機接受 BEYFORTUS 的受試者，無論體重如何，都接受一次單劑量 50 毫克肌肉注射。試驗 03 中的安全資料僅針對接受建議劑量的 BEYFORTUS 組的嬰兒[體重小於 5公斤並接受單劑量50毫克 BEYFORTUS 肌肉注射 (N=572)或安慰劑 (N=288) 的嬰兒]。

試驗04是一項在出生時胎齡大於或等於35週的晚期早產兒和足月兒中進行的3期、隨機、雙盲、安慰劑對照試驗。 試驗 04 將受試者按順序分為兩個組：主要組用於主要藥效分析*[見臨床研究 (14.3)]*和安全性評估，而安全組主要用於安全性評估。 試驗 04 的兩個組中的所有受試者都被納入安全性分析（BEYFORTUS N=1,997，安慰劑 N=997）。試驗 04 中體重小於 5 公斤的受試者接受單劑量 50 毫克的 BEYFORTUS 肌肉注射，體重大於或等於 5 公斤的嬰兒接受單劑量 100 毫克肌肉注射。

在試驗 03 中接受了建議劑量的嬰兒和試驗 04 中的嬰兒被納入BEYFORTUS (N=2,570) 與安慰劑 (N=1,284) 對比的安全性評估。 在隨機分組時，此安全性評估的族群中有22% 的嬰兒出生時胎齡不足 35 週，10% 的嬰兒出生時胎齡大於或等於 35 週且小於 37 週。68% 的受試者胎齡大於或等於 37 週；52% 為男性；57% 為白種人；15% 為黑種人；4% 為美國印第安人/阿拉斯加原住民；4% 為亞洲人；1% 為太平洋島民；19% 為其他或混合種族；30% 為西班牙裔或拉丁裔；73% 來自北半球；53% 體重低於 5 公斤。年齡中位數為 2 個月；65% 小於或等於 3 個月；28% 大於 3 個月至小於或等於 6 個月，7% 大於 6 個月。（關於試驗 03 和 04 中有效族群的簡介，請參考第 14.2 和 14.3 節，臨床研究）。

在這兩項試驗中，嬰兒在研究第 1 天接受了單劑量 BEYFORTUS 或安慰劑肌肉注射，並在給藥後觀察至少 60 分鐘。受試者在給藥後接受了為期 360 天的追蹤以評估安全性。在接受 BEYFORTUS 的受試者中，有 1.2%通 報不良反應；大多數 (97%) 不良反應為輕度到中度。

表3 總結了在試驗03和試驗 04（安全族群）中，接受 BEYFORTUS建議劑量的受試者發生的不良反應。

表3 安全族群*中通報的不良反應發生率高於安慰劑（試驗03和04）

不良反應	BEYFORTUS N=2,570 %	安慰劑 N=1,284 %
皮疹† (給藥後 14 天內發生)	0.9	0.6
注射部位不良反應‡ 給藥後 7 天內發生)	0.3	0

* 安全族群包括所有在試驗03和04中接受了BEYFORTUS建議劑量的受試者：試驗 04 的主要組和安全組；體重小於5公斤，並在試驗 03 中接受了BEYFORTUS 建議劑量（單劑量 50 毫克肌肉注射）的嬰兒。

† 皮疹由以下分組編碼用辭定義：皮疹、斑疹、斑狀丘疹、丘疹。

‡ 注射部位不良反應由以下分組編碼用辭定義：注射部位不良反應、注射部位疼痛、注射部位變硬、注射部位水腫、注射部位腫脹。

出生時胎齡小於35 週的嬰兒和患有早產兒 CLD 或血液動力學上顯著之 CHD 的嬰兒和兒童（試驗 05）

第一個RSV好發季節

試驗05評估BEYFORTUS的安全性，這是一項在嚴重RSV疾病高風險嬰兒中進行的隨機、雙盲、Palivizumab對照多中心試驗。這些受試者按照2:1的比例隨機接受BEYFORTUS (N=614) 或 Palivizumab (N=304) 肌肉注射。接受 BEYFORTUS的614例嬰兒包括 128 例出生時胎齡小於 29 週的早產兒，390 例出生時胎齡為 29 週或以上且小於 35 週的早產兒，以及 96 例出生時胎齡為 35 週或以上的晚期早產兒和足月嬰兒。在第一個 RSV 好發季節進入試驗的嬰兒中，無論胎齡，患有早產兒 CLD 或血液動力學上顯著之 CHD 的嬰兒數量分別為 214 和 103。其中，12 例嬰兒同時患有 CLD 和 CHD。

試驗 05 中體重小於 5 公斤的受試者接受單劑量 50 毫克的 BEYFORTUS 肌肉注射，體重大於或等於 5 公斤的嬰兒接受單劑量 100 毫克肌肉注射。 BEYFORTUS 在研究第 1 天給藥一次，接下來每月肌肉注射安慰劑；Palivizumab則為每月肌肉注射一次，持續 5 個月。所有受試者在給藥後觀察至少60分鐘。受試者在給藥後接受了為期360天的追蹤以評估安全性。

在第一個RSV好發季節接受了BEYFORTUS的試驗05受試者所通報的不良反應與在試驗03和04中接受了BEYFORTUS的受試者所通報的不良反應相似。

第二個 RSV 好發季節（患有早產兒 CLD 和血液動力學上顯著之 CHD 的受試者）

患有早產兒CLD或血液動力學上顯著之CHD的受試者可以繼續參加試驗05，並在第二個RSV好發季節之前接受BEYFORTUS或Palivizumab。所有在第一個RSV好發季節接受了BEYFORTUS的受試者在第二個RSV好發季節也接受了BEYFORTUS(N=180)。在第一個RSV好發季節接受了Palivizumab的受試者，在第二個RSV好發季節再次隨

機接受了BEYFORTUS(N=40)或Palivizumab(N=42)。在第二個RSV好發季節接受了BEYFRTUS(N=220)或Palivizumab(N=42)的CLD或CHD患兒在用藥後150天內的安全資料。在這些兒童的第二個RSV好發季節，BEYFORTUS的安全性與他們在第一個RSV 好發季節觀察到的 BEYFORTUS 的安全性一致。

6.2 上市後經驗

在Beyfortus核准使用後發現以下不良反應。由於這些不良反應是從一個規模不確定的族群中自發性報告得知的，因此難以估計出可信的發生頻率或建立其與藥物暴露之間的因果關係。

過敏反應*[請參閱警告和注意事項(5.1)]*

7 藥物相互作用

7.1 對 RT-PCR 或快速抗原檢測 RSV 診斷試驗的干擾

Nirsevimab-alip不會干擾反轉錄酶聚合酶鏈反應(RT-PCR)或快速抗原探測RSV診斷檢測，這些檢測採用市售抗體標靶向RSV融合(F)蛋白上的抗原位點I、II或IV。當臨床觀察結果與RSV感染一致時，如果免疫學檢測結果為陰性，建議使用基於RT-PCR的檢測方法進行確認。

8 在特定族群中使用

8.1. 懷孕

BEYFORTUS不適用於有懷孕計劃的女性。

8.2 哺乳期

BEYFORTUS不適用於有懷孕計劃的女性。

8.4 兒童用藥

BEYFORTUS的安全性和有效性已被驗證，可用於預防在第一個RSV好發季節或進入該季節時出生的新生兒和嬰兒以及在第二個RSV好發季節仍易患嚴重RSV疾病的24個月以下兒童出現RSV下呼吸道疾病。 BEYFORTUS對該適應症和族群的安全性和藥效在整張標籤中都有討論。

BEYFORTUS用於該適應症有充分和良好的對照研究作證據支援，這些研究針對出生至12個月的新生兒和嬰兒，以及24個月以下兒童開展額外藥物代謝動力學和安全性資料研究*[見不良反應 (6.1)、臨床藥理學 (12.3) 和臨床研究 (14)]*。

BEYFORTUS使用在這個群體中得到以下試驗的支持：

－試驗03：一項隨機、雙盲、安慰劑對照的多中心試驗，針對胎齡大於或等於29週且小於35週的早產兒，預防他們進入第一個RSV好發季節時感染需要醫療照護的中重度RSV下呼吸道感染。

－試驗04：一項隨機、雙盲、安慰劑對照的多中心試驗，針對胎齡大於或等於35週的足月或晚期早產兒，預防他們進入第一個RSV好發季節時感染需要醫療照護的中重度RSV下呼吸道感染。

－試驗05：一項2/3期隨機、雙盲、Palivizumab對照的多中心試驗，針對胎齡小於35週的兒科受試者，以及患有早產兒慢性肺病(CLD)或血液動力學顯著的先天性心臟病(CHD)的嬰兒，這些嬰兒正進入他們的第一或第二個RSV好發季節。

此外，BEYFORTUS在一項開放式、非對照、單劑量試驗(試驗08)中進行了評估，該試驗對象包括100名年齡小於或等於24個月的嬰兒及幼兒，他們在第一或第二個RSV好發季節時接種過BEYFORTUS，並且這些受試者患有各種導致免疫功能受損的潛在疾病或正在接受相關治療。在試驗08中使用BEYFORTUS的安全性與其他BEYFORTUS嬰幼兒試驗的安全性一致*[請參閱臨床藥理學(12.3)]*。

BEYFORTUS 的安全性和有效性尚未在24個月以上的兒童中得到驗證。

10 用藥過量

BEYFORTUS用藥過量的經驗有限。

對於BEYFORTUS用藥過量，尚無具體的治療方法。如果出現用藥過量，應監測個人是否出現不良反應，並斟酌給予症狀治療。

11 簡介

Nirsevimab-alip是一種呼吸道融合病毒F蛋白導向的融合抑制劑，是透過重組DNA技術在中國倉鼠卵巢(CHO) 細胞中生產的人類免疫球蛋白 G1 kappa (IgG1κ) 單株抗體。分子量約為 146.3 kDa。

BEYFORTUS(nirsevimab-alip)注射劑是一種無菌、不含防腐劑、透明至乳白色、無色至黃色的肌肉注射劑。藥品以帶有FluroTec 塗層柱塞的矽化Luer Lock I 型玻璃單劑量預充填注射器提供。

每 0.5 毫升含有 50 毫克 nirsevimab-alip、精胺酸鹽酸鹽(8 毫克)、組胺酸(1.1 毫克)，L-組胺酸鹽酸鹽(1.6 毫克)、聚山梨醇酯 80(0.1 毫克)、蔗糖(21 毫克)和注射用水(《美國藥典》)。pH 值為 6.0。

每1毫升含有100毫克 nirsevimab-alip、精胺酸鹽酸鹽(17毫克)、組胺酸(2.2 毫克)、L-組胺酸鹽酸鹽(3.3 毫克)、聚山梨醇酯 80(0.2 毫克)、蔗糖(41 毫克)和注射用水(《美國藥典》)。pH 值為 6.0。

12 臨床藥理學

12.1 藥物的作用機制

BEYFORTUS 是一種具有抗RSV活性的單株抗體*[見微生物學 (12.4)]*。

12.2 藥效學

血清nirsevimab-alip AUC(基於基準線時的清除率)高於 12.8 毫克*天/毫升與 MA RSV LRTI 的較低發生率呈正相關。成人在肌肉注射nirsevimab-alip後8小時，血清中 RSV 中和抗體值約為基準線的4倍，並在第6天達到最高值。BEYFORTUS的安全性和有效性尚未在成人中得到驗證。

<u>保護力持續時間</u>

根據臨床資料，單劑量BEYFORTUS提供的保護力持續時間可延長至 5 個月。

12.3 藥物動力學

在兒科受試者中，單次肌肉注射給藥的劑量從25毫克(最低核准建議劑量的0.5倍)到200毫克不等，nirsevimab-alip的PK與劑量成正比。按照建議劑量，在第一個RSV好發季節或進入第一個 RSV 好發季節時出生新生兒和嬰兒(試驗 03 和04)，以及在第一個RSV好發季節出生的胎齡小於 35 週(包括胎齡小於 29 週)的新生兒和嬰兒(試驗 05)，以及在第一個和第二個 RSV 好發季節患有 CLD 或 CHD 的 24 月齡以下的兒科受試者(試驗 05)，nirsevimab-alip的血清暴露量是相似的。

<u>吸收</u>

nirsevimab-alip的絕對生物可用率預計為84%，達到最大濃度的中位時間(範圍)為6 (1, 28) 天。

<u>分佈</u>

對於體重5公斤的嬰兒，nirsevimab-alip的總分佈容積預計為477毫升。

<u>排除</u>

對於體重5公斤的嬰兒，nirsevimab-alip的末端排除半衰期約為71天，清除率預計為3.42 毫升/天。

代謝

Nirsevimab-alip透過異化作用代謝分解為小分子胜肽。

<u>特殊族群</u>

根據對種族或嚴重RSV疾病的易感性(即CLD、CHD、胎齡＜29週或免疫功能處於低下狀態)的觀察，nirsevimab-alip的藥物動力學沒有臨床顯著差異。預計腎臟或肝臟損傷對nirsevimab-alip藥物動力學不會產生影響。

試驗08中nirsevimab-alip的平均和中位血清濃度低於試驗04和05中的濃度。然而，試驗08中的暴露量仍在試驗03、04和05中對接受建議劑量的受試者顯示為有效範圍內。*[請參閱兒童用藥(8.4)]*。

<u>藥物交互作用研究</u>

尚未對BEYFORTUS進行正式的藥物交互作用研究。根據對單株抗體作用機制的理解，預測nirsevimab-alip不會成為細胞色素P450 酶或轉運系統的基質、抑制劑或誘導劑。

臨床研究

疫苗：BEYFORTUS與疫苗同時接種的經驗有限。在臨床試驗中，當BEYFORTUS與例行性兒童疫苗同時接種時，其安全性和反應原性與單獨接種兒童疫苗的結果相似。

12.4 微生物學

藥物作用機制

Nirsevimab-alip是一種重組人類 IgG1κ 單株抗體，透過標靶向RSV F融合前的蛋白結構提供被動免疫。Nirsevimab-alip具有長效性，因為它在Fc區有三個胺基酸置換(YTE)，增加了與新生兒 Fc 受體的結合，從而延長了血清半衰期。Nirsevimab-alip 與前融合蛋白上抗原位點Ø的一個保守表位結合，RSV 亞型 A 和 B 株的解離常數分別為 K_D = 0.12 nM 和 K_D= 1.22 nM。Nirsevimab-alip 透過抑制病毒和細胞膜融合以及病毒進入所需的 F 蛋白的構象變化來中和 RSV。

<u>抗病毒活性</u>

利用培養的 Hep-2 細胞，在濃度反應模型中測定了 nirsevimab-alip 對 RSV 的細胞培養中和活性。Nirsevimab-alip 中和了 2003 年至 2017 年間從全球各地收集的臨床 RSV 分離株，對 RSV A 的中位 EC50 值為 21 pM (3.2 ng/mL) (n=70；範圍為 3 pM[0.48 ng/mL] 至 100 pM[15 ng/mL])，對 RSV B 的 EC_{50} 值為 19 pM (2.9 ng/mL) (n=49；範圍為 2 pM [0.3 ng/mL] 至 398 pM[59.7 ng/mL])。

<u>抗病毒性</u>

在細胞培養中

在有nirsevimab-alip存在的情況下，在RSV A2和B9320株的細胞培養中進行三次傳代後選擇了逃逸變異株。與參考菌株相比，重組RSV A變異株對nirsevimab-alip的敏感性降低，其中包括攜帶替代物 N67I+N208Y(降低 103 倍) 的重組 RSV A 變異株。對 nirsevimab-alip 敏感性降低的重組 RSV B變異株包括攜帶替代物 N208D(＞90,000 倍變化)、N208S(＞24,000 倍變化)、K68N+N201S(＞13,000倍變化)和 K68N+N208S(＞90,000倍變化)的變異株。在中和逃逸變異株中發現的所有耐藥性相關的替代物都位於 nirsevimab-alip 結合位點(62-69 和 196-212 個氨基酸)，並顯示降低了與 RSV F 蛋白的結合親和力。

在監視試驗中

在1956-2014 年收集的分離株中，沒有觀察到 RSV A 對 nirsevimab-alip 的敏感性出現大幅降低的多態性，RSV B 也很少 (<1%) 觀察到降低，包括 K65Q+K68N (1,239 倍變化)、K65Q+S211N (36 倍變化) 和 L203I (3005 倍變化) 等替代物。在前瞻性、觀察性的全球分子流行病學研究 (OUTSMART-RSV 和 INFORM-RSV) 中，RSV F 蛋白序列的遺傳多樣性仍然很低 (RSV A 和 RSV B 的大多數氨基酸＞99%，表現保守)。攜帶已知的 nirsevimab-alip 耐藥性相關替代物的變異株一直很罕見 (<1%)，包括 RSV B 的替代物K68Q (>369 倍變化) 、N201T (>406 倍變化) 和 N201T+I206M+Q209R (>418 倍變化)。觀察到的易感性降低的變異株包括 RSV A 的替代物 K68E (13 倍變化)、K68N (5倍變化)和 S275F (6 倍變化)，以及 RSV B 的替代物 K68N (30 倍變化)、K68Q+I206M+Q209R (46 倍變化)、N201S (127 倍變化) 和 N201S+I206M+Q209R (17倍變化)。易感性降低的臨床意義尚不清楚。2015 年到 2021 年間，在 RSV A 的所有位點和 RSV B 25 個位點中的 22 個位點上，nirsevimab-alip 結合位點的大多數胺基酸殘基都高度保守(＞99%)。自 2017 年以來，在 RSV B 中普遍存在的 nirsevimab-alip 結合位點的共存替代物 I206M+Q209R 並未降低對 nirsevimab-alip 的敏感性(＜5 倍變化)。使患病率增加的替代物 S211N (無論是單獨存在還是與 I206M+Q209R 共同存在) 也保留了對 nirsevimab-alip 的敏感性。

在臨床試驗中

在試驗04、試驗05和試驗08中，在任何採樣時間點均未發現頻率≥25%的已知耐藥性相關的替代物。新的替代表型測試正在進行。
在試驗 03（接受單劑量 50 毫克 BEYFORTUS 的受試者）中，與任何病例定義相對應的 40 例 RSV 感染受試者中有 2 例攜帶含 nirsevimab-alip 耐藥性相關替代物的變異株。這兩例受試者接受的 nirsevimab-alip 低於建議劑量，並且攜帶含共存替代物 I64T + K68E +I206M + Q209R 或替代物 N208S 的 RSV B 變異株。替代物 I64T、K68E 和 N208S 均降低了對 nirsevimab-alip 的敏感性（倍數變化分別為 >496、>283 和 >387）。
在試驗 04中，在一例接受 BEYFORTUS 治療至第 150 天的受試者中，檢測到一種攜帶結合位點替代物 L204S（無表型資料，頻率≥25%）的 RSV B 變異株，同時還存在替代物 I206M+Q209R+S211N（<5 倍變化）。在一例接受 BEYFORTUS 治療到第 150 天的受試者中，觀察到頻率 <25% 的含替代物 I64T+K68E（>280 倍變化）和N208I（>600 倍變化）替代物的 RSV B 變異株。此外，在第150天後，在一名受試者中，觀察到頻率為9%的攜帶替代物N201D的RSV B變異株（無表型數據）。
交叉耐藥性
有限的資料顯示，對nirsevimab-alip耐藥的變異株可能對Palivizumab具有交叉耐藥性。Palivizumab對試驗03和試驗04中發現的耐藥性相關替代物保有完全中和的效力。在分子流行病學研究中發現，nirsevimab-alip對帶有Palivizumab耐藥性相關替代物的重組RSV保持活性，而在Palivizumab的中和逃逸變異株中，替代物S275F使敏感性降低了6倍。

12.6 免疫誘發性

觀察到的抗藥抗體(ADA)的發生率高度依賴於測定的敏感度和特異性。測定方法的差異使得下文所述研究中ADA的發生率與其他研究中ADA的發生率無法進行有意義的比較，包括 nirsevimab-alip 或其他nirsevimab產品的研究。
在試驗 03中接受pnirsevimab-alip建議劑量的 572 例受試者中，3.3% (16/492) 的受試者在第 361 天出現 ADA 陽性。在這16例ADA陽性受試者中，94% (15/16) 有針對 YTE 的 ADA，抗 nirsevimab-alip 中和抗體檢測無受試者呈陽性。
在試驗04中，5%(95/1778)的受試者在第361天出現ADA陽性，其中21%(20/95)有中和抗體，77%(73/95)有抗YTE 的ADA。
在試驗05中，在第一個 RSV 好發季節進入試驗的受試者中，在第361天時，6% (32/538) 的受試者出現 ADA 陽性。在32例ADA陽性受試者中，6% (2/32) 有抗 nirsevimab-alip 中和抗體，91%(29/32)有抗 YTE 替代物的抗體。在連續兩個RSV好發季節接受nirsevimab-alip治療的180名受試者中，在第二個好發季節的第361天時，9%(13/144)的受試者出現ADA陽性。在13例ADA陽性受試者中，8%(1/13)有抗nirsevimab-alip中和抗體，62% (8/13)有抗YTE的抗體。
在試驗03、04、05和08中，直到第 151 天，仍無法確定 ADA 對 nirsevimab-alip 血清濃度的影響。在第 361 天時，對於接受了BEYFORTUS並產生了抗 nirsevimab-alip 抗體的受試者，抗體的受試者相比，降低40%至60%）。由於臨床試驗中ADA和MA RSV LRTI的發生率較低，因此ADA對BEYFORTUS有效性的影響尚不清楚。

13 非臨床毒理學

13.1 致癌性，致突變性，生殖能力損害

尚未對BEYFORTUS進行致癌性、致突變性和生殖力毒性研究。

14 臨床研究

14.1 臨床試驗簡介

表4 總結BEYFORTUS使用在足月兒和早產兒中的有效性和安全性評估。

表4 使用 BEYFORTUS預防 MA RSV LRTI 的試驗

試驗	族群	研究組
D5290C00003 （試驗 03） NCT02878330	進入第一個 RSV 季節時，出生胎齡 ≥29 週且 <35 週的嬰兒	BEYFORTUS (N=969)* 安慰劑 (N=484)
D5290C00004 （試驗 04） NCT03979313	進入第一個 RSV 季節時，出生胎齡 ≥35 週的嬰兒	**主要組†：** BEYFORTUS (N=994) 安慰劑 (N=496) **安全組‡：** BEYFORTUS (N=1,015) 安慰劑 (N=507)
D5290C00005 （試驗 05） NCT03959488	進入第一個 RSV 季節時，出生胎齡 <35 週的嬰兒和出生時患有 CLD 或 CHD 的嬰兒 進入第二個 RSV 季節時，僅患有 CLD 或 CHD 的嬰兒	**第一個RSV季節：** BEYFORTUS (N=616) Palivizumab (N=304) **第二個RSV季節：** BEYFORTUS (N=220) Palivizumab (N=42)

GA 胎齡；CLD 慢性肺部疾病；CHD血液動力學上顯著之先天性心臟疾病

* 試驗 03 中的所有受試者均被納入療效分析。試驗 03 中的所有受試者，無論體重，均接受50 毫克的 BEYFORTUS 肌肉注射。正值或進入第一個 RSV 好發季節時出生的新生兒和嬰兒，按照體重 <5 公斤和 ≥5 公斤，BEYFORTUS 的建議劑量分別為單次肌肉注射 50 毫克和 100 毫克*[見劑量和用藥方法 (2.1)]*。
† 試驗04依據主要組的受試者進行主要療效分析。關於試驗04的安全族群*[見不良反應 (6.1)]*。
‡ 試驗 04 的安全性分析包括主要組和安全組*[見不良反應 (6.1)]*。

14.2 預防出生時胎齡 ≥29 週且 <35 週的嬰兒發生 MA RSV LRTI（試驗03）

試驗03是一項在胎齡大於或等於29週且小於35週的早產兒中進行的隨機、雙盲、安慰劑對照的多中心試驗，用於預防 MA RSV LRTI。這些受試者以 2:1 的比例，透過肌肉注射，隨機接受BEYFORTUS(N=969或安慰劑(N=484)。所有BEYFORTUS組的受試者，無論體重如何，均透過肌肉注射接受 50 毫克的 BEYFORTUS。新生兒和出生在或出生時進入第一個 RSV 季節的嬰兒，按照體重小於 5 公斤和≥5 公斤，BEYFORTUS的建議劑量分別為肌肉注射 50 毫克或 100 毫克*[見用法和給藥途徑 (2.1)]*。
隨機分組時，20% 的受試者胎齡大於/等於 29 週且小於 32 週；80% 的胎齡大於或等於32週並小於35週；52%為男性；72%為白種人；18%為黑種人；1%為 亞洲人；1%為太平洋島民，8%為其他或混合種族；22%為西班牙裔或拉丁裔；68%來自北半球。年齡中位數為 2.8 個月（範圍：0.1 至 11.9個月）；53% 小於或等於 3 個月；33% 大於 3 個月至小於/等於 6 個月，14% 大於 6 個月。
主要療效指標為經RT-PCR 確認為RSV所引起的MA RSV LRTI的發生率，在給藥後150天內主要表現為支氣管炎或肺炎醫療服務(MA)包括所有醫療照護提供者訪視，如醫生辦公室、緊急護理、急診室就診和住院。LRTI引發的症狀包括鼾聲、囉音、劈啪聲或哮鳴；並且包括以下至少一種臨床嚴重惡化的徵兆：呼吸頻率增加、低氧血症、急性缺氧或呼吸衰竭、新發呼吸暫停、鼻翼搧動、胸部凹陷、呻吟聲或因呼吸窘迫而脫水。需要住院治療的RSV LRTI的發生率是預先指定的次要療效指標。因RSV住院的定義為因LRTI住院且RSV 檢測呈陽性。
表5 顯示試驗03的主要療效結果。

表5 出生時≥29 週至＜35 週的嬰兒在給藥後 150天 內 MA RSV LRTI 的發生率（試驗 03）

	N	發生率 % (n)	療效* (95% CI)
BEYFORTUS	969	2.6 % (25)	70.1 % (52.3, 81.2) †‡
安慰劑	484	9.5 % (46)	

* 對MA RSV LRTI的療效為對照安慰劑時相對風險降低，並根據隨機分組時的年齡及測試區域（南北半球）校正
† P 值=<0.001。
‡ 在對試驗03中基準線時體重<5公斤且接受了BEYFORTUS建議劑量的所有隨機分組嬰兒進行事後分析，與安慰劑相比，對MA RSV LRTI的療效為相對風險降低 86.2% (95% CI 68.0, 94.0)；與安慰劑相比，對 RSV LRTI 住院治療的療效為相對風險降低 86.5% (95% CI 53.5, 96.1)。
在試驗03中，出生時胎齡大於/等於29週且小於35週的嬰兒，在接受單劑量50毫克 BEYFORTUS給藥後的 150 天內，BEYFORTUS對 MA RSV LRTI 住院治療為相對風險降低 78.4% (95% CI 51.9, 90.3; p=0.0002)。

14.3 預防出生時胎齡≥35 週的嬰兒發生 MA RSV LRTI（試驗 04）。

在一項3期隨機、雙盲、安慰劑對照的多中心試驗（試驗04）中，對BEYFORTUS用於預防進入第一個RSV好發季節時出生的足月兒和胎齡大於或等於35週的晚期早產兒發生 MA RSV LRTI 的情況進行了評估。
主要分析族群（主要組）包括1,490例足月和晚期早產兒（胎齡大於或等於35週）。受試者以2:1的比例隨機接受單劑量肌肉注射BEYFORTUS(N=994)（如果用藥時體重小於5公斤，則注射50毫克；如果用藥時體重大於或等於5公斤，則注射100毫克），或安慰劑(N=496)。 隨機分組時，14%的受試者胎齡大於/等於35週且小於 37 週； 86%的受試者胎齡大於或等於37週； 52%為男性； 53% 為白種人； 28%為黑種人； 6%為美國印第安人/阿拉斯加原住民； 4%為亞洲人； 1%為太平洋島民；8%為其他或混合種族； 10%為西班牙裔或拉丁裔；69%來自北半球；40% 體重低於 5 公斤。年齡中位數為 2.6 個月（範圍：0.03至11.10個月）； 58%小於或等於3個月； 32%大於3個月至小於/等於6個月，10%大於6個月。
在試驗 04 中，主要療效指標為經由RT-PCR確認為RSV所導致的MA RSV LRTI的發生率，如試驗03所定義。需要住院治療的RSV LRTI的發生率是預先指定的次要療效指標。因RSV住院的定義為因 LRTI 住院且RSV檢測呈陽性。
表6 顯示了試驗04的主要療效結果。

表6 出生時≥35 週的嬰兒在給藥後 150天內MA RSV LRTI 的發生率（試驗 04）*

	N	發生率 % (n)	療效† (95% CI)
BEYFORTUS	994	1.2 % (12)	74.9 % (50.6, 87.3) ‡
安慰劑	496	5.0 % (25)	

* 試驗 04 依據主要組的受試者進行主要療效分析。MA RSV LRTI的療效為對照安慰劑時相對風險降低，並根據隨機分組時的年齡校正。
† p 值=<0.001。
‡ 在試驗 04 中，出生時胎齡大於/等於 35 週、體重小於5公斤和大於/等於5公斤的嬰兒），在分別接受單劑量肌肉注射50毫克或 100 毫克 BEYFORTUS 後的150 天內，該藥物對 MA RSV LRTI住院治療為相對風險降低 60.2% (95% CI-14.6, 86.2; p=0.09)。

14.4 預防出生時胎齡＜35週的嬰兒和患有早產兒慢性肺部疾病(CLD)或血液動力學上顯著之先天性心臟疾病 (CHD) 的嬰兒發生 MA RSV LRTI（試驗 05）

在一項針對出生時胎齡小於35週的兒科受試者，以及患有早產兒CLD或血液動力學上顯著之CHD的嬰兒進行的2/3期隨機、雙盲、Palivizumab對照的多中心試驗（試驗05）

中，對 BEYFORTUS 的安全性和 PK 進行了評估。該試驗不考慮藥效，但藥效作為次要療效指標進行了評估。BEYFORTUS 對於在第一個 RSV 好發季節的早產兒（胎齡小於 35 週）和對於在第一個和第二個 RSV 好發季節24 個月以下並患有 CLD 或 CHD 的兒科受試者的療效，是基於與試驗 04 和 05 中的受試者接受的相似的 nirsevimab-alip 暴露量，透過將 BEYFORTUS 在試驗 03 和試驗 04 中的療效外推到試驗 05 的受試者身上來確定的。*[見臨床藥理學 (12.3)]*。

試驗 05：第一個 RSV 季節

試驗 05 在進入第一個 RSV 好發季節，將有嚴重 RSV 疾病高風險的嬰兒分為兩組：早產兒（胎齡小於 35 週）和患有早產兒 CLD 或有血液動力學上顯著之 CHD 的嬰兒。在早產兒 (n=615) 和 CLD/CHD (n=310) 兩組中，共有 925 名嬰兒以 2:1 的比例隨機接受 BEYFORTUS 或 Palivizumab。嬰兒接受單劑量肌肉注射 BEYFORTUS（如果用藥時體重小於 5 公斤，則注射 50 毫克；如果用藥時體重大於 5 公斤，則注射 100 毫克），然後分別接受安慰劑肌肉注射，每月一次，共 4 次；或Palivizumab 肌肉注射，劑量為15毫克/公斤，每月一次，共 5 次。在隨機分組時，在早產兒組中，77 例 (13%) 嬰兒的 胎齡 小於 29 週；499 例 (81%) 的 胎齡 大於/等於 29 且小於 35 週。在 CLD/CHD 組中，70% 有早產兒 CLD；34% 患有血液動力學上顯著之 CHD；123 例 (40%) 嬰兒的 胎齡 小於29週，28% 的胎齡大於/等於 29 週且小於 35 週；32% 的 胎齡 大於或等於 35 週。在兩組中，54% 是男性；79% 為白種人；10% 為黑種人；5% 為亞洲人；2% 為美國印第安人/阿拉斯加原住民；15% 為西班牙裔或拉丁裔；57% 體重低於 5 公斤。年齡中位數為3.5 個月（範圍：0.07 至 12.3 個月）；45% 小於或等於 3 個月；34% 大於 3 個月至小於/等於 6 個月，21% 大於 6 個月。

在試驗 05 的第一個 RSV 季節，BEYFORTUS 組在給藥後 150 天內的 MA RSV LRTI 的發生率為 0.6% (4/616)，Palivizumab組為 1.0% (3/309)。

試驗 05：第二個 RSV 季節

患有早產兒CLD或24個月以下且患有血液動力學上顯著之CHD的兒科受試者在第二個 RSV 好發季節繼續參加試驗 (n=262)。在第一個 RSV 好發季節接受了 BEYFORTUS 的受試者在進入第二個RSV好發季節時也接受了單劑量200毫克BEYFORTUS，然後接受安慰劑肌肉注射(n=180)，每月一次，共4 次。在第一個 RSV 季節接受Palivizumab的受試者 以 1:1的比例重新隨機分組，在進入第二個 RSV 季節時接受 BEYFORTUS 或Palivizumab。在第一個 RSV 好發季節接受了 Palivizumab 的四十例受試者，在第二個 RSV 好發季節接受了單劑量 BEYFORTUS 肌肉注射，然後接受安慰劑肌肉注射，每月一次，共 4 次；42 例受試者在第一個和第二個 RSV 好發季節接受了Palivizumab（Palivizumab 肌肉注射，劑量為15 毫克/公斤，每月一次，共 5 次）。

在試驗05的第二個RSV好發季節，接受了BEYFORTUS或Palivizumab的受試者在給藥後的第150天內皆未出現MA RSV LRTI病例。

16　如何供應/儲存與管理

包裝方式

BEYFORTUS注射劑是一種無菌的、不含防腐劑的、透明至乳白色、無色至黃色的溶液，包裝方式如下：

- 一盒 1 支 50 毫克/0.5 毫升單劑量預充填注射器：NDC 49281-575-00
- 一盒 5 支 50 毫克/0.5 毫升單劑量預充填注射器：NDC 49281-575-15
- 一盒 1 支 100 毫克/毫升單劑量預充填注射器：NDC 49281-574-88
- 一盒 5 支 100 毫克/毫升單劑量預充填注射器：NDC 49281-574-15

每個BEYFORTUS預充填注射器僅供使用一次。

儲存與處理

在 36°F 至 46°F（2°C 至 8°C）之間冷藏儲存。本產品可在 68°F 至 77°F（20°C 至 25°C）室溫下儲存最多 8 小時。從冰箱中取出後，本產品必須在 8 小時內使用，否則將被丟棄。在使用前，請將本產品儲存在原包裝盒內，避免光照。

請勿冷凍。請勿搖晃。請勿暴露在高溫下。

17　患者諮詢資訊

建議兒童照護者閱讀FDA核准的患者標籤（患者資訊）。

包括全身性過敏的過敏反應

告知照顧者潛在過敏反應的徵兆和症狀，並建議照顧者若發現孩子對BEYFORTUS產生過敏反應，應立即就醫 *[請參閱警告與注意事項(5.1)]*。

劑量和用藥方法

告知照護者，醫療人員將透過肌肉注射的方式為兒童注射一劑BEYFORTUS。如果兒童仍然處於RSV的高風險狀態，可以在第二個RSV季節接受第二劑*[見劑量和用藥方法(2.1)]*。

生產商：AstraZeneca AB, Södertälje, Sweden SE-15185

美國執照號：2059

經銷商: Sanofi Pasteur, Inc., Swiftwater, PA 18370 USA

BEYFORTUS 是Sanofi集團公司的商標。

患者資訊
BEYFORTUS™（Bay for tus）
(nirsevimab-alip)
注射劑，用於肌肉注射

什麼是 BEYFORTUS？

BEYFORTUS 為處方藥物，用於幫助以下群體預防因感染呼吸道融合病毒(RSV)而導致的嚴重肺部疾病:

- 正值或進入第一個RSV好發季節時出生的新生兒或未滿1歲的嬰兒。
- 在第二個RSV好發季節仍有高風險罹患嚴重RSV疾病的24個月以下兒童。

BEYFORTUS是一種含有nirsevimab-alip的抗體，用於幫助預防RSV 疾病，保護力持續時間為5個月。

BEYFORTUS對24個月以上兒童的安全性和有效性仍不清楚。

若您的孩子對nirsevimab-alip或BEYFORTUS 的任何成分有嚴重的過敏反應史，**請勿接種BEYFORTUS**。欲瞭解BEYFORTUS完整成分清單，請參見本患者資訊頁末。

在您的孩子接種BEYFORTUS之前，請將孩子的所有醫療狀況告知您的醫療保健人員，包括如果孩子：

- 曾對BEYFORTUS出現反應。
- 曾發生出血或瘀青問題。若您的孩子有容易出血或瘀青的問題，可能因注射導致傷害。

請告知醫療保健人員關於孩子的所有用藥情況，包括處方和非處方藥物，維他命以及草本保健品。如果嬰兒在同一個RSV好發季節已經接種BEYFORTUS，請勿再使用Palivizumab藥物。

BEYFORTUS 如何給藥？

- BEYFORTUS是一種注射劑，通常由醫療保健人員注射於大腿肌肉。
- **您的孩子應該在RSV好發季節之前或期間接受BEYFORTUS。**

RSV季節是一年中RSV感染最普遍的時期，通常發生在秋季至春季。您可以詢問醫療保健人員您所在地區何時開始進入RSV好發季節。

- **您的孩子在注射BEYFORTUS後仍有可能感染RSV疾病。**

請和孩子的醫療保健人員討論該注意哪些可能出現的症狀。

- 如果您的孩子接受心臟手術，孩子的醫療保健人員可能需要在術後盡快幫孩子注射額外的BEYFORTUS注射劑。

BEYFORTUS 可能有哪些副作用？

- 使用BEYFORTUS藥物曾發生過**嚴重的過敏反應。**
- 若您的孩子有以下嚴重過敏反應的徵兆或症狀，請立即尋求醫療協助：

o 臉部、口腔或舌頭腫脹
o 皮膚、嘴唇或指甲內的顏色呈藍色
o 吞嚥或呼吸困難
o 肌肉無力
o 無意識
o 嚴重紅疹、蕁麻疹或瘙癢

BEYFORTU最常見的副作用為紅疹與注射部位疼痛、腫脹或出現硬塊。但BEYFORTUS仍可能引發其他副作用。關於副作用，請致電醫生尋求醫療建議。您可以透過1-800-FDA-1088向FDA通報副作用。

關於安全有效使用BEYFORTUS的一般資訊

藥品有時會被使用於患者資訊手冊中所列之外的醫療用途。您可以向您的藥師或醫療保健人員詢問有關BEYFORTUS的資訊，這些資訊是為醫療專業人員所編寫的。

BEYFORTUS的成分有哪些？
活性成分：nirsevimab-alip
非活性成分：精胺酸鹽酸鹽、組胺酸、L-組胺酸鹽酸鹽、聚山梨醇酯 80、蔗糖和注射用水。

生產商：AstraZeneca AB, Södertälje, Sweden SE-15185
美國執照號：2059
經銷商：Sanofi Pasteur, Inc., Swiftwater, PA 18370 USA。

欲瞭解更多資訊，請瀏覽 https://www.Beyfortus.com/cn，或致電 1-855-239-3678 (1-855-BEYFORTUS)。

本患者資訊已獲美國食品和藥物管理局核准。
發佈日期：2024年 2 月

MAT-US-2305877-v3.0-09/2024

僅供處方使用

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BEYFORTUS™ safely and effectively. See full prescribing information for BEYFORTUS.

BEYFORTUS™ (nirsevimab-alip) injection, for intramuscular use

Initial U.S. Approval: 2023

RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 02/2024

INDICATIONS AND USAGE

BEYFORTUS is a respiratory syncytial virus (RSV) F protein-directed fusion inhibitor indicated for the prevention of RSV lower respiratory tract disease in:

- Neonates and infants born during or entering their first RSV season. (1)
- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. (1)

DOSAGE AND ADMINISTRATION

Administer as an intramuscular injection. (2.1)

Recommended dosage:

Neonates and infants born during or entering their first RSV season:

- 50 mg if less than 5 kg in body weight. (2.1)
- 100 mg if greater than or equal to 5 kg in body weight. (2.1)

Children who remain vulnerable through their second RSV season:

- 200 mg (2 x 100 mg injections). (2.1)

DOSAGE FORMS AND STRENGTHS

Injection:

- 50 mg/0.5 mL in a single-dose pre-filled syringe. (3)
- 100 mg/mL in a single-dose pre-filled syringe. (3)

CONTRAINDICATIONS

BEYFORTUS is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions Including Anaphylaxis: Serious hypersensitivity reactions have been reported following BEYFORTUS administration. These reactions included urticaria, dyspnea, cyanosis, and/or hypotonia. Anaphylaxis has been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reactions occur, initiate appropriate treatment. (5.1)

ADVERSE REACTIONS

Most common adverse reactions were rash (0.9%) and injection site reactions (0.3%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi at 1-855-239-3678 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

The safety and effectiveness of BEYFORTUS in children older than 24 months of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BEYFORTUS is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in:

- Neonates and infants born during or entering their first RSV season.
- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

First RSV Season for Neonates and Infants

For neonates and infants born during the RSV season, administer BEYFORTUS starting from birth. For neonates and infants born outside the RSV season, administer BEYFORTUS once prior to the start of the RSV season considering duration of protection provided by BEYFORTUS *[see Clinical Pharmacology (12.2)]*.

The recommended dosage of BEYFORTUS for neonates and infants born during or entering their first RSV season is based on body weight (see Table 1) and is administered as a single intramuscular (IM) injection.

Table 1 Recommended Dosage of BEYFORTUS for the First RSV Season

Body Weight at Time of Dosing	Recommended Dosage
Less than 5 kg	50 mg by IM injection
5 kg and greater	100 mg by IM injection

Second RSV Season for Children Who Remain at Increased Risk for Severe RSV Disease

For children up to 24 months of age, regardless of body weight, who remain at increased risk for severe RSV disease in their second RSV season, refer to Table 2 below for recommended dosage.

Table 2 Recommended Dosage of BEYFORTUS for the Second RSV Season for Children Who Remain at Increased Risk for Severe RSV Disease

Child's Age at Time of Dosing	Recommended Dosage
Up to 24 months of age*	200 mg administered as two IM injections of (2 x 100 mg)

*Regardless of body weight

First and Second RSV Season for Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass

For children undergoing cardiac surgery with cardiopulmonary bypass, an additional dose of BEYFORTUS is recommended as soon as the child is stable after surgery to ensure adequate nirsevimab-alip serum levels. The recommended dosage of BEYFORTUS is administered as an IM injection.

First RSV season:

- If surgery is within 90 days after receiving BEYFORTUS, the additional dose should be based on body weight at the time of the additional dose. Refer to Table 1 for weight-based dosing.

- If more than 90 days have elapsed since receiving BEYFORTUS, the additional dose should be 50 mg regardless of body weight.

Second RSV season:

- If surgery is within 90 days after receiving BEYFORTUS, the additional dose should be 200 mg, regardless of body weight.
- If more than 90 days have elapsed since receiving BEYFORTUS, the additional dose should be 100 mg, regardless of body weight.

2.2 Administration Instructions

BEYFORTUS must be administered by a healthcare provider.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. BEYFORTUS is a clear to opalescent, colorless to yellow solution. Do not inject BEYFORTUS if the liquid is cloudy, discolored, or it contains large particles or foreign particulate matter.

Do not use if the BEYFORTUS pre-filled syringe has been dropped or damaged, the security seal on the carton has been broken, or the expiration date has passed.

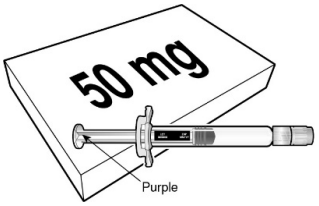
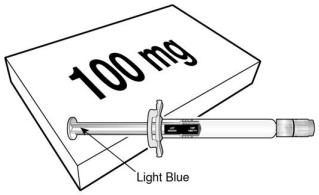
BEYFORTUS is available in a 50 mg and a 100 mg pre-filled syringe. Check the labels on the BEYFORTUS carton and pre-filled syringe to ensure the correct 50 mg or 100 mg product is being used.

Co-administration with Childhood Vaccines and Immunoglobulin Products

BEYFORTUS can be given concomitantly with childhood vaccines *[see Clinical Pharmacology (12.3)]*. When administered concomitantly with injectable vaccines, they should be given with separate syringes and at different injection sites. Do not mix BEYFORTUS with any vaccines or medications in the same syringe or vial.

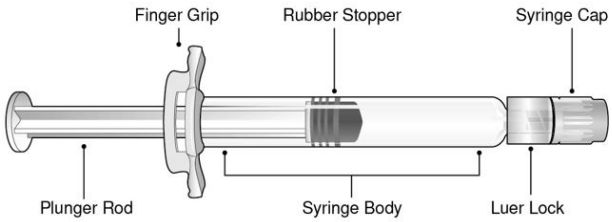
There is no information regarding co-administration of BEYFORTUS with other immunoglobulin products. Palivizumab should not be administered to infants who have already received BEYFORTUS in the same season. There are no data regarding substitution of BEYFORTUS for palivizumab once prophylaxis treatment is initiated with palivizumab for the RSV season. BEYFORTUS may be administered prior to or during the second RSV season to children up to 24 months of age who remain vulnerable to severe RSV disease, and who received palivizumab in their first RSV season *[see Adverse Reactions (6.1) and Clinical Studies (14.3)]*.

Administration Instructions for Single-Dose Pre-filled Syringe

BEYFORTUS 50 mg (50 mg/0.5 mL) pre-filled syringe with a purple plunger rod.	BEYFORTUS 100 mg (100 mg/mL) pre-filled syringe with a light blue plunger rod.
	

Refer to Figure 1 for pre-filled syringe components.

Figure 1 Luer Lock Syringe Components



Step 1: Holding the Luer lock in one hand (avoid holding the plunger rod or syringe body), unscrew the syringe cap by twisting it counter-clockwise with the other hand.

Step 2: Attach a Luer lock needle to the pre-filled syringe by gently twisting the needle clockwise onto the pre-filled syringe until slight resistance is felt.

Step 3: Hold the syringe body with one hand and carefully pull the needle cover straight off with the other hand. Do not hold the plunger rod while removing the needle cover or the rubber stopper may move. Do not touch the needle or let it touch any surface. Do not recap the needle or detach it from the syringe.

Step 4: Administer the entire contents of the BEYFORTUS pre-filled syringe as an IM injection, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used as an injection site because of the risk of damage to the sciatic nerve.

Step 5: Discard syringe into a sharps container.

If two injections are required, repeat Steps 1-5 in a different injection site.

3 DOSAGE FORMS AND STRENGTHS

BEYFORTUS is a clear to opalescent, colorless to yellow solution available as follows:

- Injection: 50 mg/0.5 mL in a single-dose pre-filled syringe.
- Injection: 100 mg/mL in a single-dose pre-filled syringe.

4 CONTRAINDICATIONS

BEYFORTUS is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients *[see Warnings and Precautions (5.1) and Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Serious hypersensitivity reactions have been reported following BEYFORTUS administration. These reactions included urticaria, dyspnea, cyanosis, and/or hypotonia. Anaphylaxis has been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reactions occur, initiate appropriate treatment.

5.2 Use in Individuals with Clinically Significant Bleeding Disorders

As with any other IM injections, BEYFORTUS should be given with caution to infants and children with thrombocytopenia, any coagulation disorder, or to individuals on anticoagulation therapy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 3,224 pediatric subjects received the recommended dose of BEYFORTUS in Phase 2 and Phase 3 clinical trials (Trials 03, 04, and 05) including 2,119 infants who were born at 35 weeks gestational age (GA) or older, and 1,105 infants who were born at less than 35 weeks GA. A total of 247 infants of any GA with chronic lung disease (CLD) of prematurity or hemodynamically significant congenital heart disease (CHD) in Trial 05 received the recommended dose of BEYFORTUS.

Neonates and Infants Entering Their First RSV Season (Trial 03 and Trial 04)

Trial 03 was a randomized, double-blind placebo-controlled trial conducted in preterm infants born at a GA of greater than or equal to 29 weeks to less than 35 weeks. Subjects were randomized 2:1 to receive BEYFORTUS (N=968) or placebo (N=479) by IM injection. All subjects randomized to BEYFORTUS received a single 50 mg IM dose regardless of body weight. Safety data in Trial 03 are presented only for the infants in the BEYFORTUS arm who received the recommended dose [infants who weighed less than 5 kg and who received a single dose of 50 mg BEYFORTUS IM (N=572) or placebo (N=288)].

Trial 04 was a Phase 3, randomized, double-blind, placebo-controlled trial conducted in late preterm and term infants born at greater than or equal to 35 weeks GA. Trial 04 enrolled subjects sequentially into two cohorts: the Primary Cohort was used for the primary efficacy analysis *[see Clinical Studies (14.3)]* and for assessment of safety, and the Safety Cohort was used primarily for safety assessment. All subjects from both cohorts of Trial 04 were included in the safety analysis (BEYFORTUS N=1,997 and placebo N=997). Subjects in Trial 04 weighing less than 5 kg received a single 50 mg IM dose of BEYFORTUS and infants weighing greater than or equal to 5 kg received a single 100 mg IM dose.

Infants who received the recommended dose in Trial 03 and infants in Trial 04 were pooled to evaluate the safety of BEYFORTUS (N=2,570) compared to placebo (N=1,284). At randomization, in this pooled Safety Population from Trials 03 and 04 cohorts, 22% of infants were born at less than 35 weeks GA, 10% of infants were GA greater than or equal to 35 weeks and less than 37 weeks; 68% were GA greater than or equal to 37 weeks; 52% were male; 57% were White; 15% were Black; 4% were American Indian/Alaskan native; 4% were Asian; 1% were Pacific Islander; and 19% were Other or Mixed Race; 30% were Hispanic or Latino; 73% were from Northern Hemisphere; and 53% weighed less than 5 kg. The median age was 2 months; 65% were less than or equal to 3 months; 28% were greater than 3 to less than or equal to 6 months, and 7% were greater than 6 months of age. (Refer to Sections 14.2 and 14.3, Clinical Studies, for a description of the efficacy populations in Trials 03 and 04). In both trials, infants received a single dose of IM BEYFORTUS or placebo on Study Day 1 and were monitored for at least 60 minutes post-dose. Subjects were followed for 360 days post-dose to assess safety. Adverse reactions were reported in 1.2% of subjects who received BEYFORTUS; most (97%) of adverse reactions were mild to moderate in intensity.

Table 3 summarizes the adverse reactions that occurred in Trial 03 and Trial 04 (Safety Population) in subjects who received the recommended dose of BEYFORTUS.

Table 3 Adverse Reactions Reported at an Incidence Higher Than Placebo in the Safety Population* (Trials 03 and 04)

Adverse Reaction	BEYFORTUS N=2,570 %	Placebo N=1,284 %
Rash† (occurring within 14 days post-dose)	0.9	0.6
Injection site reaction‡ (occurring within 7 days post-dose)	0.3	0

*The Safety Population includes all subjects who received the recommended dose of BEYFORTUS in Trials 03 and 04: Primary and Safety cohorts from Trial 04; infants who weighed less than 5 kg and who received the recommended dose of BEYFORTUS (single 50 mg IM dose) in Trial 03.

†Rash was defined by the following grouped preferred terms: rash, rash macular, rash maculo-papular, rash papular.

‡Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site edema, injection site swelling.

Infants Born at <35 Weeks Gestational Age and Infants and Children with CLD of Prematurity or Hemodynamically Significant CHD (Trial 05)

RSV Season One

The safety of BEYFORTUS was evaluated in Trial 05, a randomized, double-blind, palivizumab-controlled multicenter trial in infants at high risk for severe RSV disease. These subjects were randomized 2:1 to receive BEYFORTUS (N=614) or palivizumab (N=304) by IM injection. The 614 infants who received BEYFORTUS included 128 preterm infants born at GA less than 29 weeks, 390 preterm infants who were born at 29 weeks or older to less than 35 weeks GA, and 96 late preterm and term infants born at 35 weeks GA or older. Among infants enrolled during their first RSV season, the number of infants with CLD of prematurity or hemodynamically significant CHD were overall 214 and 103, respectively, regardless of gestational age. Of these, 12 infants had both CLD and CHD.

Subjects in Trial 05 weighing less than 5 kg received a single 50 mg IM dose of BEYFORTUS and infants weighing greater than or equal to 5 kg received a single 100 mg IM dose. BEYFORTUS was administered once on Study Day 1 followed by 4 monthly IM doses of placebo; palivizumab was administered IM monthly for 5 months. All subjects were monitored for at least 60 minutes post-dose. Subjects were followed for 360 days post-dose to assess safety.

Adverse reactions reported among Trial 05 subjects who received BEYFORTUS in their first RSV season were similar to those reported in subjects who received BEYFORTUS in Trials 03 and 04.

RSV Season Two (Subjects with CLD of Prematurity and Hemodynamically Significant CHD)

Subjects with CLD of prematurity or hemodynamically significant CHD could continue in Trial 05 and receive BEYFORTUS or palivizumab prior to their second RSV season. All subjects who received BEYFORTUS in the first RSV season also received BEYFORTUS in the second RSV season (N=180). Subjects who received palivizumab in the first RSV season were re-randomized to receive BEYFORTUS (N=40) or palivizumab (N=42) in the second RSV season. Safety data were available for 150 days after dosing in children with CLD or CHD who received BEYFORTUS (N=220) or palivizumab (N=42) in their second RSV season. The safety profile of BEYFORTUS in these children during their second RSV season was consistent with the safety profile of BEYFORTUS observed during their first RSV season.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of BEYFORTUS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Interference with RT-PCR or Rapid Antigen Detection RSV Diagnostic Assays

Nirsevimab-alip does not interfere with reverse transcriptase polymerase chain reaction (RT-PCR) or rapid antigen detection RSV diagnostic assays that employ commercially available antibodies targeting antigenic site I, II, or IV on the RSV fusion (F) protein. For immunological assay results which are negative when clinical observations are consistent with RSV infection, it is recommended to confirm using an RT-PCR-based assay.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

BEYFORTUS is not indicated for use in females of reproductive potential.

8.2 Lactation

BEYFORTUS is not indicated for use in females of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of BEYFORTUS have been established for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The safety and efficacy of BEYFORTUS for this indication and populations are discussed throughout the labeling.

Use of BEYFORTUS for this indication is supported by evidence from adequate and well-controlled studies in neonates and infants from birth up to 12 months of age with additional pharmacokinetic and safety data in children up to 24 months of age *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Use of BEYFORTUS in this population is supported by the following:

- Trial 03, a randomized, double-blind, placebo-controlled multicenter trial for the prevention of MA RSV LRTI conducted in preterm infants born at GA greater than or equal to 29 weeks and less than 35 weeks entering their first RSV season;
- Trial 04, a double-blind, placebo-controlled multicenter trial, for the prevention of MA RSV LRTI in term and late preterm infants GA greater than or equal to 35 weeks entering their first RSV season;
- Trial 05, a Phase 2/3 randomized, double-blind, palivizumab-controlled multicenter trial in pediatric subjects born less than 35 weeks GA and infants with CLD of prematurity or hemodynamically significant CHD entering their first or second RSV season.

In addition, BEYFORTUS was evaluated in an open-label, uncontrolled, single-dose trial (Trial 08) in 100 infants and children who were less than or equal to 24 months of age, who received BEYFORTUS in their first or second RSV season, and who had a wide variety of underlying diseases or treatments resulting in immune compromise. The safety profile of BEYFORTUS administered in Trial 08 was consistent with the safety profile of other trials of BEYFORTUS in infants and children *[see Clinical Pharmacology (12.3)]*.

The safety and effectiveness of BEYFORTUS have not been established in children older than 24 months of age.

10 OVERDOSAGE

There is limited experience of overdose with BEYFORTUS.

There is no specific treatment for an overdose with BEYFORTUS. In the event of an overdose, the individual should be monitored for the occurrence of adverse reactions and provided with symptomatic treatment as appropriate.

11 DESCRIPTION

Nirsevimab-alip, a respiratory syncytial virus F protein-directed fusion inhibitor, is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The molecular weight is approximately 146.3 kDa.

BEYFORTUS (nirsevimab-alip) injection is a sterile, preservative-free, clear to opalescent, colorless to yellow solution for intramuscular injection. It is supplied in a single-dose siliconized Luer lock Type I glass pre-filled syringe with a FluroTec coated plunger stopper. Each 0.5 mL contains 50 mg nirsevimab-alip, arginine hydrochloride (8 mg), histidine (1.1 mg), L-histidine hydrochloride monohydrate (1.6 mg), polysorbate 80 (0.1 mg), sucrose (21 mg), and water for injection (USP). The pH is 6.0.

Each 1 mL contains 100 mg nirsevimab-alip, arginine hydrochloride (17 mg), histidine (2.2 mg), L-histidine hydrochloride monohydrate (3.3 mg), polysorbate 80 (0.2 mg), sucrose (41 mg), and water for injection (USP). The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BEYFORTUS is a monoclonal antibody with anti-RSV activity *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

There is a positive correlation between a serum nirsevimab-alip AUC (based on clearance at baseline) above 12.8 mg*day/mL and a lower incidence of medically attended RSV lower respiratory tract infection (MA RSV LRTI). Following IM administration of nirsevimab-alip in adults, RSV neutralizing antibody levels in serum were approximately 4 times higher than baseline at 8 hours after nirsevimab-alip dosing, and maximum levels were reached by day 6 following IM administration of nirsevimab-alip in adults. The safety and effectiveness of BEYFORTUS have not been established in adults.

Duration of Protection

Based on clinical data, the duration of protection offered by a single dose of BEYFORTUS extends through 5 months.

12.3 Pharmacokinetics

The PK of nirsevimab-alip is dose-proportional following a single IM administration of doses ranging from 25 mg (0.5 times the lowest approved recommended dosage) to 200 mg in pediatric subjects. Following the recommended dose, the nirsevimab-alip serum exposures were similar in neonates and infants born during or entering their first RSV season (Trials 03 and 04), and in neonates and infants born at less than 35 weeks GA (including less than 29 weeks GA) in their first RSV season (Trial 05), and in pediatric subjects up to 24 months of age with CLD or CHD in their first and second RSV season (Trial 05).

Absorption

The estimated nirsevimab-alip absolute bioavailability is 84% and the median time (range) to maximum concentration is 6 (1, 28) days.

Distribution

The estimated nirsevimab-alip total volume of distribution is 477 mL, for an infant weighing 5 kg.

Elimination

The nirsevimab-alip terminal half-life is approximately 71 days and the estimated clearance is 3.42 mL/day for an infant weighing 5 kg.

Metabolism

Nirsevimab-alip is degraded into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences in the pharmacokinetics of nirsevimab-alip were observed based on race or vulnerability to severe RSV disease (i.e., CLD, CHD, GA <29 weeks).

The mean and median serum nirsevimab-alip concentrations in Trial 08 were lower than the concentrations in Trials 04 and 05. However, Trial 08 exposures were within the range shown to be effective in those who received the recommended dosage in Trials 03, 04, and 05 *[see Pediatric Use (8.4)]*.

Drug Interaction Studies

No formal drug interaction studies have been performed with BEYFORTUS. Nirsevimab-alip is not predicted to be a substrate of, inhibitor or inducer of cytochrome P450 enzymes or transporter systems based on a mechanistic understanding of monoclonal antibodies.

Clinical Studies

Vaccines: There is limited experience with co-administration of BEYFORTUS with vaccines. In clinical trials, when BEYFORTUS was given concomitantly with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given alone.

12.4 Microbiology

Mechanism of Action

Nirsevimab-alip is a recombinant human IgG1κ monoclonal antibody that provides passive immunity by targeting the prefusion conformation of the RSV F protein. Nirsevimab-alip is long-acting due to a triple amino acid substitution (YTE) in the Fc region which increases binding to the neonatal Fc receptor and thereby extends serum half-life. Nirsevimab-alip binds to a conserved epitope in antigenic site Ø on the prefusion protein with dissociation constants KD = 0.12 nM and KD = 1.22 nM for RSV subtype A and B strains, respectively; it neutralizes RSV by inhibiting conformation changes in the F protein necessary for fusion of the viral and cellular membranes and viral entry.

Antiviral Activity

The cell culture neutralization activity of nirsevimab-alip against RSV was measured in a concentration-response model using cultured Hep-2 cells. Nirsevimab-alip neutralized clinical RSV isolates collected from global locations between 2003 and 2017 with median EC50 values for RSV A of 21 pM (3.2 ng/mL) (n=70; range 3 pM [0.48 ng/mL] to 100 pM [15 ng/mL]) and for RSV B of 19 pM (2.9 ng/mL) (n=49; range 2 pM [0.3 ng/mL] to 398 pM [59.7 ng/mL]).

Antiviral Resistance

In Cell *Culture*

Escape variants were selected following three passages in cell culture of RSV A2 and B9320 strains in the presence of nirsevimab-alip. Recombinant RSV A variants that showed reduced susceptibility to nirsevimab-alip compared with the reference strain included those with substitutions N67I+N208Y (103-fold reduction). Recombinant RSV B variants that showed reduced susceptibility to nirsevimab-alip included those with substitutions N208D (>90,000-fold change), N208S (>24,000-fold change), K68N+N201S (>13,000-fold change), and K68N+N208S (>90,000-fold change). All resistance-associated substitutions identified among neutralization escape variants were located in the nirsevimab-alip binding site (amino acids 62-69 and 196-212) and were shown to reduce binding affinity to RSV F protein.

In Surveillance Trials

Polymorphisms conferring large fold-reductions in susceptibility to nirsevimab-alip in isolates collected from 1956-2014 were not observed for RSV A and seen rarely (<1%) for RSV B, and included K65Q+K68N (1,239-fold change), K65Q+S211N (36-fold change), and L203I (3,005-fold change) substitutions. In prospective, observational, global molecular epidemiology studies (OUTSMART-RSV and INFORM-RSV) genetic diversity of RSV F protein sequences has remained low (most amino acids in both RSV A and RSV B >99% conserved). Variants harboring known nirsevimab-alip resistance-associated substitutions have been rare (<1%) and include RSV B substitutions K68Q (>369-fold change), N201T (>406-fold change) and N201T+I206M+Q209R (>418-fold change). Variants observed with reduced susceptibility include RSV A substitutions K68E (13-fold change), K68N (5-fold change), and S275F (6-fold change), and RSV B substitutions

K68N (30-fold change), K68Q+I206M+Q209R (46-fold change), N201S (127-fold change) and N201S+I206M+Q209R (17-fold change). The clinical significance of these reductions in susceptibility is not known. From 2015 to 2021, most amino acid residues in the nirsevimab-alip binding site were highly conserved (>99%) at all positions in RSV A and 22 of the 25 positions in RSV B. Co-occurring substitutions I206M+Q209R in the nirsevimab-alip binding site that have become prevalent in RSV B since 2017 did not confer reduced susceptibility (<5-fold change) to nirsevimab-alip. The S211N substitution which has increased in prevalence also retains susceptibility to nirsevimab-alip, both individually and concurrently with I206M+Q209R.

In Clinical Trials

In Trial 04, Trial 05 and Trial 08 no known resistance-associated substitutions were identified at ≥25% frequency at any sampling time points. Phenotypic testing of novel substitutions is ongoing.

In Trial 03 (who received a single dose of 50 mg BEYFORTUS), 2 of 40 subjects with RSV infections corresponding to any case definition had a variant containing nirsevimab-alip resistance-associated substitutions. The two subjects received less than the recommended nirsevimab-alip dose and had RSV B variants harboring I64T+K68E+I206M+Q209R co-occurring substitutions or an N208S substitution. I64T, K68E, and N208S substitutions individually have reduced susceptibility to nirsevimab-alip (fold changes: >496, >283, and >387, respectively).

In Trial 04, an RSV B variant harboring binding site substitution L204S (no phenotypic data) concurrent with I206M+Q209R+S211N substitutions (<5-fold change) was detected at ≥25% frequency in one subject who received BEYFORTUS through Day 150. RSV B variants present at <25% frequency with I64T+K68E substitutions (>280-fold-change) and N208I substitution (>600-fold change) were seen in one subject each who received BEYFORTUS through Day 150. In addition, an RSV B N201D substitution (no phenotypic data) was observed at 9% frequency in one subject after Day 150.

Cross-resistance

Limited data are available that show that variants resistant to nirsevimab-alip could have cross-resistance to palivizumab. Palivizumab retained full neutralization potency against resistance-associated substitutions identified in Trial 03 and Trial 04. Nirsevimab-alip retained activity against recombinant RSV harboring palivizumab resistance-associated substitutions identified in molecular epidemiology studies and in neutralization escape variants of palivizumab; S275F substitution had reduced susceptibility of 6-fold.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of nirsevimab-alip or of other nirsevimab products.

Of 572 subjects receiving the recommended dose of nirsevimab-alip in Trial 03, 3.3% (16/492) subjects were ADA-positive on Day 361. Among the 16 ADA-positive subjects, 94% (15/16) had ADA against YTE and none tested positive for neutralizing antibodies against nirsevimab-alip.

In Trial 04, 5% (95/1778) of subjects were ADA-positive on Day 361, of whom 21% (20/95) had neutralizing antibodies and 77% (73/95) had ADA against YTE.

In Trial 05, among subjects enrolled during their first RSV season, on Day 361, 6% (32/538) of subjects were positive for ADA. Among the 32 ADA-positive subjects, 6% (2/32) had neutralizing antibodies against nirsevimab-alip and 91% (29/32) had antibodies against the YTE substitution. Of 180 subjects who received nirsevimab-alip in two consecutive RSV seasons, on season 2 Day 361, 9% (13/144) of subjects were positive for ADA. Among the 13 ADA-positive subjects, 8% (1/13) had neutralizing antibodies against nirsevimab-alip and 62% (8/13) had antibodies against YTE.

In Trial 08, among subjects receiving nirsevimab-alip in their first or second RSV season, 13% (9/67) of subjects were positive for ADA on Day 361. Among the 9 ADA-positive subjects, 11% (1/9) had neutralizing antibodies against nirsevimab-alip and 100% (9/9) were positive for ADA against YTE.

In Trials 03, 04, 05, and 08 the effect of ADA on nirsevimab-alip serum concentrations through Day 151 could not be determined. Subjects who received BEYFORTUS who developed anti-nirsevimab-alip antibodies had reduced nirsevimab-alip concentrations at Day 361 (40% to 60% lower compared to subjects who received BEYFORTUS who did not develop anti-nirsevimab-alip antibodies). Because of the low occurrence of ADA and MA RSV LRTI in clinical trials, the effect of these ADA on effectiveness of BEYFORTUS is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed with BEYFORTUS.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of BEYFORTUS were evaluated in term and preterm infants and children in the trials summarized in Table 4.

Table 4 Trials Conducted with BEYFORTUS for the Prevention of MA RSV LRTI

Trial	Population	Study Arms
D5290C00003 (Trial 03) NCT02878330	Infants born at ≥29 to <35 weeks GA entering their first RSV season	BEYFORTUS (N=969)* Placebo (N=484)
D5290C00004 (Trial 04) NCT03979313	Infants born at ≥35 weeks GA entering their first RSV season	**Primary Cohort**†: BEYFORTUS (N=994) Placebo (N=496) **Safety Cohort**‡**:** BEYFORTUS (N=1,015) Placebo (N=507)
D5290C00005 (Trial 05) NCT03959488	Infants born at <35 weeks GA and infants born with CLD or CHD entering their first RSV season Infants with CLD or CHD only entering their second RSV season	**RSV Season One:** BEYFORTUS (N=616) Palivizumab (N=304) **RSV Season Two:** BEYFORTUS (N=220) Palivizumab (N=42)

GA gestational age; CLD chronic lung disease; CHD hemodynamically signicant chronic heart disease

*All subjects in Trial 03 were included in the efficacy analysis. All subjects in Trial 03 received 50 mg of BEYFORTUS IM injections regardless of body weight. The recommended BEYFORTUS dose in neonates and infants born during or entering their first RSV season is single IM 50 mg and 100 mg dose for those who weigh <5 kg and ≥5 kg, respectively *[see Dosage and Administration (2.1)]*.

†The primary efficacy analysis for Trial 04 is based on subjects from the Primary Cohort. For Trial 04 safety population *[see Adverse Reactions (6.1)]*.

‡Trial 04 safety analysis included both Primary and Safety Cohorts *[see Adverse Reactions (6.1)]*.

14.2 Prevention of MA RSV LRTI in Infants Born at ≥29 to <35 Weeks Gestational Age (Trial 03)

Trial 03 was a randomized, double-blind, placebo-controlled multicenter trial for the prevention of Medically Attended Respiratory Syncytial Virus Lower Respiratory Tract Infection (MA RSV LRTI) conducted in preterm infants born at gestational age (GA) greater than or equal to 29 weeks and less than 35 weeks. These subjects were randomized 2:1 to receive BEYFORTUS (N=969) or placebo (N=484) by IM injection. All subjects in the BEYFORTUS arm received 50 mg IM of BEYFORTUS regardless of body weight. The recommended BEYFORTUS dose in neonates and infants born during or entering their first RSV season is a single IM 50 mg or 100 mg dose for those who weigh less than 5 kg and greater than or equal to 5 kg, respectively *[see Dosage and Administration (2.1)]*.

At randomization, 20% were GA greater than or equal to 29 weeks and less than 32 weeks; 80% were GA greater than or equal to 32 and less than 35 weeks; 52% were male; 72% were White; 18% were Black; 1% were Asian; 1% were Pacific Islander, and 8% were Other or Mixed Race; 22% were Hispanic or Latino; 68% were from Northern Hemisphere. The median age was 2.8 months (range: 0.1 to 11.9 months); 53% were less than or equal to 3 months; 33% were greater than 3 to less than or equal to 6 months, and 14% were greater than 6 months of age.

The primary endpoint was the incidence of MA RSV LRTI caused by RT-PCR-confirmed RSV, characterized predominantly as bronchiolitis or pneumonia through 150 days after dosing. Medically Attended (MA) includes all healthcare provider visits such as physician office, urgent care, emergency room visits and hospitalizations. Signs of LRTI involvement included rhonchi, rales, crackles, or wheezing; and at least one sign of worsening clinical severity including at least one of the following: increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions, grunting, or dehydration due to respiratory distress. Incidence of RSV LRTI with hospitalization was a prespecified secondary endpoint. RSV hospitalization was defined as hospitalization for LRTI with a positive RSV test.

Table 5 displays the primary efficacy result for Trial 03.

Table 5 Incidence of MA RSV LRTI in Infants Born at ≥29 Weeks to <35 Weeks Through 150 Days Post Dose (Trial 03)

	N	Incidence % (n)	Efficacy* (95% CI)
BEYFORTUS	969	2.6% (25)	70.1% (52.3, 81.2)†‡
Placebo	484	9.5% (46)	

*Efficacy for MA RSV LRTI based on relative risk reduction against placebo adjusted for age at randomization and hemisphere.

†p-value =<0.001.

‡In a post-hoc analysis of all randomized infants in Trial 03 weighing <5 kg at baseline, and who received the recommended dose of BEYFORTUS, efficacy for MA RSV LRTI, based on relative risk reduction against placebo was 86.2% (95% CI 68.0, 94.0); efficacy for RSV LRTI with hospitalization based on relative risk reduction against placebo was 86.5% (95% CI 53.5, 96.1).

In Trial 03, the efficacy of BEYFORTUS against MA RSV LRTI with hospitalization in infants born at GA greater than or equal to 29 weeks and less than 35 weeks, who received a single dose of 50 mg BEYFORTUS, based on the relative risk reduction was 78.4% (95% CI 51.9, 90.3; p=0.0002), through 150 days post dose.

14.3 Prevention of MA RSV LRTI in Infants Born at ≥35 Weeks Gestational Age (Trial 04)

BEYFORTUS was evaluated in one Phase 3 randomized, double-blind, placebo-controlled multicenter trial, Trial 04, for the prevention of MA RSV LRTI in term and late preterm infants GA greater than or equal to 35 weeks entering their first RSV season.

The primary analysis population (Primary Cohort) included 1,490 term and late preterm infants (GA greater than or equal to 35 weeks). Subjects were randomized 2:1 to receive a single IM dose of BEYFORTUS (N=994) (50 mg if less than 5 kg body weight or 100 mg if greater than or equal to 5 kg body weight at the time of dosing), or placebo (N=496). At randomization, 14% were GA greater than or equal to 35 weeks and less than 37 weeks; 86% were GA greater than or equal to 37 weeks; 52% were male; 53% were White; 28% were Black; 6% were American Indian/Alaskan native; 4% were Asian; 1% were Pacific Islander; and 8% were Other or Mixed Race; 10% were Hispanic or Latino; 69% were from Northern Hemisphere; and 40% weighed less than 5 kg. The median age was

2.6 months (range: 0.03 to 11.10 months); 58% were less than or equal to 3 months; 32% were greater than 3 to less than or equal to 6 months, and 10% were greater than 6 months of age.
In Trial 04, the primary endpoint was the incidence of MA RSV LRTI caused by RT-PCR-confirmed RSV, as defined in Trial 03. Incidence of RSV LRTI with hospitalization was a prespecified secondary endpoint. RSV hospitalization was defined as hospitalization for LRTI with a positive RSV test.
Table 6 displays the primary efficacy result from Trial 04.

Table 6 Incidence of MA RSV LRTI in Infants Born at ≥35 Weeks Through 150 Days Post Dose (Trial 04)*

	N	Incidence % (n)	Efficacy† (95% CI)
BEYFORTUS	994	1.2% (12)	74.9% (50.6, 87.3)‡
Placebo	496	5.0% (25)	

*The primary efficacy analysis for Trial 04 is based on subjects from the Primary Cohort.
†Efficacy for MA RSV LRTI based on relative risk reduction against placebo adjusted for age at randomization.
‡p-value =<0.001.

In Trial 04, the efficacy of BEYFORTUS against MA RSV LRTI with hospitalization in infants born at GA greater than or equal to 35 weeks, who received a single IM 50 mg or 100 mg dose for those who weigh less than 5 kg and greater than or equal to 5 kg, respectively, based on the relative risk reduction was 60.2% (95% CI -14.6, 86.2; p=0.09), through 150 days post dose.

14.4 Prevention of MA RSV LRTI in Infants Born at <35 Weeks Gestational Age and Infants with CLD of Prematurity or Hemodynamically Significant CHD (Trial 05)

The safety and PK of BEYFORTUS were evaluated in a Phase 2/3 randomized, double-blind, palivizumab-controlled multicenter trial (Trial 05) in pediatric subjects born less than 35 weeks GA and infants with CLD of prematurity or hemodynamically significant CHD. This trial was not powered for efficacy, but efficacy was assessed as secondary endpoint. The efficacy of BEYFORTUS in preterm infants (GA less than 35 weeks) during their first RSV season and in pediatric subjects up to 24 months of age with CLD or CHD during their first and second RSV season was established by extrapolation of efficacy of BEYFORTUS from Trials 03 and Trial 04 to the population enrolled in Trial 05 based on similar nirsevimab-alip exposures among subjects enrolled in Trial 04 and 05 *[see Clinical Pharmacology (12.3)]*.

Trial 05: RSV Season One

Trial 05 enrolled infants at higher risk for severe RSV disease entering their first RSV season into one of two cohorts: preterm infants (GA less than 35 weeks) and infants with CLD of prematurity or hemodynamically significant CHD. A total of 925 infants were randomized 2:1 in each of the preterm (n=615) and CLD/CHD (n=310) cohorts to receive BEYFORTUS or palivizumab. Infants received a single IM dose of BEYFORTUS (50 mg if less than 5 kg body weight or 100 mg if greater than 5 kg body weight at the time of dosing), followed by 4 once-monthly IM doses of placebo, or 5 once-monthly IM doses of 15 mg/kg palivizumab, respectively. At randomization, in the preterm cohort, 77 infants (13%) were less than 29 weeks GA; and 499 (81%) were GA greater than or equal to 29 to less than 35 weeks. In the CLD/CHD cohort, 70% had CLD of prematurity; 34% had hemodynamically significant CHD; 123 infants (40%) were less than 29 weeks GA, 28% were greater than or equal to 29 weeks to less than 35 weeks GA; and 32% were greater than or equal to 35 weeks GA. In both cohorts together, 54% were male; 79% were White; 10% were Black; 5% were Asian; 2% were American Indian/Alaskan Native; 15% were Hispanic or Latino; and 57% weighed less than 5 kg. The median age was 3.5 months (range: 0.07 to 12.3 months); 45% were less than or equal to 3 months; 34% were greater than 3 months to less than or equal to 6 months, and 21% were greater than 6 months of age.
In the first RSV season of Trial 05, the incidence of MA RSV LRTI through 150 days post dose was 0.6% (4/616) in the BEYFORTUS group and 1.0% (3/309) in the palivizumab group.

Trial 05: RSV Season Two

Pediatric subjects with CLD of prematurity or hemodynamically significant CHD up to 24 months of age continued in the trial for a second RSV season (n=262). Subjects who received BEYFORTUS during their first RSV season also received a single dose of 200 mg BEYFORTUS entering their second RSV season followed by 4 once-monthly IM doses of placebo (n=180). Subjects who received palivizumab during their first RSV season were re-randomized 1:1 to either receive BEYFORTUS or palivizumab entering their second RSV season. Forty subjects who received palivizumab in the first RSV season received a single IM dose of BEYFORTUS followed by 4 once-monthly IM doses of placebo in their second RSV season; and 42 subjects received palivizumab (5 once-monthly IM doses of 15 mg/kg palivizumab) in both first and second RSV seasons.
In the second RSV season of Trial 05, there were no cases of MA RSV LRTI through Day 150 post-dose in subjects who received either BEYFORTUS or palivizumab.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

BEYFORTUS injection is a sterile, preservative-free, clear to opalescent, colorless to yellow solution supplied as follows:

- One 50 mg/0.5 mL single-dose pre-filled syringe in a carton: NDC 49281-575-00
- Five 50 mg/0.5 mL single-dose pre-filled syringes in a carton: NDC 49281-575-15
- One 100 mg/mL single-dose pre-filled syringe in a carton: NDC 49281-574-88
- Five 100 mg/mL single-dose pre-filled syringes in a carton: NDC 49281-574-15

Each BEYFORTUS pre-filled syringe is for one time use only.

Storage and Handling

Store refrigerated between 36°F to 46°F (2°C to 8°C). BEYFORTUS may be kept at room temperature 68°F to 77°F (20°C to 25°C) for a maximum of 8 hours. After removal from the refrigerator, BEYFORTUS must be used within 8 hours or discarded.
Store BEYFORTUS in original carton to protect from light until time of use.
Do not freeze. Do not shake. Do not expose to heat.

17 PATIENT COUNSELING INFORMATION

Advise the child's caregiver to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions Including Anaphylaxis

Inform the patient's caregiver of the signs and symptoms of potential hypersensitivity reactions, and advise the caregiver to seek medical attention immediately if the child experiences a hypersensitivity reaction to BEYFORTUS *[see Warnings and Precautions (5.1)]*.

Dosage and Administration

Advise the caregiver that the child will receive one dose of BEYFORTUS by IM injection by a healthcare provider. If the child remains at increased risk for RSV, they may receive a second dose in the second RSV season *[see Dosage and Administration (2.1)]*.

Manufactured by: AstraZeneca AB, Södertälje, Sweden SE-15185

US License No. 2059

Distributed by: Sanofi Pasteur, Inc., Swiftwater, PA 18370 USA

BEYFORTUS is a trademark of the Sanofi group of companies.

PATIENT INFORMATION
BEYFORTUS™ (Bay for tus)
(nirsevimab-alip)
injection, for intramuscular use

What is BEYFORTUS?
BEYFORTUS is a prescription medicine that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV) in:

- newborns and babies under 1 year of age born during or entering their first RSV season.
- children up to 24 months of age who remain at risk of severe RSV disease through their second RSV season.

BEYFORTUS is an antibody that contains nirsevimab-alip which is used to help prevent RSV disease for 5 months. It is not known if BEYFORTUS is safe and effective in children older than 24 months of age.

Your child should not receive BEYFORTUS if your child has a history of serious allergic reactions to nirsevimab-alip or any of the ingredients in BEYFORTUS. See the end of this Patient Information leaflet for a complete list of ingredients in BEYFORTUS.

Before your child receives BEYFORTUS, tell your healthcare provider about all of your child's medical conditions, including if your child:

- has ever had a reaction to BEYFORTUS.
- has bleeding or bruising problems. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.

Tell your child's healthcare provider about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Your infant should not receive a medicine called palivizumab if they have already received BEYFORTUS in the same RSV season.

How is BEYFORTUS given?

- BEYFORTUS is given as an injection, usually in the thigh (leg) muscle, by your child's healthcare provider.
- **Your child should receive BEYFORTUS before or during the RSV season**. RSV season is the time of year when RSV infections are most common, usually occurring fall through spring. Your healthcare provider can tell you when the RSV season starts in your area.
- **Your child may still get RSV disease after receiving BEYFORTUS**. Talk to your child's healthcare provider about what symptoms to look for.
- If your child has heart surgery, your child's healthcare provider may need to give your child an additional BEYFORTUS injection soon after surgery.

What are the possible side effects of BEYFORTUS?

- **Serious allergic reactions** have happened with BEYFORTUS.
- Get medical help right away if your child has any of the following signs or symptoms of a serious allergic reaction:
  - swelling of the face, mouth, or tongue
  - difficulty swallowing or breathing
  - unresponsiveness
  - bluish color of skin, lips or under fingernails
  - muscle weakness
  - severe rash, hives or itching

The most common side effects of BEYFORTUS include rash, and pain, swelling or hardness at the site of your child's injection. These are not all of the possible side effects of BEYFORTUS. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BEYFORTUS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about BEYFORTUS that is written for health professionals.

What are the ingredients in BEYFORTUS?

Active ingredient: nirsevimab-alip

Inactive ingredients: arginine hydrochloride, histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose and water for injection.

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For more information, go to https://www.Beyfortus.com or call 1-855-239-3678 (1-855-BEYFORTUS).

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: February 2024

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