

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                                                                  |                                                                                                                       |                                                                                                                      |  |
|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--|
| Applicant's or agent's file reference<br><div style="text-align: center;"><b>RPH-00125</b></div> |                                                                                                                       | <b>FOR FURTHER ACTION</b><br>see Form PCT/ISA/220 as well as,<br>where applicable, item 5 below.                     |  |
| International application No.<br><div style="text-align: center;"><b>PCT/US2023/012487</b></div> | International filing date ( <i>day/month/year</i> )<br><div style="text-align: center;"><b>07 February 2023</b></div> | (Earliest) Priority Date ( <i>day/month/year</i> )<br><div style="text-align: center;"><b>07 February 2022</b></div> |  |
| Applicant<br><div style="text-align: center;"><b>RIPARIAN PHARMACEUTICALS, INC.</b></div>        |                                                                                                                       |                                                                                                                      |  |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.  
☐ a translation of the international application into \_\_\_\_\_ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.  
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_  
☐ as suggested by the applicant.  
☐ as selected by this Authority, because the applicant failed to suggest a figure.  
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☒ none of the figures is to be published with the abstract.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/012487

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br><b>C07D 498/04</b> (2023.01)i; <b>C07D 498/14</b> (2023.01)i; <b>A61K 31/553</b> (2023.01)i; <b>A61P 9/10</b> (2023.01)i; <b>A61P 9/12</b> (2023.01)i; <b>A61P 29/00</b> (2023.01)i; <b>A61P 31/00</b> (2023.01)i; <b>A61P 37/00</b> (2023.01)i; <b>A61P 37/06</b> (2023.01)i<br>CPC:C07D 498/04; C07D 498/14; A61K 31/553; A61P 9/10; A61P 9/12; A61P 29/00; A61P 31/00; A61P 37/00; A61P 37/06<br>According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                            |                                                                          |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------|------------------------------------------------------------------------------------|-----------------------|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>C07D 498/04; C07D 498/14; A61K 31/553; A61P 9/10; A61P 9/12; A61P 29/00; A61P 31/00; A61P 37/00; A61P 37/06<br>CPC:C07D 498/04; C07D 498/14; A61K 31/553; A61P 9/10; A61P 9/12; A61P 29/00; A61P 31/00; A61P 37/00; A61P 37/06<br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>Databases consulted: PATENTSCOPE, CAPLUS, MARPAT, REGISTRY, PubMed, Google Scholar, PatBase, DWPI Search terms used: KLF2, Kruppel-like transcription factor, lung Kruppel-like Factor, LKLF, ?endothel?, ?inflamm?, vascular, tricyclic, ?oxazepin?, statin?.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                            |                                                                          |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>CAS Registry Number: 1215615-88-5; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 4-(3,5-dimethylphenyl)-2,3,4,5-tetrahydro-N-[(4-methoxyphenyl)methyl]-3-methyl-5-oxo-; Entered STN: 02 April 2010. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2010/04/02)</td> <td>1,2,4-9,14-18,37-39</td> </tr> <tr> <td>X</td> <td>CAS Registry Number: 1189959-66-7; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, N-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-3-methyl-5-oxo-4-phenyl; Entered STN: 25 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2009/10/25)</td> <td>1,2,4-9,14-18,37-39</td> </tr> <tr> <td>X</td> <td>CAS Registry Number: 1189706-00-0; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 2,3,4,5-tetrahydro-3-methyl-5-oxo-4-phenyl-N-(phenylmethyl)-; Entered STN: 23 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2009/10/23)</td> <td>1,2,4-9,14-18,37</td> </tr> </tbody> </table>                                          |                                                                                                                                                                                                                                                                                                            |                                                                          | Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | X | CAS Registry Number: 1215615-88-5; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 4-(3,5-dimethylphenyl)-2,3,4,5-tetrahydro-N-[(4-methoxyphenyl)methyl]-3-methyl-5-oxo-; Entered STN: 02 April 2010. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2010/04/02) | 1,2,4-9,14-18,37-39 | X | CAS Registry Number: 1189959-66-7; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, N-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-3-methyl-5-oxo-4-phenyl; Entered STN: 25 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2009/10/25) | 1,2,4-9,14-18,37-39 | X | CAS Registry Number: 1189706-00-0; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 2,3,4,5-tetrahydro-3-methyl-5-oxo-4-phenyl-N-(phenylmethyl)-; Entered STN: 23 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2009/10/23) | 1,2,4-9,14-18,37 |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                         | Relevant to claim No.                                                    |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | CAS Registry Number: 1215615-88-5; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 4-(3,5-dimethylphenyl)-2,3,4,5-tetrahydro-N-[(4-methoxyphenyl)methyl]-3-methyl-5-oxo-; Entered STN: 02 April 2010. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2010/04/02) | 1,2,4-9,14-18,37-39                                                      |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | CAS Registry Number: 1189959-66-7; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, N-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-3-methyl-5-oxo-4-phenyl; Entered STN: 25 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2009/10/25)               | 1,2,4-9,14-18,37-39                                                      |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | CAS Registry Number: 1189706-00-0; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 2,3,4,5-tetrahydro-3-methyl-5-oxo-4-phenyl-N-(phenylmethyl)-; Entered STN: 23 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2009/10/23)                        | 1,2,4-9,14-18,37                                                         |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                            |                                                                          |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| * Special categories of cited documents:<br>“A” document defining the general state of the art which is not considered to be of particular relevance<br>“D” document cited by the applicant in the international application<br>“E” earlier application or patent but published on or after the international filing date<br>“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>“O” document referring to an oral disclosure, use, exhibition or other means<br>“P” document published prior to the international filing date but later than the priority date claimed<br>“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>“&” document member of the same patent family |                                                                                                                                                                                                                                                                                                            |                                                                          |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| Date of the actual completion of the international search<br><b>29 May 2023</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                            | Date of mailing of the international search report<br><b>30 May 2023</b> |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |
| Name and mailing address of the ISA/IL<br><b>Israel Patent Office</b><br><b>Technology Park, Bldg.5, Malcha, Jerusalem, 9695101,</b><br><b>Israel</b><br><b>Israel</b><br>Telephone No. <b>972-73-3927252</b><br>Email: <b>pctoffice@justice.gov.il</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                            | Authorized officer<br><br><b>SOMECH Erez</b><br><br>Telephone No.        |           |                                                                                    |                       |   |                                                                                                                                                                                                                                                                                                            |                     |   |                                                                                                                                                                                                                                                                                              |                     |   |                                                                                                                                                                                                                                                                                     |                  |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/012487

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                 | Relevant to claim No.     |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| X         | CAS Registry Number: 1185009-90-8; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 4-butyl-2,3,4,5-tetrahydro-N-[(4-methoxyphenyl)methyl]-3-methyl-5-oxo-; Entered STN: 16 September 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals. (2009/09/16)                                                                                                                                                                                    | 1,2,4-9,14-18,28,37-39    |
| X         | RU 2281947 C1 (Obshchestvo s ogranichennoj otvetstvennost'ju &quot;Issledovatel'skij Institut Khimicheskogo Raznoobrazija&quot; [RU])20 August 2006 (2006-08-20)<br>Compound G215-0724 (table 3, ex. 1.11(6), which is the last compound on page 45).                                                                                                                                                                                                                              | 1,2,4-9,14-18,37-39,41,43 |
| X         | WO 2005/105805 A1 (CHEMICAL DIVERSITY RESEARCH INSTITUTE LTD)10 November 2005 (2005-11-10)<br>Compound 10 on table 1.14 (which is the last compound on page 398).                                                                                                                                                                                                                                                                                                                  | 1,2,4-9,14-18,37-39,41,43 |
| A         | DABRAVOLSKI, Siarhei A., et al. The role of KLF2 in the regulation of atherosclerosis development and potential use of KLF2-targeted therapy. Biomedicines, 2022, 10.2: 254.# Published: 24 January 2022. DOI: <10.3390/biomedicines10020254>. URL: <https://www.mdpi.com/2227-9059/10/2/254>. (2022/01/24)<br>The whole document. Particularly see figure 2.                                                                                                                      | 1-45                      |
| A         | WO 2004/091660 A1 (KOWA CO., LTD. [JP])28 October 2004 (2004-10-28)<br>Formula 1.                                                                                                                                                                                                                                                                                                                                                                                                  | 1-45                      |
| A         | WO 2008/132458 A1 (INION LIMITED [GB])06 November 2008 (2008-11-06)<br>Abstract, claims and examples.                                                                                                                                                                                                                                                                                                                                                                              | 1-45                      |
| A         | LAHA, Dipranjan; DEB, Moonmoon; DAS, Hiranmoy. KLF2 (kruppel-like factor 2 [lung]) regulates osteoclastogenesis by modulating autophagy. Autophagy, 2019, 15.12: 2063-2075.# Accepted author version posted online: 20 March 2019. DOI: <10.1080/15548627.2019.1596491>. Retrieved from URL: <https://www.tandfonline.com/doi/full/10.1080/15548627.2019.1596491>. (2019/03/20)<br>Abstract (compound GGTI298).                                                                    | 1-45                      |
| A         | GRACIA-SANCHO, Jorge, et al. Endothelial expression of transcription factor Kruppel-like factor 2 and its vasoprotective target genes in the normal and cirrhotic rat liver. Gut, 2011, 60.4: 517-524.# First published 26 November 2010. DOI: <10.1136/gut.2010.220913>. Retrieved from Google Scholar. (2010/11/26)<br>See &quot;In-vivo KLF2 induction&quot; (the compound Simvastatin).                                                                                        | 1-45                      |
| A         | PABBISETTY, Sudheer K., et al. KLF2 is a rate-limiting transcription factor that can be targeted to enhance regulatory T-cell production. Proceedings of the National Academy of Sciences, 2014, 111.26: 9579-9584. Published: 16 June 2014. DOI: <10.1073/pnas.1323493111>. Retrieved from URL: <https://www.pnas.org/doi/pdf/10.1073/pnas.1323493111>. (2014/06/16)<br>See &quot;Drugs That Stabilize KLF2 Expression Enhance iTreg Production&quot; (the compound simvastatin). | 1-45                      |
| A         | US 5,489,586 A (Warner-Lambert Company [US])06 February 1996 (1996-02-06)<br>Abstract, formula I and table I.                                                                                                                                                                                                                                                                                                                                                                      | 1-45                      |
| A         | WO 2021/184059 A1 (NEWSOUTH INNOVATIONS PTY LIMITED [AU])23 September 2021 (2021-09-23)<br>Formula II.                                                                                                                                                                                                                                                                                                                                                                             | 1-45                      |

**INTERNATIONAL SEARCH REPORT**  
**Information on patent family members**

International application No.

**PCT/US2023/012487**

| Patent document<br>cited in search report |             |    | Publication date<br>(day/month/year) | Patent family member(s) |              |    | Publication date<br>(day/month/year) |
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|                                           |             |    |                                      | WO                      | 2008132458   | A8 | 16 July 2009                         |
| US                                        | 5,489,586   | A  | 06 February 1996                     | US                      | 5489586      | A  | 06 February 1996                     |
|                                           |             |    |                                      | AT                      | 187728       | T  | 15 January 2000                      |
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|                                           |             |    |                                      | AU                      | 688466       | B2 | 12 March 1998                        |
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|                                           |             |    |                                      | CA                      | 2181354      | A1 | 14 September 1995                    |
|                                           |             |    |                                      | CA                      | 2211179      | A1 | 26 September 1996                    |
|                                           |             |    |                                      | CZ                      | 259796       | A3 | 11 June 1997                         |
|                                           |             |    |                                      | CZ                      | 292009       | B6 | 16 July 2003                         |
|                                           |             |    |                                      | DE                      | 69513961     | D1 | 20 January 2000                      |
|                                           |             |    |                                      | DE                      | 69513961     | T2 | 29 June 2000                         |
|                                           |             |    |                                      | DE                      | 69632726     | D1 | 22 July 2004                         |
|                                           |             |    |                                      | DE                      | 69632726     | T2 | 14 October 2004                      |
|                                           |             |    |                                      | DK                      | 0749434      | T3 | 29 May 2000                          |
|                                           |             |    |                                      | DK                      | 0817635      | T3 | 27 September 2004                    |
|                                           |             |    |                                      | EP                      | 0749434      | A1 | 27 December 1996                     |
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|                                           |             |    |                                      | EP                      | 0817635      | B1 | 16 June 2004                         |
|                                           |             |    |                                      | ES                      | 2141922      | T3 | 01 April 2000                        |
|                                           |             |    |                                      | ES                      | 2222477      | T3 | 01 February 2005                     |
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**INTERNATIONAL SEARCH REPORT**  
**Information on patent family members**

International application No.

**PCT/US2023/012487**

| Patent document<br>cited in search report |  | Publication date<br>(day/month/year) |  | Patent family member(s) |            | Publication date<br>(day/month/year) |                   |
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|                                           |  |                                      |  | NO                      | 963744     | D0                                   | 06 September 1996 |
|                                           |  |                                      |  | NO                      | 963744     | L                                    | 06 September 1996 |
|                                           |  |                                      |  | NO                      | 313384     | B1                                   | 23 September 2002 |
|                                           |  |                                      |  | NZ                      | 279737     | A                                    | 27 July 1997      |
|                                           |  |                                      |  | PH                      | 31163      | A                                    | 20 March 1998     |
|                                           |  |                                      |  | PL                      | 316197     | A1                                   | 23 December 1996  |
|                                           |  |                                      |  | PL                      | 180457     | B1                                   | 28 February 2001  |
|                                           |  |                                      |  | PT                      | 817635     | E                                    | 29 October 2004   |
|                                           |  |                                      |  | RO                      | 117919     | B1                                   | 30 September 2002 |
|                                           |  |                                      |  | RU                      | 2144033    | C1                                   | 10 January 2000   |
|                                           |  |                                      |  | SI                      | 0749434    | T1                                   | 30 April 2000     |
|                                           |  |                                      |  | SI                      | 0817635    | T1                                   | 31 October 2004   |
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