2.2　個別有害事象の文章による説明

試験参加中の死亡又は他の重篤な有害事象を発現した被験者の記述は、個別の治験総括報告書に含めた（モジュール 5.3）。他の重要な有害事象については、臨床的に問題となる所見が認められた場合に治験総括報告書に記述した。

3.　臨床検査値の評価

測定したすべての臨床検査項目について、測定値の要約統計量及びベースラインからの変化をまとめ、モジュール 5 の個々の治験総括報告書に示す。グレードが利用可能な測定項目については、シフトテーブルについてもモジュール 5.3.7 に示す。血清カルシウムに関連する臨床検査結果は第 3.1 項に要約する。抗デノスマブ抗体評価の要約は第 3.2 項に示し、その他の安全性に関する臨床検査値の評価は、すべて第 3.3 項に要約する。骨代謝マーカーについては、モジュール 2.7.3 で考察した。

主な臨床検査値の異常値の発現率は、CTCAE version 4.0 日本語訳 JCOG 版に従って定義した重症度評価基準を用いた。臨床検査項目について、グレード別の CTCAE version 4.0 日本語訳 JCOG 版を表 7-7 に示す。なお、参考とした骨量減少に関する外国承認申請時の安全性解析では、CTCAE version 3.0 に従って定義した重症度評価基準を用いた（M2.7.4-G-PMO/HALT 表 57）。

3.1　アルブミン補正血清カルシウム値

3.1.1　Japan Safety Analysis Set におけるアルブミン補正血清カルシウム値

グレード 2 に該当するアルブミン補正血清カルシウム値の低下は、デノスマブ群合計 0.6%（4/633）、プラセボ群合計 0.4%（2/535）、グレード 3 の低下はデノスマブ群合計 0.2%（1/633）、グレード 4 の低下はデノスマブ合計 0.2%（1/633）（IAS 表 5-1.2）、ベースラインから 2 グレード以上変化した被験者は、デノスマブ群合計 0.9%（6/633）及びプラセボ群合計 0.2%（1/535）に認められた（IAS 表 5-1.3）。デノスマブ群合計 0.5%（3/633）は、治験実施計画書に規定された評価時点のうち、少なくとも 1 回以上でアルブミン補正血清カルシウム値が 7.5 g/dL 未満であった（IAS 表 5-1.1）。アレンドロネート群では上記に該当するアルブミン補正血清カルシウム値の低下はいずれも認められなかった。

試験 AMG162-A-J301 及び 20050172 のいずれにおいても、デノスマブ群の投与開始 1 ヵ月後の血清カルシウム濃度中央値はベースラインに比してわずかに低下した。この初期の血清カルシウム低下は長期間持続することはなく、以後の評価時点で平均濃度はベースラインの水準に戻った（試験 AMG162-A-J301　治験総括報告書［二重盲検期］図 15.3.1-6.3 及び IAS 図 5-1.1）。

試験 AMG162-A-J301 では、デノスマブ群で、プラセボ群と比較して、アルブミン補正血清カルシウム値のわずかな低下が投与開始 1 ヵ月後に認められた（デノスマブ群のベースラインからの変化率中央値［四分位数範囲］: −3.2%［−6.3%～0.0%］、プラセボ群の値: 0.0%［−2.1%～2.2%］、アレンドロネート群の値: −2.1%［−4.2%～1.1%］）（試験 AMG162-A-J301　治験総括

報告書［二重盲検期］ 表 15.3.1-7.7.3）。その他の全時点では、変化率の中央値に投与群間で大きな違いはなく、ベースライン値から約±4%の範囲内を維持した（試験 AMG162-A-J301 治験総括報告書［二重盲検期］ 図 15.3.1-6.3 及び表 15.3.1-7.7.3）。投与 24 ヵ月後（この試験での盲検投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）はデノスマブ群で−1.1%（−3.2%、2.2%）、プラセボ群で 0.0%（−3.1%、2.2%）、アレンドロネート群で−1.1%（−4.3%、1.1%）であった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］ 表 15.3.1-7.7.3）。

試験 20050172 では、デノスマブ群で、プラセボ群と比較して、アルブミン補正血清カルシウム値のわずかな低下が 8 日目及び投与開始 1 ヵ月後に認められた（8 日目: 14 mg Q6M 群 −5.8%［−7.8%、−2.7%］、60 mg Q6M 群−6.4%［−8.2%、−3.1%］、100 mg Q6M 群−3.3%［−5.5%、−1.0%］、プラセボ群 0.0%［−3.2%、3.2%］、投与 1 ヵ月後: −4.4%［−8.0%、−2.1%］、−5.4%［−8.3%、−2.2%］、−2.2%［−5.2%、1.1%］、0.0%［−2.1%、3.2%］）（試験 20050172 治験総括報告書 表 14-7.12.1）。その他の全時点では、変化率の中央値に投与群間で大きな違いはなく、ベースライン値から±4%の範囲内を維持した（試験 20050172 治験総括報告書 図 11-1 及び表 14-7.12.1）。投与 12 ヵ月後（この試験での投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）は 14 mg Q6M 群−2.0%（−3.2%、1.1%）、60 mg Q6M 群−2.0%（−3.3%、0.0%）、100 mg Q6M 群−0.5%（−4.1%、3.3%）、プラセボ群で 0.0%（−3.2%、2.2%）であった（試験 20050172 治験総括報告書 表 14-7.12.1）。

3.1.2 外国参考試験におけるアルブミン補正カルシウム値

1) Primary PMO Safety Analysis Set におけるアルブミン補正カルシウム値

Primary PMO Safety Analysis Set では、デノスマブ群の 6 名（0.1%）及びプラセボ群の 4 名（0.1%未満）において、アルブミン補正血清カルシウムの低下が CTCAE（version 3.0）グレード 2 に達した（それぞれベースラインから 2 グレードの変化）。デノスマブ群では、いずれかの評価時点でグレード 3 又は 4 の血清カルシウム低下を示した被験者はいなかったが、プラセボ群の 1 名では、グレード 3 の低下が認められた（M2.7.4-G-PMO/HALT 表 40、M2.7.4-G-PMO/HALT IAS 表 SP2-7.2.2 及び表 SP2-7.3）。両投与群の各 2 名（0.1%未満）は、治験実施計画書に規定された評価時点のうち、少なくとも 1 回以上でアルブミン補正血清カルシウム値が 7.5 g/dL 未満であった（M2.7.4-G-PMO/HALT IAS 表 SP2-7.4）。別の 1 名（試験 20030216 の被験者*****0071）では、デノスマブ開始から約 33 ヵ月後の敗血症性ショックを伴う大腸菌性敗血症による入院中に、医療機関での測定で血清カルシウム値が 7.36 mg/dL（1.84 mmol/L）であった。

試験 20030216 では、デノスマブ群で、プラセボ群に比して、アルブミン補正血清カルシウム値のわずかな低下が投与開始 1 ヵ月後に認められた（デノスマブ群のベースラインからの変化率中央値［四分位数範囲］: −2.1%［−5.2%～1.0%］、プラセボ群の値: 1.0%［−2.0%～3.2%］）（試験 20030216 治験総括報告書 表 14-7.5.1）。他の全時点では変化率の中央値に投与群間の違いはなく、ベースライン値から約±3%の範囲内を維持した（M2.7.4-G-PMO/HALT 図 3）。投与 36 ヵ月後（この試験での投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、

Q3）はデノスマブ群で−2.0%（−5.0%、1.1%）、プラセボ群で−2.1%（−5.0%、1.0%）であった。

試験 20040132 では、投与 1 ヵ月後のアルブミン補正血清カルシウム値のベースラインからの変化率（中央値［Q1、Q3］）は、デノスマブ群−3.1%（−5.7%、0.0%）、プラセボ群 0.0%（−2.2%、3.2%）であった（試験 20040132 治験総括報告書 表 14-16.2.2）。その他の全時点では、変化率の中央値に投与群間の違いはなく、ベースライン値から約±1%の範囲内を維持した（M2.7.4-G-PMO/HALT 図 4）。投与 24 ヵ月後（この試験での投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）はデノスマブ群で−1.1%（−5.1%、1.9%）、プラセボ群で−1.0%（−4.0%、2.4%）であった。

2) Primary HALT Safety Analysis Set におけるアルブミン補正カルシウム値

Primary HALT Safety Analysis Set では、デノスマブ群の 3 名（0.3%）及びプラセボ群の 1 名（0.1%）において、アルブミン補正血清カルシウムの低下が CTCAE（version 3.0）グレード 2 に達した（それぞれベースラインから 2 グレードの変化）。両投与群において、いずれかの評価時点でグレード 3 又は 4 の血清カルシウム低下を示した被験者（M2.7.4-G-PMO/HALT 表 41、M2.7.4-G-PMO/HALT IAS 表 SH-7.2.1 及び表 SH-7.3）、及びいずれかの評価時点でアルブミン補正血清カルシウム値が 7.5 g/dL 未満となった被験者はいなかった（M2.7.4-G-PMO/HALT IAS 表 SH-7.4）。

試験 20040135 では、デノスマブ群で、プラセボ群に比して、アルブミン補正血清カルシウム値のわずかな低下が投与開始 1 ヵ月後に認められた（デノスマブ群のベースラインからの変化率中央値［Q1、Q3］: −2.7%［−6.4%、0.0%］、プラセボ群の値: 0.0%［−2.2%、3.0%］）（試験 20040135 治験総括報告書 表 14-7.3.7）。以後の時点のアルブミン補正血清カルシウム値の中央値には、デノスマブ群とプラセボ群の間の違いは認められなかった（M2.7.4-G-PMO/HALT 図 5）。投与 12 ヵ月後の両投与群のアルブミン補正血清カルシウム値はベースライン値を超え、以後ベースラインを超える値を維持した。

試験 20040138 では、デノスマブ群で、プラセボ群に比して、アルブミン補正血清カルシウム値のわずかな低下が投与 1 ヵ月後に認められた（デノスマブ群のベースラインからの変化率中央値［Q1、Q3］: −3.3%［−6.5%、0.0%］、プラセボ群の値: 0.0%［−2.1%、3.1%］）（試験 20040138 治験総括報告書 表 14-7.5.5）。以後の評価時点で平均値はベースラインの水準に戻った（M2.7.4-G-PMO/HALT 図 6）。投与 36 ヵ月後（この試験での投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）はデノスマブ群で 2.6%（−1.0%、5.6%）及びプラセボ群で 2.1%（−2.0%、4.8%）であった。

3) 低骨密度患者におけるデノスマブ投与開始 4 日目及び 10 日目の血清カルシウム評価

試験 20010223 及び試験 20060289 においてデノスマブ投与開始早期に血清カルシウムを測定した結果を以下に示す。

試験 20010223 では投与開始 4 日目に血清カルシウムを測定した。この試験ではアルブミン補正血清カルシウム中央値がすべてのデノスマブ群でわずかに低下し、変化率は 4 日目で

−3.0%～−4.3%、1ヵ月時点で−1.1%～−3.9%であった（試験 20010223 治験総括報告書 表 14-7.1.2.3）。カルシウム変化率の中央値は時間の経過とともにベースライン水準近くに戻り、いずれの時点においても、全デノスマブ群においてベースラインからの変化率が−4.3%を下回ることはなかった。

試験 20060289 は試験 20030216 の進行中の延長投与試験であり、血清カルシウム値は 10 日目及び投与開始以後 6 ヵ月ごとに評価した。この試験では全被験者に対して非盲検下でデノスマブを投与した（60 mg Q6M）。20[redacted]年[redacted]月[redacted]日時点で、少なくとも 10 日目の時点まで試験を継続したプラセボからデノスマブへの切り替え投与群 2080 名（試験 20030216 のプラセボ群）及びデノスマブ継続投与群 2207 名（試験 20030216 のデノスマブ群）からのデータが得られている（試験 20060289 治験総括報告書［24 ヵ月］ 表 03-7.1.7 及び表 03-7.2.2）。ベースライン時（試験 20030216 の投与 36 ヵ月後来院）の血清カルシウム値の中央値には投与群間に違いは認められなかった（新規投与群 9.70 mg/dL［2.43 mmol/L］、長期投与群 9.70 mg/mL［2.43 mmol/L］）（試験 20060289 治験総括報告書［24 ヵ月］ 表 03-2.5.1）。アルブミン補正血清カルシウム値の試験 20060289 のベースラインから 10 日目までの低下率の中央値（Q1、Q3）に、プラセボからデノスマブへの切り替え投与群（−3.1%［−6.1%、0.0%］）とデノスマブ継続投与群（−2.0%［−5.1%、1.1%］）との間で大きな違いは認められなかった（試験 20060289 治験総括報告書［24 ヵ月］ 表 03-7.8.5）。

4) アレンドロネート対照試験における血清カルシウム評価

試験 20050141 及び 20050179 を用いて、デノスマブによる血清カルシウム値の変動をアレンドロネートと比較した。両試験とも試験実施期間は 12 ヵ月間であった（デノスマブ 2 回投与）。いずれの試験においても、両投与群で一過性の軽度な血清カルシウム減少が認められたが、随伴する臨床症状はなかった。投与 12 ヵ月後デノスマブ投与群での変化率の中央値はアレンドロネート投与群での値と一致していた（試験 20050141 0.0%、試験 20050179 −2.1%）（試験 20050141 治験総括報告書 図 11-1 及び表 14-7.1.5、試験 20050179 治験総括報告書 図 11-1 及び表 14-7.1.5）。

3.2 抗デノスマブ抗体形成

たん白質製剤の投与は、免疫反応を誘発する可能性がある。デノスマブはヒト型モノクローナル抗体であるため、6 ヵ月以上デノスマブを投与されたヒト以外の霊長類では、高頻度で結合抗体（35%～76%）及び中和抗体（20%～47%）の形成が認められた。これらの抗体により、デノスマブのクリアランスは増加し、薬力学パラメータの変化は小さくなった。その他には高い抗体産生に起因する毒性学的所見は見られなかった（モジュール 2.4 第 4.7.1 項）。一方、臨床試験における抗体産生の頻度は低かった。

すべての非臨床試験及び臨床試験でデノスマブに対する抗体を検出するため、感度の高い特異的な分析手法を開発し、妥当性を検証した。電気化学発光ブリッジング免疫測定法により、結合抗体の有無をスクリーニングした。陽性の場合は、細胞を用いた化学発光 mRNA 発現の

測定により、中和抗体の確認を行った。免疫原性測定法に関する詳細な手順及び個々の試験結果は、モジュール 5.3.5.3 の免疫原性に関する併合報告書に示す。

試験 AMG162-A-J301 ではデノスマブ投与群にて 1 名（被験者*****0019）に治験薬投与開始 1 ヵ月時点で結合抗体が検出された（0.2%［1/474 名］）。結合抗体の検出は一過性であり本被験者のその後の測定時点では結合抗体及び中和抗体は検出されなかった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］表 15.3.1-10.1.1、［長期］表 15.3.1-10.1.1、及び 15.3.1-10.1.2）。また、結合抗体検出の前後で特徴的な有害事象の発現は認められなかった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］一覧表 16.2.7-3）。

日本人被験者を対象とした試験 20030164、20050172、及び AMG162-A-J301 において抗体が検出されたのはこの 1 名のみであり、その他には結合抗体及び中和抗体は検出されなかった。

本承認申請に用いたすべての臨床試験でデノスマブを投与し、抗体検査を受けた 10895 名の被験者のうち 41 名（0.4%）に結合抗体陽性が認められたが、検出された抗体のほとんどは一過性の発現であった。デノスマブの臨床開発計画（他の疾患領域を含む）において、これまでに中和抗体は認められていない。また、結合抗体陽性を示した被験者において、デノスマブの安全性プロファイルに影響は認められていない。製造場所が異なる製剤及び剤型が異なる製剤でも、抗体産生に及ぼす影響は認められていない（第 5.2.2 項）。

3.3　その他の全臨床検査パラメータ

3.3.1　Japan Safety Analysis Set におけるその他の全臨床検査パラメータ

CTCAE グレード上の変化を指標とした血液生化学検査及び血液学的検査結果への影響に関する検討において、ほとんどの検査項目で投与群間で明らかな違いは認められなかった。デノスマブ群にてアルブミン補正カルシウム値減少、血清マグネシウム値増加、及び血清リン値減少の変動を示した被験者の割合がプラセボ群と比較し数値上高い傾向を示した（IAS 表 5-2.1.1～表 5-2.1.19）が、有害事象として報告されたものはまれであり、多くの変動が治験責任医師により臨床上問題となるものではないと判断された（IAS 表 4-2.1）。

グレード 3 又は 4 のトランスアミナーゼ値増加は両投与群で認められなかった（IAS 表 5-2.2）。グレード 3 のビリルビン増加を示した被験者はプラセボ群 0.2%（1/535）であり、デノスマブ群にはなかった（IAS 表 5-2.1.10）。

個々の試験結果では、これまで実施された臨床試験で認められているアルブミン補正血清カルシウム減少、リン減少、及び ALP 減少を除き、血液生化学検査及び血液学的検査で明らか変化は認められなかった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］表 15.3.1-7.1.1～表 15.3.1-7.6.3、試験 20050172 治験総括報告書 表 14-7.1.1～表 14-7.11.28）。

試験 AMG162-A-J301 では、デノスマブ群及びアレンドロネート群で、プラセボ群と比較して、わずかなリン減少が投与開始 1 ヵ月後に認められた（デノスマブ群のベースラインからの変化率中央値［四分位数範囲］: −10.1%［−17.1%～0.0%］、プラセボ群の値: 0.0%［−7.4%～8.6%］、アレンドロネート群の値: −5.3%［−12.8%～3.7%］）。投与 24 ヵ月後（この試験での盲検投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）はデノスマブ群で−3.2%

（−12.2%、3.0%）、プラセボ群で 0.0%（−7.4%、7.5%）、アレンドロネート群で−7.4%（−14.6%、4.2%）であった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］ 表 15.3.1-7.7.2）。

ALP に関しては、デノスマブ群及びアレンドロネート群でプラセボ群と比較して投与 6 ヵ月後に減少が認められた（デノスマブ群のベースラインからの変化率中央値［四分位数範囲］: −36.0%［−45.2%～−28.0%］、プラセボ群の値: −11.5%［−20.4%～−1.9%］、アレンドロネート群の値: −31.1%［−40.3%～−21.4%］）。投与 24 ヵ月後（この試験での盲検投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）はデノスマブ群で−34.6%（−44.8%、−25.3%）、プラセボ群で−5.7%（−15.0%、4.8%）、アレンドロネート群で−31.7%（−41.4%、−22.3%）であった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］表 15.3.1-7.7.1）。なお、リン及び ALP を含め試験 AMG162-A-J301 で測定したすべての臨床検査値において試験開始時に正常値を示していた被験者が試験期間中に異常値を示した割合に投与群間で差は認められなかった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］表 15.3.1-7.5.1～表 15.3.1-7.6.3）。

試験 20050172 では、デノスマブ群で、プラセボ群と比較して、血清リン減少が試験期間を通じて認められた（試験 20050172 治験総括報告書 表 14-7.12.2）。最も大きな減少は投与 8 日目の 60 mg Q6M 群で認められ、ベースラインからの変化率中央値［四分位数範囲］は−16.3%（−22.2%、−5.7%）であった。同時点でプラセボ群では 2.3%（−5.1%、7.9%）、14 mg Q6M 群では−0.2%（−0.2、−0.0）、及び 100 mg Q6M 群では−0.2%（−0.2、0.0）であった。投与 12 ヵ月後（この試験での投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）は、14 mg Q6M 群−2.8%（−10.0%、3.9%）、60 mg Q6M 群−6.1%（−12.5%、0.0%）、100 mg Q6M 群−5.7%（−13.2%、0%）、及びプラセボ群で 0%（−2.6%、5.9%）であった（試験 20050172 治験総括報告書 表 14-7.12.2）。デノスマブ群の被験者 15 名（14 mg Q6M 群 5 名［9%］、60 mg Q6M 群 7 名［13%］、及び 100 mg Q6M 群 3 名［6%］）で、ベースラインのグレード 0 からグレード 2 への血清リン減少が認められた。プラセボ群ではベースラインのグレード 0 からグレード 2 への血清リン減少が認められた被験者はいなかった。また、すべての投与群でグレード 3 以上の変化を認めた被験者はいなかった（試験 20050172 治験総括報告書 表 14-7.6.5）。

ALP に関しては、デノスマブ群で、プラセボ群と比較して、投与 2 ヵ月後より減少が認められた（試験 20050172 治験総括報告書 表 14-7.12.3）。最も大きな減少は投与 3 ヵ月後の 60 mg Q6M 群で認められ、ベースラインからの変化率中央値［四分位数範囲］は−37.1%（−40.7%、−25.5%）であった。プラセボ群では同時点で−4.0%（−13.0%、−0.8%）であった。投与 12 ヵ月後（この試験での投与期の最終測定時点）のベースラインからの変化率の中央値（Q1、Q3）は、14 mg Q6M 群−31.6%（−37.7%、−18.4%）、60 mg Q6M 群−33.9%（−47.3%、−28.4%）、100 mg Q6M 群−35.8%（−48.1%、−29.5%）、及びプラセボ群で−2.6%（−10.9%、5.3%）であった（試験 20050172 治験総括報告書 表 14-7.12.3）。いずれの投与群においても、2 段階以上のグレードの ALP 減少を認めた被験者はいなかった（試験 20050172 治験総括報告書 表 14-7.6.11）。

3.3.2　外国参考試験におけるその他の臨床検査パラメータ

1)　Primary PMO Safety Analysis Set におけるその他の臨床検査パラメータ

Primary PMO Safety Analysis Set では、血液生化学検査及び血液学的検査に投与群間で明らかな違いは認められなかった。各血液生化学検査及び血液学的検査結果において、CTCAE グレード上の変化はまれであり、大部分の被験者でベースライン値からの臨床的に意味のある変化（グレードの 1 段階以上の変化）は認められなかった（M2.7.4-G-PMO/HALT IAS 表 SP2-7.1.1～表 SP2-7.1.17）。

グレード 3 又は 4 の臨床検査異常の頻度は低く、発現率に投与群間で違いは認められなかった。ただし、グレード 3 の血清リン減少の発現率はデノスマブ投与群（7 名［0.2%］）でプラセボ群（発現被験者なし）と比較してわずかに高かった（M2.7.4-G-PMO/HALT 表 42）。なお、プラセボ群の 1 名（0.1%未満）ではグレード 4 のリン減少が認められた。

グレード 3 又は 4 のトランスアミナーゼ値上昇の発現率に、投与群間で違いは認められなかった。（M2.7.4-G-PMO/HALT 表 42）。グレード 3 のビリルビン増加を示した被験者はデノスマブ群 5 名（0.1%）であり、プラセボ群では認められなかった。2 名（被験者*****0072 及び*****0073）で、正常範囲上限の 3 倍のアミノトランスフェラーゼ増加が、正常範囲上限の 2 倍のビリルビン増加と同時に発現した（試験 20030216 治験総括報告書 一覧表 1-5.1.4）。被験者*****0072 は、856 日目に肝新生物 hepatic neoplasm が認められ、そのため非代償性慢性肝毒性「decompensated chronic hepatoxicity」及び腹水 ascites をきたした（試験 20030216 治験総括報告書 一覧表 1-4.1.4）。1020 日目にグレード 3 のアラニンアミノトランスフェラーゼ増加 alanine aminotransferase increased（［ALT］212 U/L）及び 1097 日目にグレード 3 のビリルビン増加 blood bilirubin increased（68.4 μmol/L）が発現した。被験者*****0073 は、709 日目に膵癌 pancreatic carcinoma と診断され、737 日目にグレード 3 の ALT、アスパラギン酸アミノトランスフェラーゼ（AST）増加 aspartate aminotransferase increased、及びビリルビン増加 blood bilirubin increased が発現した（それぞれ 504 U/L、280 U/L、及び 138.5 μmol/L）（試験 20030216 治験総括報告書 一覧表 1-4.1.4 及び一覧表 1-5.1.4）。この被験者は膵癌の事象発現から約 1 ヵ月半後に膵癌のため死亡した。

2)　Primary HALT Safety Analysis Set におけるその他の臨床検査パラメータ

Primary HALT Safety Analysis Set では、血液生化学検査及び血液学的検査に投与群間で明らかな違いは認められなかった。各血液生化学検査及び血液学的検査結果において、CTCAE グレード上の変化はまれであり、大部分の被験者でベースライン値からの臨床的に意味のある変化（グレード上 1 段階以上の変化）は認められなかった（M2.7.4-G-PMO/HALT IAS 表 SH-7.1.1～表 SH-7.1.18）。

グレード 3 又は 4 の臨床検査異常の頻度は低く、発現率に投与群間で違いは認められなかった（M2.7.4-G-PMO/HALT 表 43）。デノスマブ群の 4 名（0.5%）では、グレード 3 又は 4 の血清リン減少が認められた。グレード 3 及び 4 のトランスアミナーゼ値上昇の発現率は、デノスマブ群よりプラセボ群でわずかに高かった。トランスアミナーゼ値上昇の事象のうち、正常範

囲上限の 2 倍以上のビリルビン増加と同時に発現したものはなかった（試験 20040135 治験総括報告書 一覧表 14-7.5.1 及び試験 20040138 治験総括報告書 一覧表 1-4.19）。

4. バイタルサイン、身体的所見及び安全性に関連する他の観察項目

4.1 バイタルサイン

4.1.1 国内第 II 相試験及び国内第 III 相試験におけるバイタルサイン

試験 AMG162-A-J301 及び 20050172 のいずれにおいても、収縮期及び拡張期血圧、脈拍数、体温、体重、又は BMI に対し、デノスマブの影響は認められなかった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］ 第 12.5.1 項、［長期］及び試験 20050172 治験総括報告書 第 11.12.1 項）。バイタルサインに関係する臨床的事象（低血圧、高血圧、頻脈、徐脈、発熱、低体温）の発現率に、投与群間で違いは認められなかった（試験 AMG162-A-J301 治験総括報告書［二重盲検期］ 第 12.2 項、［長期］及び試験 20050172 治験総括報告書 第 11.1 項）。

4.1.2 外国参考試験におけるバイタルサイン

試験 20030216、20040132、20040135、及び 20040138 のいずれにおいても、収縮期及び拡張期血圧、脈拍数、体温、体重、又は BMI に対し、デノスマブの影響は認められなかった（M2.7.4-G-PMO/HALT IAS 表 SP2-8.1.500、試験 20030216 治験総括報告書及び 20040132 治験総括報告書、M2.7.4-G-PMO/HALT IAS 表 SH2-8.1.500、並びに試験 20040135 治験総括報告書及び 20040138 治験総括報告書）。バイタルサインに関係する臨床的事象（低血圧、高血圧、頻脈、徐脈、発熱）の発現率に、デノスマブ群とプラセボ群との間で違いは認められなかった（M2.7.4-G-PMO/HALT IAS 表 SP2-6.2.3 及び表 SH-6.2.3）。

4.2 心電図評価

デノスマブは RANKL に対する高い親和性（Kd: 3×10^{-12} M）と特異性を有し、また、分子量は約 150 kD であることから、in vivo での心筋細胞の細胞内区画への分布は制限される。したがって、human ether-à-go-go-related gene（hERG）カリウムチャネルを阻害する低分子の「薬物様」阻害物質とは異なり、デノスマブには hERG チャネルを直接阻害する作用はないと考えられる。非臨床評価では、カニクイザルを用いた心血管系の安全性薬理試験の他、12 ヵ月間毒性試験で投与期間中及び回復期間中に心電図評価を行った。これらの試験についてはモジュール 2.4 第 2.3 項で要約する。

健康な日本人閉経後女性を対象とした試験 20030164 及び日本人閉経後骨粗鬆症患者を対象とした試験 20050172 では、心電図検査を実施した。いずれの試験においても、臨床的に意味のある所見はなく、デノスマブ投与による QT/QT c 間隔への影響は示唆されなかった（試験 20030164 治験総括報告書 第 11.12 項及び試験 20050172 治験総括報告書 第 11.12.2 項）。

これら 2 試験を含む 17 試験から得られた心電図評価結果の統合概要をモジュール 5 第 5.3.5.3 項に示す。統合概要には、心電図評価を実施した全試験で報告されたすべての心電図異常の一覧表を含めた。全般的に、デノスマブ投与による臨床的に重要な心電図異常は認められ

なかった。さらに、正常範囲を下回る血清カルシウム値の低下が認められた被験者においても、臨床的に重要な心電図異常は認めらなかった。

4.3　骨組織学的評価及び骨組織形態学的評価

非臨床試験では、成熟（9～16 歳）卵巣摘出カニクイザルに、デノスマブ 25 又は 50 mg/kg を月 1 回 16 ヵ月間皮下投与したところ（AUC に基づき、申請臨床用量の約 100 倍に相当）（試験 103981）、骨代謝マーカーが低下し、骨石灰化面及び石灰化速度は大きく低下した（97%～99%の減少、溶媒投与の卵巣摘出対照動物との比較で $p < 0.05$）（Atkinson et al, 2005）。また、椎体の海綿骨の骨強度試験における最大荷重が 69%～82%増加した（溶媒投与の卵巣摘出対照動物との比較で $p < 0.05$）。以上のことから、骨代謝回転の抑制に比例した骨強度の上昇が示唆された。

試験 20010223（12 ヵ月）、試験 20050234（12 ヵ月）、試験 20030216（24 ヵ月及び／又は 36 ヵ月）、及び試験 20080098 のそれぞれの骨生検サブスタディ、並びに試験 20080287（試験 20050179、20050141、20060237、及び 20030216 の各試験の中止後）において骨組織学的評価及び骨組織形態学的評価が実施された（試験 20010223 治験総括報告書 表 14-9.3.1 及び第 11.12.5 項、試験 20050234 治験総括報告書 表 14-9.2.1 及び第 11.12.2 項、試験 20030216 治験総括報告書 表 14-17.2.1 及び第 11.12.3 項、試験 20080098 治験総括報告書 表 14-11.2.1 及び第 10.1 項、並びに試験 20080287 治験総括報告書 表 9-1 及び第 9.2.1 項）。

骨組織学的評価の結果、正常な層板骨及び正常な石灰化の所見が認められた。一方、骨軟化症又は線維性骨の所見は認められなかった（試験 200300216 治験総括報告書 表 14-17.2.6 及び表 14-17.4.27、試験 20010223 治験総括報告書 表 14-9.3.1、試験 20050234 治験総括報告書 表 14-9.2.4 及び表 14-9.3.26、試験 20080098 治験総括報告書 表 14-11.2.5、14-11.4.19、及び表 14-11.4.27、並びに試験 20080287 治験総括報告書 表 9-2）。

骨組織形態学的評価の結果、デノスマブ群では、プラセボ群又はアレンドロネート群と比較して骨リモデリングの低下が示された（試験 20030216 治験総括報告書 表 14-17.4.25、試験 20010223 治験総括報告書 表 11-11～表 11-14、及び試験 20050234 治験総括報告書 表 14-9.3.25、試験 20080098 治験総括報告書 表 10-2）。さらに、デノスマブ投与による骨代謝回転の著明な抑制により、テトラサイクリン標識の減少が観察された（試験 20030216 治験総括報告書 表 11-18、試験 20010223 治験総括報告書 表 11-15、試験 20050234 治験総括報告書 表 14-9.2.5、及び表 14-9.2.5.500、試験 20080098 治験総括報告書 表 10-1）。また、デノスマブ投与中止後に骨組織学的評価及び骨組織形態学的評価を実施した試験 20080287 の結果、テトラサイクリンの標識は 1 検体除くすべての検体で確認され（試験 2080287 試験総括報告書 表 9-3）、デノスマブか骨代謝に与える効果は可逆的であることが示唆された。

5. 特別な患者集団及び状況下における安全性

5.1 内因性要因

5.1.1 部分集団解析の安全性の結果

5.1.1.1 Japan Safety Analysis Set における部分集団解析の安全性の結果

Japan Safety Analysis Set の年齢（65 歳未満又は以上、及び 75 歳未満又は以上）による部分集団での有害事象及び重篤な有害事象の結果を IAS 表 7-1.2.1～IAS 表 7-1.2.8 に示す。なお、部分集団解析は、デノスマブ群合計及びプラセボ群合計で比較検討する。大部分の有害事象において、部分集団間及び各部分集団における投与群間で発現率に大きな違い（数値上 10%以上の差）は見られなかったが、鼻咽頭炎 nasopharyngitis（デノスマブ群での 65 歳未満 46.7%［78/167］と 75 歳以上 35.9%［52/145］）、変形性関節症 osteoarthritis（デノスマブ群での 65 歳未満 6.6%［11/167］及び 75 歳未満 10.5%［51/488］と 75 歳以上 20.7%［30/145］）、及び齲歯 dental caries（プラセボ群での 65 歳未満 18.1%［28/155］と 75 歳以上 6.2%［8/129］）については、部分集団間で発現率に違いが見られた。また、投与群間で発現率に違いが見られた有害事象は、変形性関節症 osteoarthritis（75 歳以上でのデノスマブ群 20.7%［30/145］とプラセボ群 8.5%［11/129］）であった（IAS 表 7-1.2.2）。これらの事象の全体発現率には大きな違いは見られなかった（IAS 表 4-2.2）ことから、今回認められた違いは 65 歳未満及び 75 歳以上の被験者数が少なかったことから、偶発的に有害事象の発現に偏りが生じ、発生したと考えた。デノスマブ群合計及びプラセボ群合計での高齢層の被験者（65 歳以上及び 75 歳以上）における重篤な有害事象の全体発現率は若年層より高い傾向が認められたが、投与群間で大きな違いは認められなかった。（IAS 表 7-1.2.5 及び IAS 表 7-1.2.6）。投与群間で重篤な有害事象の全体発現率に大きな違いは認められなかった（IAS 表 4-4.2）。

Japan Safety Analysis Set の体重（40 kg 未満、40 kg 以上 50 kg 未満、50 kg 以上 60 kg 未満又は 60 kg 以上）による部分集団での有害事象及び重篤な有害事象の結果を IAS 表 7-1.3.1～IAS 表 7-1.3.8 に示す。大部分の有害事象において、部分集団間及び各部分集団における投与群間で発現率に大きな違い（数値上 10%以上の差）は見られなかった。いくつかの有害事象で部分集団間及び各部分集団における投与群間で発現率に数値上の差がみられたが、これら事象の全体発現率には大きな違いはなく（IAS 表 4-2.2）、40 kg 未満及び 60 kg 以上の被験者数が少なかったことから偶発的に有害事象の発現に偏りが生じ、発生したと考えた（IAS 表 7-1.3.2）。重篤な有害事象の全体発現率に、部分集団間及び投与群間で大きな違いは認められなかった（IAS 表 7-1.3.6）。

Japan Safety Analysis Set の性別（女性又は男性）による部分集団での有害事象及び重篤な有害事象の結果を IAS 表 7-1.1.1～IAS 表 7-1.1.8 に示す。大部分の有害事象において、性別間及び各性別における投与群間で発現率に大きな違いは（数値上 10%以上の差）見られなかった。性別間で発現率に大きな違いが見られた事象はなく、齲歯 dental caries、歯周炎 periodontitis、口内炎 stomatitis、及び筋痙縮 muscle spasms については男性の被験者で投与群間に発現率に違いが見られた（IAS 表 7-1.1.2）。これらの事象の全被験者での発現率には大きな違いは見られなかった（IAS 表 4-2.2）ことから、今回見られた違いは男性の被験者数が少なかったこと

から、偶発的に有害事象の発現に偏りが生じ、発生したと考えた。重篤な有害事象の発現率に、性別間及び投与群間で大きな違いは認められなかった（IAS 表 7-1.1.6）。

5.1.1.2　外国参考試験における部分集団解析の安全性の結果

1)　Primary PMO Safety Analysis Set における部分集団解析の安全性の結果

Primary PMO Safety Analysis Set の年齢（65 歳未満又は以上、及び 75 歳未満又は以上）による部分集団での有害事象及び重篤な有害事象の結果を M2.7.4-G-PMO/HALT IAS 表 SP2-6.7.1、表 SP2-6.7.2、及び表 SP2-6.7.9 に示す。有害事象の全体発現率に大きな違いは見られず、大部分の有害事象において、部分集団間及び投与群間で発現率に違いは認められなかった。高血圧 hypertension（年齢 65 歳未満のデノスマブ群 9.3%、プラセボ群 11.6%に対して 75 歳以上のデノスマブ群 16.8%、プラセボ群 18.4%）及び鼻咽頭炎 nasopharyngitis（65 歳未満のデノスマブ群 25.9%、プラセボ群 22.6%に対して 75 歳以上のデノスマブ群 13.4%、プラセボ群 12.6%）では年齢による発現率の違いが見られたが（M2.7.4-G-PMO/HALT IAS 表 SP2-6.7.1）、投与群間で大きな違いはなかった。高齢層の被験者（65 歳以上及び 75 歳以上）では両投与群とも重篤な有害事象の全体発現率が若年層より高かった（M2.7.4-G-PMO/HALT IAS 表 SP2-6.7.9）。65 歳以上、75 歳未満、及び 75 歳以上の部分集団では、投与群間で重篤な有害事象の発現率に大きな違いは認められなかった。65 歳未満の部分集団における重篤な有害事象の発現率は、デノスマブ群 17.8%、プラセボ群 10.7%であったが、75 歳未満の部分集団では投与群間に違いは認められなかった（23.2%、21.7%）（M2.7.4-G-PMO/HALT IAS 表 SP2-6.7.9）。したがって、65 歳未満の部分集団で認められた投与群間の違いは、少ない被験者数（全被験者集団の 10%未満）が一因となった可能性がある。

ベースライン時の BMI 別部分集団解析では（30 kg/m^2 未満、30 kg/m^2 以上）、両投与群とも、有害事象及び重篤な有害事象の全体発現率に部分集団間の違いはなく、高血圧 hypertension の発現率が、BMI 30 kg/m^2 以上の部分集団（デノスマブ群 17.2%、プラセボ群 22.5%）で 30 kg/m^2 未満（デノスマブ群 15.0%、プラセボ群 14.9%）より高かった点を除き、個別の有害事象（基本語）の発現率の違いは、部分集団間及び投与群間のいずれにおいても 5%未満であった（M2.7.4-G-PMO/HALT IAS 表 SP2-6.7.7、表 SP2-6.7.8、及び表 SP2-6.7.12）。

2)　Primary HALT Safety Analysis Set における部分集団解析の安全性の結果

Primary HALT Safety Analysis Set の年齢（65 歳未満又は以上、及び 75 歳未満又は以上）による部分集団での有害事象及び重篤な有害事象の結果を M2.7.4-G-PMO/HALT IAS 表 SH-6.7.1 及び表 SH-6.7.2 に示す。有害事象の全体発現率に大きな違いは認められず、大部分の有害事象において、部分集団間及び投与群間で発現率に大きな違いは認められなかった（M2.7.4-G-PMO/HALT IAS 表 SH-6.7.1）。関節痛 arthralgia の発現率において、投与群間で違いは認められなかったものの、部分集団間では違いが認められた（年齢 65 歳未満のデノスマブ群 24.3%、プラセボ群 21.9%、65 歳以上のデノスマブ群 12.4%、プラセボ群 11.3%）。なお、75 歳未満と 75 歳以上の比較では違いが認められなかった。他の有害事象については、部分集

団間での発現率の違いは概ね 5%以下であった。高齢層の被験者（65 歳以上及び 75 歳以上）では両投与群とも重篤な有害事象の発現率が若年層より高かった（M2.7.4-G-PMO/HALT IAS 表 SH-6.7.2）。65 歳以上及び 75 歳未満の部分集団では、投与群間で重篤な有害事象の発現率に大きな違いは認められなかった（65 歳以上のデノスマブ群 33.9%、プラセボ群 30.8%、75 歳未満のデノスマブ群 24.4%、プラセボ群 23.0%）。65 歳未満の部分集団では、デノスマブ群 20.0%及びプラセボ群の 10.9%に重篤な有害事象が発現した。75 歳以上の重篤な有害事象の発現率はデノスマブ群 39.2%、プラセボ群 32.0%であった。この 2 つの部分集団における投与群間の違いは、少ない被験者数に起因する可能性がある。

ベースライン時の BMI 別部分集団解析では（30 kg/m^2 未満、30 kg/m^2 以上）、両投与群とも、有害事象の全体発現率に部分集団間の大きな違いはなく、個別の有害事象（基本語）の発現率の違いは、部分集団間及び投与群間のいずれにおいても 5%以下であった（M2.7.4-G-PMO/HALT IAS 表 SH-6.7.7）。重篤な有害事象の発現率は、両投与群とも、ベースライン時の BMI 30 kg/m^2 以上（デノスマブ群 35.5%、プラセボ群 31.7%）で低 BMI 群（デノスマブ群 29.9%、プラセボ群 26.1%）と比べて、約 5%高かった（M2.7.4-G-PMO/HALT IAS 表 SH-6.7.8）。

試験 20040135 ではすべて女性被験者が組み入れられ、試験 20040138 ではすべて男性被験者が組み入れられた。2 試験とも、有害事象、重篤な有害事象、死に至った有害事象、治験薬の投与中止に至った有害事象の全体発現率に、投与群間で違いは認められなかった（M2.7.4-G-PMO/HALT 表 12）。

5.1.2　男性骨粗鬆症患者での安全性

Japan Safety Analysis Set の男性被験者及び試験 20080098（参考試験）を用いて男性骨粗鬆症患者でのデノスマブの安全性を評価した。

Japan Safety Analysis Set の男性被験者では第 5.1.1.1 項に記述したとおり、性別間で発現率に大きな違いが見られた有害事象はなかった。

試験 20090098 は、男性骨粗鬆症患者おけるデノスマブの有効性と安全性をプラセボと比較する第 III 相、二重盲検、プラセボ対照試験である（試験 20080098 治験総括報告書）。被験者を 1: 1 の比で無作為割付し、24 ヵ月の投与期間中、最初の 12 ヵ月間はデノスマブ 60 mg もしくはプラセボを 6 ヵ月に 1 回皮下投与し、残りの 12 ヵ月間はすべての被験者にデノスマブ 60 mg を 6 ヵ月に 1 回皮下投与する。本試験は現在実施中のため、試験開始 1 年後までの中間安全性データを要約する。本試験で少なくとも 1 回以上の治験薬の投与を受けた各群 120 名が安全性解析対象となった。

有害事象、重篤な有害事象、死に至った有害事象の発現率は投与群間で類似していた。デノスマブ群の 72%（86/120）及びプラセボ群の 70%（84/120）に 1 件以上の有害事象が発現した。比較的よく見られた有害事象（いずれかの投与群で発現率 5%以上）は、背部痛 back pain（デノスマブ群 8%、プラセボ群 7%）、関節痛 arthralgia（7%、6%）、鼻咽頭炎 nasopharyngitis（7%、6%）、及び便秘 constipation（0%、6%）であった。ほとんどの有害事象は軽症及び中等症であ

った。治験薬との関連性があると判断された有害事象はデノスマブ群 1.7%及びプラセボ群 5.0%であった。重篤な有害事象はデノスマブ群 9.2%及びプラセボ群 8.3%に報告された。2 名以上の被験者にて発現した重篤有害事象はデノスマブ群の 3 名（2.5%）に報告された前立腺癌 prostate cancer（うち 2 名は被験者の医療記録から治験開始時に合併していた可能性があるとされた）及びデノスマブ群の 2 名（1.7%）に報告された四肢動脈血栓症 arterial thrombosis limb であった。いずれの事象もプラセボ群では報告されなかった。本試験中、2 名の死亡が報告された（デノスマブ群での心筋梗塞 myocardial infarction 及びプラセボ群での脳底動脈血栓症 basilar artery thrombosis）。治験薬の投与中止に至った有害事象がデノスマブ群の 3 名に報告されたがいずれも治験薬との関連性はなしと判断された。本試験において低カルシウム血症、ONJ、骨折遷延治癒、及び非定型骨折の発現は認められなかった。皮膚感染症はデノスマブ群では発現せず、感染症の有害事象、急性膵炎、血管障害、及び過敏症と関連のある事象の発現率は両投与群間で類似していた（試験 20080098 治験総括報告書）。

5.1.3　腎機能障害患者における安全性解析

腎機能の低下は低カルシウム血症と関連しており、これは、25-ヒドロキシビタミンＤから活性型である 1,25-ジヒドロキシビタミンＤ（カルシトリオール）への変換の減少が一因とされている。この変換が減少することにより、カルシウムの消化管吸収が減少し、血清カルシウム値が低下するため、副甲状腺ホルモン（parathyroid hormone: PTH）による骨からのカルシウム流出が起こり、血清カルシウム値を維持しようとするが、骨吸収抑制剤の投与はこの機序に対して抵抗性を示す。したがって、腎機能が低下した患者に骨吸収抑制薬を投与すると、骨からのカルシウム流出がさらに低下し、低カルシウム血症を発現するリスクが高まる可能性がある。そのため、腎機能障害患者を対象にデノスマブ 60 mg の薬物動態、安全性、及び忍容性を検討した（試験 20040245）。その結果を第 5.1.3.1 項に要約する。また、Japan Safety Analysis Set を用いて、腎機能別に血清カルシウム値の変動を検討した（第 5.1.3.2 項）。参考として、Primary PMO Safety Analysis Set 及び Primary HALT Safety Analysis Set における血清カルシウム値の腎機能別集計結果、並びに試験 20060289 におけるデノスマブ初回投与 10 日（±5 日）後の血清カルシウム値に関する腎機能別集計結果を第 5.1.3.3 項に示す。

5.1.3.1　腎機能障害患者を対象とした試験 20040245 における安全性解析

試験20040245では腎機能障害患者を対象にデノスマブ60 mgの薬物動態、安全性、及び忍容性を評価した。治験実施計画書にて、臨床的に意味のある低カルシウム血症を、アルブミン補正血清カルシウム濃度7.5 mg/dL未満（1.9 mmol/L未満）又は症候性の低カルシウム血症と定義した。臨床的に意味のある低カルシウム血症は、試験に組み入れられた最初の19名の被験者のうち3名（軽度腎機能障害1名、重度腎機能障害2名）で認められた。3件中2件が重篤な有害事象として報告され、両被験者（被験者 *****0002 及び *****0003 ）ともグルコン酸カルシウムの静脈内投与を受けた。重要な点として、臨床的に意味のある低カルシウム血症が発現した3名の被験者はいずれもカルシウム及びビタミンDの補充を受けておらず、3名中2名は重度腎機能障

害及び続発性の副甲状腺機能亢進症を合併していた。これらの事象の発現後、米国食品医薬品局（FDA）との協議を経て、腎機能障害を有する被験者での低カルシウム血症発現の可能性を最小限にするため、治験実施計画書に同意取得後より最大1000 mgのカルシウムと800 IUのビタミンDを補充及び重度腎機能障害患者に除外基準を追加する改訂を行った。改訂後の治験実施計画書のもとでは、腎機能正常の被験者、あるいは軽度、中等度、又は重度の腎機能障害を有する被験者のいずれにおいても、治験実施計画書で定義した臨床的に意味のある低カルシウム血症（血清カルシウム濃度7.5 mg/dL未満［1.9 mmol/L未満］又は症候性の低カルシウム血症）は認められなかった。改訂した治験実施計画書のもとで組み入れられた透析を受けている末期腎疾患患者2名に、無症候性のアルブミン補正血清カルシウム濃度7.5 mg/dL未満への低下が認められた（被験者 *****0004 は投与8日目に7.28 mg/dL［1.82 mmol/L］、被験者 *****0005 は投与43日目に7.36 mg/dL［1.84 mmol/L］）（試験20040245 治験総括報告書 一覧表9.1）。しかし、両被験者ともカルシウムの補充を遵守しておらず、断続的な低カルシウム血症の既往があった（試験20040245 治験総括報告書 第11.8.1項及び一覧表4）。いずれの被験者においてもカルシウム値の低下と関連した有害事象の発現はなかった。各腎機能群におけるアルブミン補正血清カルシウム濃度のベースラインからの変化率の中央値（Q1、Q3）をM2.7.4-G-PMO/HALT 図7に、アルブミン補正血清カルシウムのベースラインからの変化量の中央値（Q1、Q3）をM2.7.4-G-PMO/HALT 図8に示す。

本試験の被験者集団で、デノスマブ投与と腎機能障害との関連を示す安全性上の重要な所見は認められず、また、本試験で認められた有害事象の発現率及び種類は他の臨床試験での結果と類似していた。デノスマブの骨吸収抑制作用から予想されたアルブミン補正血清カルシウム値、リン、及びアルカリフォスファターゼの低下、並びに血清インタクト副甲状腺ホルモン（intact parathyroid hormone: iPTH）の上昇（代償性反応）を除き、血液生化学検査、血液学的検査、又は尿検査に大きな変化は認められなかった。安全性の結果に加え、本試験では腎機能障害がデノスマブの薬物動態に影響しないことが示された。

5.1.3.2 Japan Safety Analysis Set におけるベースライン時のクレアチニンクリアランス別の血清カルシウム値に関する評価

ベースライン時のクレアチニンクリアランス（Cockcroft-Gault 式）に基づき、被験者を 15～< 30 mL/min（デノスマブ群合計 9 名、プラセボ群合計 1 名）、30～< 60 mL/min（144 名、121 名）、60～< 90 mL/min（362 名、312 名）、90 mL/min 以上（117 名、101 名）に分類した。なお、クレアチニンクリアランス別の部分集団解析は、デノスマブ群合計及びプラセボ群合計で比較検討した。投与 1 ヵ月後のアルブミン補正血清カルシウムについて、CTCAE グレードのベースライン値からの臨床的に意味のある変化（グレードの 1 段階以上の変化を示した被験者）、グレード 2 以上の低下を示した被験者、及びグレード 3 又はグレード 4 の低下を示した被験者、並びに試験期間を通じて血清カルシウムが 7.5 mg/dL 未満となった被験者の割合に、ベースライン時のクレアチニンクリアランス別部分集団間で違いは認められなかった（IAS 表 7-2.2～表 7-2.5）。

また、ベースライン時のアルブミン補正血清カルシウム濃度（中央値）は投与群間及びクレアチニンクリアランス別部分集団間で類似していた（中央値の範囲: 9.10～9.40 mg/dL［2.28～2.35 mmol/L］）（IAS 表 7-2.1.1 及び IAS 表 7-2.1.2）。すべてのデノスマブ群で、いずれの測定時点でもベースラインからのわずかな濃度低下が認められたが、投与群間又はベースライン時のクレアチニンクリアランス別部分集団間で、アルブミン補正血清カルシウム値の変動に特筆すべき傾向は認められなかった（IAS 表 7-2.1.1～IAS 表 7-2.1.5）。

5.1.3.3 外国参考試験におけるベースライン時クレアチニンクリアランス別のカルシウム評価

1) Primary PMO Safety Analysis Set におけるベースライン時のクレアチニンクリアランス別の血清カルシウム値に関する評価

Primary PMO Safety Analysis Set において、ベースライン時のクレアチニンクリアランス（Cockcroft-Gault 式）に基づき、被験者を 15～30 mL/min（デノスマブ群 36 名、プラセボ群 37 名）、30～60 mL/min（デノスマブ群 1425 名、プラセボ群 1408 名）、60～90 mL/min（2089 名、2124 名）、90 mL/min 以上（498 名、469 名）に分類した（M2.7.4-G-PMO/HALT IAS 表 SP2-7.5.1）。ベースライン時のアルブミン補正血清カルシウム濃度（中央値）は、投与群間及びクレアチニンクリアランス別部分集団間で類似していた（中央値の範囲: 9.60～9.80 mg/dL［2.40～2.45 mmol/L］）（M2.7.4-G-PMO/HALT IAS 表 SP2-7.5.1 及び表 SP2-7.5.2）。15～30 mL/min 群の被験者数が比較的少なく、被験者間でのばらつきがあったが、全デノスマブ群で投与開始後初期に軽度のベースラインからの低下（投与 1 ヵ月後の変化率中央値:　約−1%～−2%）が認められた点を除き、投与群間又はベースライン時のクレアチニンクリアランス別部分集団間で、アルブミン補正血清カルシウム値の変動に特筆すべき傾向は認められなかった（M2.7.4-G-PMO/HALT IAS 表 SP2-7.5.1～表 SP2-7.5.5）。血清カルシウム値のベースラインからの変化、又は血清カルシウム値 7.5 g/dL 未満を示した被験者の割合に、ベースライン時のクレアチニンクリアランス値による傾向は認められなかった（M2.7.4-G-PMO/HALT IAS 表 SP2-7.9）。M2.7.4-G-PMO/HALT 図 9 には、各投与群におけるアルブミン補正血清カルシウムのベースラインからの変化量の中央値をベースライン時のクレアチニンクリアランス別に示した。また、投与 1 ヵ月後の測定値及び経時的な変化の散布図を M2.7.4-G-PMO/HALT IAS 図 SP2-1.1.1 及び図 SP2-1.1.2 に示す。

2) 延長投与試験 20060289 におけるベースライン時のクレアチニンクリアランス別の血清カルシウム値に関する評価

試験 20030216 の延長投与試験である試験 20060289（進行中）では血清カルシウム値を治験薬投与開始 10 日目（±5 日）に測定した。本製造販売承認申請の時点で、プラセボからデノスマブへの切り替え投与群 2080 名及びデノスマブ継続投与群 2207 名が、試験開始 10 日目の血清カルシウム値を測定していた（試験 20060289 治験総括報告書［24 ヵ月］ 表 03-7.1.7）。ベースライン時のクレアチニンクリアランス（Cockcroft-Gault 式）に基づき、15～< 30 mL/min

（重度腎機能障害群）、30～< 60 mL/min（中等度腎機能障害群）、30～< 60 mL/min（軽度腎機能障害群）、及び 90 mL/min 以上（腎機能正常群）に分類し、血清カルシウム値の変化率の中央値を部分集団別に集計した。なお、本試験では腎不全の被験者は組み入れられなかった。

デノスマブ継続投与群では、腎機能正常群で−2.1%（178 名）、軽度腎機能障害群で−2.0%（1068 名）、中等度腎機能障害群で−1.1%（930 名）、重度腎機能障害群で−3.8%（23 名）であり、プラセボからデノスマブへの切り替え投与群では、腎機能正常群で−3.2%（198 名）、軽度腎機能障害群で−3.1%（1050 名）、中等度腎機能障害群で−3.1%（806 名）、重度腎機能障害群で−5.7%（20 名）であった（試験 20060289 治験総括報告書［24 ヵ月］ 表 04-7.23.4）。プラセボからデノスマブへの切り替え投与群及びデノスマブ継続投与群のいずれにおいても、血清カルシウム値の変化率とクレアチニンクリアランスとの間に関連性は認められなかったが（M2.7.4-G-PMO/HALT 図 10）、重度腎機能障害群では血清カルシウム値の低下が増大する傾向が見られた。なお、デノスマブ継続投与群の 1 名（< 0.1%）及びプラセボからデノスマブへの切り替え投与群の 5 名（0.2%）に低カルシウム血症を認めたがいずれも非重篤で一過性の事象であった。

3) Primary HALT Safety Analysis Set におけるベースライン時のクレアチニンクリアランス別の血清カルシウム値に関する評価

Primary HALT Safety Analysis Set において、ベースライン時のクレアチニンクリアランス（Cockcroft-Gault 式）に基づき、被験者を 15～30 mL/min（デノスマブ群 4 名、プラセボ群 2 名）、30～60 mL/min（デノスマブ群 185 名、プラセボ群 194 名）、60～90 mL/min（デノスマブ群 408 名、プラセボ群 398 名）、90 mL/min 以上（デノスマブ群 262 名、プラセボ群 250 名）に分類した（M2.7.4-G-PMO/HALT IAS 表 SH-7.5.1）。ベースライン時のアルブミン補正血清カルシウム濃度（中央値）は、投与群間及びクレアチニンクリアランス別部分集団間で類似していた（中央値の範囲: 9.40～9.55 mg/dL［2.35～2.39 mmol/L］）（M2.7.4-G-PMO/HALT IAS 表 SH-7.5.1 及び表 SH-7.5.2）。15～30 mL/min 群の被験者数がわずか 6 名と少なく、被験者間でのばらつきがあったが、全デノスマブ群で投与開始後初期に軽度のベースラインからの低下（投与 1 ヵ月後の変化率の中央値: 約−3%～−6%）が認められた点を除き、投与群間又はベースライン時のクレアチニンクリアランス別部分集団間で、アルブミン補正血清カルシウム値の変動に特筆すべき傾向は認められなかった（M2.7.4-G-PMO/HALT IAS 表 SH-7.5.1～表 SH-7.5.5）。血清カルシウム値のベースラインからの変化、又は血清カルシウム値 7.5 g/dL 未満を示した被験者の割合に、ベースライン時のクレアチニンクリアランス値による傾向は認められなかった（M2.7.4-G-PMO/HALT IAS 表 SP2-7.9）。M2.7.4-G-PMO/HALT 図 11 には、各投与群におけるアルブミン補正血清カルシウムのベースラインからの変化量の中央値をベースライン時のクレアチニンクリアランス別に示した。また、投与 1 ヵ月後の測定値及び経時的な変化の散布図を M2.7.4-G-PMO/HALT IAS 図 SH-1.1.1 及び図 SH-1.1.2 に示す。

5.1.4　その他の疾患でのデノスマブの安全性

5.1.4.1　関節リウマチ患者

試験 20040144 において、関節リウマチ患者に対するデノスマブの有効性と安全性を検討している。本試験はメトトレキサートにより治療中の関節リウマチ患者を対象とした第 II 相、二重盲検、プラセボ対照、並行群間試験である。被験者を 1: 1: 1 の割合で無作為割付し（試験計画時 1 群 70 名）、24 ヵ月の試験期間中、最初の 12 ヵ月間はデノスマブ 60 mg、180 mg もしくはプラセボを投与開始時と初回投与 6 ヵ月後の 2 回皮下投与し（治療期）、その後の 12 ヵ月間は無治療にて追跡調査を行った（無治療期）。

治療期ではデノスマブ群の 79%（113 名）及びプラセボ群の 91%（68 名）で有害事象が報告された。治験薬との関連性ありと判断された有害事象が認められたのはデノスマブ群 13%（18 名）及びプラセボ群 9%（7 名）であった。このうち 2 名以上で発現した有害事象は、上気道感染 upper respiratory tract infection（デノスマブ群 3 名、プラセボ群 1 名）、頭痛 headache（2 名、0 名）、帯状疱疹 herpes zoster（2 名、0 名）、及び筋痙縮 muscle spasms（2 名、1 名）であった。重篤な有害事象はデノスマブ群 6%（9 名）、及びプラセボ群 9%（7 名）にて報告された。デノスマブ 180 mg 群とプラセボ群のそれぞれ 1 名に乳癌 breast cancer が発現し、いずれも治験中止に至った（試験 20040144 治験総括報告書）。

無治療期ではデノスマブ群の 60%（75 名）及びプラセボ群の 68%（41 名）で有害事象が報告された。治験薬との関連性ありと判断された有害事象が認められたのはデノスマブ群 2 名（60 mg 群、180 mg 群でそれぞれ 1 名に報告された副鼻腔炎 sinusitis）及びプラセボ群 1 名（関節リウマチ rheumatoid arthritis）であった。重篤な有害事象はいずれの投与群でも治療期と同程度に発生し、デノスマブ群 8%（10 名）、及びプラセボ群 10%（6 名）にて報告された。

試験期間を通じて治験薬との関連性がありと判断された重篤な有害事象はなかった。死亡例は認められず、デノスマブに対する結合抗体及び中和抗体は検出されなかった（試験 20040144 治験総括報告書）。

5.1.4.2　骨転移を有する進行固形癌患者を対象とした第 II 相試験及び第 III 相試験、並びに骨巨細胞腫患者を対象とした第 II 相試験の要約

本剤は、「多発性骨髄腫による骨病変及び固形癌骨転移による骨病変」を適応症、デノスマブ 120 mg の 4 週間に 1 回皮下投与を用法・用量として、平成 23 年 2 月 28 日に承認申請しており、その承認申請データパッケージに骨病変を有する進行がん患者における安全性データを示している。提出された資料から、本剤の多発性骨髄腫による骨病変及び固形癌骨転移による骨病変に対する有効性は示され、認められたベネフィットを踏まえると安全性は許容範囲であると判断された（審査報告書作成日：平成[redacted]年[redacted]月[redacted]日）。

5.2 外因性要因

5.2.1 ビスフォスフォネート療法から移行した低骨密度患者におけるデノスマブの安全性

試験 20050241（評価試験）及び 20050234（参考試験）を用いて、アレンドロネートからデノスマブに移行した被験者におけるデノスマブの安全性を評価した。試験 20050241 の内容は以下に簡潔に記述し、詳細な要約はモジュール 2.7.2「臨床薬理の概要」第 2.4 項（外因性要因）に示す。試験 20050234 についても以下に簡潔に記述する。なお、試験 20050234 は、実薬（アレンドロネート）対照試験として実施した試験 20050141 及び 20050179 とともに Secondary PMO Safety Analysis Set を構成する試験のひとつであり、本試験を含む Secondary PMO Safety Analysis Set の解析結果を第 2.1 項、第 2.1.1 項、第 2.1.2 項、及び第 2.1.3 項に示す。またデノスマブ及びアレンドロネートの服薬遵守、選好、満足度を評価する非盲検クロスオーバー試験 20060232（参考試験）についても以下に簡潔に記述する。これら試験のデザイン、ベースライン特性、試験成績に関する詳細を含む治験総括報告はモジュール 5 に添付する。

これらの結果より、ビスフォスフォネート（アレンドロネート）投与からデノスマブに移行しても安全であることが示唆された。

1) 試験 20050241 の要約

試験 20050241 はアレンドロネート投与歴のある 20 名の閉経後女性を対象とした非盲検、単回投与の第 I 相試験である（試験 20050241 治験総括報告書）（デノスマブ 60 mg 皮下投与 12 名、デノスマブ 15 mg 皮下投与 3 名、アレンドロネート 70 mg 週 1 回［又は同等量］経口投与 5 名）。本試験の結果、安全性、薬物動態、及び薬力学のいずれにおいても、アレンドロネートからデノスマブ投与への移行による影響は認められなかった。治験薬との関連性があると判断された有害事象の発現はなく、血清カルシウムの低下は軽度かつ一過性であった。血清カルシウムの変化量にデノスマブ群とアレンドロネート継続群で違いは認められなかった。試験期間を通して、いずれの投与群においても平均総カルシウム濃度は 8.0 mg/dL 以上であった。

2) 試験 20050234 の要約

試験 20050234 は試験開始前 6 ヵ月以上にわたりアレンドロネートを投与（70 mg 週 1 回［又は同等量］経口投与）していた低骨密度（腰椎又は大腿骨近位部 T スコア−2.0～−4.0）の閉経後女性を対象とした第 III 相、二重盲検、アレンドロネート対照、並行群間比較試験である（試験 20050234 治験総括報告書）。試験前のアレンドロネートの投与期間（6～12 ヵ月未満、12～24 ヵ月、24 ヵ月超）を層別因子として被験者を 1 : 1 の比で無作為割付し、12 ヵ月の投与期間中、デノスマブ 60 mg Q6M を 1 回皮下投与（n = 253）、又はアレンドロネートを週 1 回経口投与した（n = 251）。

有害事象、治験薬との関連性がある有害事象、重篤な有害事象、中止に至った有害事象の全体発現率に、デノスマブ群とアレンドロネート群との間で大きな違いはなかった。試験中に 1 名が死亡したが（デノスマブ群、脳血管発作により死亡）、治験薬との関連性は否定された。

比較的よく見られた有害事象（いずれかの投与群で発現率 5%以上）は、鼻咽頭炎 nasopharyngitis（デノスマブ群 13.4%、アレンドロネート群 10.8%）、背部痛 back pain（10.7%、11.6%）、細気管支炎 bronchiolitis（6.3%、5.6%）、関節痛 arthralgia（5.9%、10.4%）、便秘 constipation（5.1%、4.8%）、四肢痛 pain in extremity（4.7%、8.4%）、変形性関節症 osteoarthritis（4.3%、5.2%）であった。本試験では、デノスマブ投与後 2 週間以内の血清カルシウム変化を評価した（M2.7.4-G-PMO/HALT 図 12）。投与初期の血清カルシウム値に、他の時点の血清カルシウム値との違いは見られなかった（平均変化量はベースラインから 2%［0.05 mmol/L］の範囲内を維持）。デノスマブ群の 1 名が 1 時点で血清カルシウム値 7.9 mg/L となったが無症候であった。他の被験者では、試験期間中、血清カルシウム濃度の 8.0 mg/dL（2.0 mmol/L）未満への低下は認められなかった。

3) 試験 20060232 の要約

試験 20060232 はデノスマブの服薬遵守、選好、及び満足度をアレンドロネートと比較するための低骨密度閉経後女性患者を対象とした第 III 相、非盲検、アレンドロネート対照、クロスオーバー試験である（試験 20060232 治験総括報告書）。被験者を 1 : 1 の比で無作為割付し、24 ヵ月の投与期間中、最初の 12 ヵ月（投与期 1）はデノスマブ 60 mg Q6M を 1 回皮下投与又はアレンドロネートを週 1 回経口投与し、残りの 12 ヵ月間（投与期 2）は投与群を入れ替え、観察した。デノスマブの投与を受けた被験者はのべ 231 名（投与期 1 ; 125 名、投与期 2 ; 106 名）でアレンドロネートの投与を受けた被験者はのべ 228 名（投与期 1 ; 118 名、投与期 2 ; 110 名）であった。

有害事象及び重篤な有害事象の全体発現率に投与群間で差は認められなかった。比較的よく見られた有害事象（いずれかの投与群で発現率 5%以上）は、関節痛 arthralgia（デノスマブ群 6.1%、アレンドロネート群 6.6%）、四肢痛 pain in extremity（6.1%、3.9%）、背部痛 back pain（3.9%、5.7%）であった。個々の有害事象の発現率に投与群間で差は認められなかった。本試験期間中に死亡した被験者及び低カルシウム血症を認めた被験者はいなかった。

5.2.2 製造施設間及び剤型間でのデノスマブの安全性

デノスマブの原薬は、遺伝子組み換えしたチャイニーズハムスター卵巣細胞により、流加培養式の無血清哺乳動物細胞培養工程を用いて製造される。本承認申請に含まれているデノスマブの非臨床試験及び大半の臨床試験は、当初 製造所C（和名）* （製造所C（英名）* ：C所* ）で製造されたデノスマブ原薬（C所* 原薬）を使用した。デノスマブの市販に備えて、臨床試験用デノスマブ原薬の供給に使用した工程を 製造所A（和名）* （製造所A（英名）* ：A所* ）及び 製造所B（和名）* （ 製造所B（英名）* ：B所* ）の両原薬製造施設に技術移転した（それぞれ A所* 原薬及びB所* 原薬）。本モジュールでは、原薬の製造場所（C所* 、A所* 、又はB所* ）別の安全性について記述する。国内で実施した臨床試験については、試験 20030164 及び 20050172 は C所* 原薬、試験 AMG162-A-J301 は A所* 原薬のバイアル製剤を使用した。骨粗鬆症を効能・効果として市販を

予定している製剤は 60 mg/ml の PFS である。PFS 製剤はバイアル製剤と同じ酢酸／ソルビトール処方が用いられているが、微粒子の形成を防止するためポリソルベート 20（0.01%）が添加されている。

デノスマブ原薬と製剤に関する臨床生物薬剤学試験の結果は、モジュール 2.7.1 に示す。デノスマブ原薬並びに製剤の製造工程の開発経緯はモジュール 2.3 に示す。

健康被験者を対象とした、以下の 3 つの無作為化、単回投与、並行群間比較、生物学的同等性試験の結果、C所* 原薬、A所* 原薬、及びB所* 原薬の安全性に違いは認められず、また、バイアル製剤と PFS 製剤の比較においても安全性の違いは認められなかった。

- 試験 20050227（n ＝ 122）では、A所* 原薬の薬物動態プロファイルをC所* 原薬（ともにバイアル製剤）と比較した。
- 試験 20060286（n ＝ 116）では、B所* 原薬の薬物動態プロファイルをC所* 原薬（ともにバイアル製剤）と比較した。
- 試験 20050146（n ＝ 148）では、60 mg PFS 製剤の薬物動態プロファイルを 60 mg バイアル製剤（ともに A所* 原薬）と比較した。

また、A所* 原薬の薬力学及び安全性プロファイルを試験 20050233 で、A所* 原薬の安全性プロファイル、及び PFS 製剤とバイアル製剤におけるデノスマブ 60 mg/mL の安全性及び免疫原性を試験 20060237 で評価した。これらの試験から得られた結果を、試験 20010223（試験 20050233 の親試験）を含む他の試験から得られたC所* 原薬の結果と比較した。その結果、低骨密度閉経後女性に A所* 原薬を投与したときの安全性、免疫原性、及び薬力学は、C所* 原薬で観察された結果と異なるものではなかった。また、低骨密度閉経後女性におけるデノスマブ 60 mg PFS 製剤の安全性及び免疫原性は、60 mg バイアル製剤の結果と一致していた。

試験 20060289 では、バイアル製剤（C所* 原薬）及び PFS 製剤（B所* 原薬）を使用している。試験 20060289 の中間解析（24 ヵ月）の結果、バイアル製剤（C所* 原薬）及び PFS 製剤（B所* 原薬）の安全性及び免疫原性に関する新たな所見は認められていない（試験 20060289 治験総括報告書［24 ヵ月］）。

以上のことから、デノスマブは、製造施設及び剤型を問わず忍容性が良好であり、一貫した安全性プロファイル（有害事象及び免疫原性解析に関する）を示した。

5.3 薬物相互作用

デノスマブは RANKL に特異的なモノクローナル抗体であり、肝臓の代謝機構（例えば、チトクローム P450［CYP］など）では消失しない。CYP の発現調節に対する RANKL の関与は示されておらず、デノスマブが炎症性サイトカインの量や活性に影響を与えるという非臨床及び臨床試験の結果は得られていない。つまり、デノスマブが CYP の発現や活性に対して直接的又は間接的に影響を与える可能性は低い。また、デノスマブと他のモノクローナル抗体の併用による薬物相互作用は、抗体医薬の特異性や生体内での高い IgG 異化能を踏まえると考えにくい。

米国では、「骨折リスクの高い閉経後骨粗鬆症の治療」の適応症に関する承認取得時に、製

造販売後の要件として、デノスマブと CYP3A4 基質との潜在的な薬物相互作用のリスクを評価する臨床薬物相互作用試験の実施を FDA より指示され、閉経後骨粗鬆症被験者を対象としたデノスマブとミダゾラム（CYP3A4 基質）との臨床薬物相互作用試験（試験[redacted]1131）を実施した。その結果、ミダゾラムの薬物動態はデノスマブの併用投与によって変化しないことが示された。

ビスフォスフォネート投与からデノスマブ投与に移行した被験者におけるデノスマブの薬物動態プロファイルは、ビスフォスフォネートを投与していなかった被験者と類似しており、また、これらの被験者での安全性プロファイルは他の臨床試験と一致していた（モジュール 2.7.2 第 2.4 項及び第 3.4 項）。

5.4　妊娠及び授乳時の使用

RANK/RANKL シグナル伝達系の遺伝子を欠損させたマウス（RANK/RANKL ノックアウトマウス）では、妊娠中に小葉腺胞構造が発達せず、母動物は新生仔に十分に授乳できなかった（モジュール 2.4 第 2.2 項）。ラット新生仔に骨吸収を強く抑制する高用量の OPG を投与した場合、歯の萌出が抑制されたが、OPG 投与を中止することで部分的な可逆性を示した（モジュール 2.4 第 2.2 項）。さらに、OPG を投与したラット新生仔では、骨密度及び骨強度が上昇したが、骨長及び靭性が低下し、成長板の異常な発達が認められた。骨の成長と成長板の変化は可逆性を示した（モジュール 2.4 第 2.2 項）。妊娠カニクイザルに器官形成期から分娩までの間、デノスマブ（50 mg/kg）を 4 週間に 1 回皮下投与し、母動物、妊娠、出生前及び出生後の発生に対する影響を評価した結果、死産の増加、出生児の死亡の増加、骨の形態異常、末梢リンパ節の形成不全などの発生異常が認められた（モジュール 2.4 第 4.5 項）。また、親動物の乳腺はほぼ正常に発達していた（モジュール 2.6.6 第 6.3 項）。試験 R[redacted]0340（新生仔ラット試験）のデザイン及び結果に関する詳細を含め、雌の受胎能及び生殖発生毒性に関する非臨床評価の包括的な概要についてはモジュール 2.4 に示す。

妊婦又は授乳婦を対象としたデノスマブの試験は実施していない。したがって、添付文書（案）では、妊婦又は妊娠している可能性のある婦人への投与は禁忌とした。デノスマブがヒト乳汁中に移行するかどうかについては不明であるが、乳児に対するデノスマブの潜在的な副作用のため、授乳の中止又は投与の中止を判断する必要がある。

デノスマブの開発プログラムが開始されて以降、20[redacted] 年[redacted] 月[redacted] 日までの間に 11 名に妊娠が報告された（適応症を問わない全臨床試験からの情報）。該当例の臨床的転帰は以下のとおりである。

- 4 名は合併症を伴わず、正常な妊娠期間後に出産した（うち 1 名は父親及び母親の両名がデノスマブに曝露された）。
- 2 名は人工中絶手術を選択した（家族計画によるもの）。
- 1 名は自然流産した。
- 4 名の臨床的転帰は不明であった（うち 1 名は父親がデノスマブに曝露された）。

自然流産は骨巨細胞腫を有する 27 歳の被験者に発生した。本被験者には膣出血及びヒト絨

毛性ゴナドトロピン（HCG）濃度低下が認められ、超音波検査では子宮内妊娠を認めなかった。臨床的転帰不明の 4 名に関し、3 名は追跡不能となったが、1 名は転帰調査中である。

5.5　過量投与

デノスマブの反復投与トキシコキネティクスは、最高用量 50 mg/kg の月 1 回皮下投与を用いてカニクイザルで 16 ヵ月まで評価されている（モジュール 2.6.4 第 8.2 項）。曝露量は検討用量の範囲では、ほぼ用量に比例して増加し、顕著な蓄積（2 倍超）は認められなかった。デノスマブを 12 ヵ月間投与されたカニクイザルの無毒性量（no observed adverse effect level: NOAEL）は皮下投与で 50 mg/kg／月である（モジュール 2.4 第 4.2 項）。この用量を 6 ヵ月間の全身曝露量に換算すると、臨床推奨用量である 60 mg Q6M による全身曝露量の 150 倍であり（投与間隔全体での濃度-時間曲線下面積［AUC］に基づく）、進行がん患者を対象とした第 III 相試験で申請中の 120 mg Q4W による全身曝露量の約 15 倍に相当する（6 ヵ月間の AUC に基づく）。

デノスマブは、臨床試験で様々な用量及び投与スケジュールで評価されており、単回投与量として安全に投与可能なデノスマブの最大用量は決定していない。試験 20030164 では、日本人閉経後健康女性を対象に、最高 3 mg/kg（n = 6）までの単回投与を行った。試験 20050172 では、日本人閉経後骨粗鬆症女性を対象に、最高用量として 100 mg Q6M（n = 50）の 2 回投与を行った。試験 20010223 では、外国人閉経後低骨密度患者を対象に、最高用量として 210 mg Q6M（n = 46）の 4 回投与を行った。申請中の進行がん患者を対象とした臨床試験では、日本人乳癌骨転移患者を対象に、試験 20040176 で最高 180 mg Q4W（n = 6）の 3 回投与、骨転移を有する進行乳癌患者を対象に日本を含む国際共同試験として実施した試験 20050136（全盲検投与期）では、120 mg Q4W（n = 69）の平均（中央値）25 回投与（最大 38 回投与）を行った。外国人進行がん骨転移患者では、試験 20040113 及び試験 20040114 で、180 mg Q4W（試験 20040113: n = 43、試験 20040114: n = 38）の 6 回投与を行った。これらの用法・用量で、用量制限毒性の徴候は認められていない。

5.6　薬物乱用

デノスマブに習慣性及び依存性を示唆する所見は認められていない。

5.7　離脱症状及び反跳現象

第 I 相及び第 II 相試験における薬物動態・薬力学的評価の結果、デノスマブの 60 mg Q6M の効果は少なくとも 6 ヵ月間持続すると考えられた。そのため、複数の試験で、デノスマブの投与終了後の長期的な影響（第 5.7.1 項）、及び投与中断後（上限 2 年）の投与再開の影響（第 5.7.2 項）を評価した。

- 試験 20040132 のデノスマブ投与終了後 24 ヵ月間の解析: 有害事象、重篤な有害事象、及び臨床検査値の評価、並びに有効性パラメータ（BMD、骨代謝マーカー及び骨折）の評価を含む（詳細についてはモジュール 2.7.3 及び試験 20040132 治験総括報告書［24

ヵ月］を参照)。

- 試験 20010223 の最終解析及びその延長投与試験 20050233 のデノスマブ投与後 48 ヵ月間の解析: デノスマブ投与終了群、投与再開群、及び投与継続群における有害事象、重篤な有害事象、臨床検査値の評価、及び有効性パラメータ、並びに有効性パラメータ（BMD、骨代謝マーカー、及び骨折）の評価を含む（詳細についてはモジュール 2.7.3、試験 20010223 治験総括報告書、及び 20050233 治験総括報告書を参照)。
- 試験 20040144 の最終解析: デノスマブ 2 用量（60 mg Q6M 及び 180 mg Q6M）を皮下投与された軽症～中等症の活動性関節リウマチ患者における、デノスマブ投与終了後 12 ヵ月間の有害事象、重篤な有害事象、併用薬、及び臨床検査値の評価、並びに有効性パラメータ（X 線及び DXA による評価）の評価を含む（詳細については試験 20040144 治験総括報告書を参照)。
- 試験 20030216 の最終解析: 治験薬投与後 36 ヵ月以前に治験薬（盲検下）の投与を中止した被験者における、デノスマブ最終投与後 6 ヵ月間の重篤な有害事象及びすべての治験薬投与中止被験者における治験薬投与 36 ヵ月後の BMD を評価した（詳細については試験 20030216 治験総括報告書を参照)。
- 試験 20040135 のデノスマブ投与終了後 24 ヵ月間の解析: 有害事象、重篤な有害事象、及び臨床検査値の評価について評価した（詳細については試験 20040135 治験総括報告書［48 ヵ月］を参照)。
- 試験 20040138 のデノスマブ投与終了後 24 ヵ月間の解析: 有害事象、重篤な有害事象、及び臨床検査値の評価について評価した（詳細については試験 20040138 治験総括報告書［60 ヵ月］を参照)。
- 試験 20080747 の最終解析: 試験 20050179 の各被験者の最終観察後、少なくとも 12 ヵ月経過後から 30 日間の重篤な有害事象について評価した（詳細については試験 20080747 治験総括報告書を参照)。

5.7.1 治療休止の影響

試験 20010223、20040132、20040144、20030216、20040135、20040138、及び 20080747 の結果、デノスマブ投与終了後の評価期間中の有害事象プロファイルにデノスマブ群とプラセボ群で違いは認められなかった。血液生化学検査又は血液学的検査に特定の傾向は認められず、デノスマブの投与終了と臨床検査値の変化に関連性は認められなかった。

骨折発現率の解析では、デノスマブの作用が可逆的であることによる臨床的な徴候は認められなかった（試験 20010223 治験総括報告書、試験 20040132 治験総括報告書［24 ヵ月］、試験 20040144 治験総括報告書、試験 20060216 治験総括報告書、試験 20040135 治験総括報告書［48 ヵ月］、試験 20040138 治験総括報告書［60 ヵ月］、試験 20080747 治験総括報告書)。

5.7.2 離脱後の治療再開の影響

試験 20010223 では、デノスマブの投与を 1～2 年間中断し、その間も予定された評価を継続

する群（210 mg 群及び 30 mg 群）を含めた。約 1 年間の投与中断後、30 mg 群の被験者はデノスマブの投与（60 mg Q6M）を再開できることとした。210 mg 群の被験者は、約 2 年間の投与中断後、試験 20050233 開始時にデノスマブの投与（60 mg Q6M）を再開できることとした。被験者 39 名（デノスマブ 210 mg 群 22 名、デノスマブ 30 mg 群 17 名）に対するデノスマブ投与再開後の安全性の評価を試験 20050233 治験総括報告書（48 ヵ月）に含めた。対象被験者数は比較的少ないものの、1～2 年間の投与中断後のデノスマブ投与再開により、有害事象、重篤な有害事象、臨床検査結果（例: 血清カルシウム低下）、骨折発生及び治癒、又は抗体産生に関して、新たな所見は認められなかった。なお、BMD 及び骨代謝マーカーについては、デノスマブ投与再開被験者で有効性が確認された（モジュール 2.7.3）。

5.8 自動車運転及び機械操作に対する影響又は精神機能の障害

デノスマブの投与を受けている被験者において、運転又は重機の操作に対する影響を確認する試験は実施されていない。

6. 市販後データ

デノスマブは 2010 年 5 月 26 日（国際誕生日）に、EU にて骨量減少に関連した適応症（閉経後骨粗鬆症患者もしくは HALT に伴う骨量減少）にて Prolia®の商標名で最初に承認された。20[redacted] 年[redacted] 月現在、60 mg（バイアル製剤もしくは PFS 製剤）、6 ヵ月に 1 回皮下投与の用法用量にて 60 ヵ国以上で承認されている。デノスマブの市販後、これまでに 4 回の定期的安全性最新報告（PSUR Number 01～PSUR Number 04［モジュール 5.3.6］）が各地域の規制当局に提出された。以下にその内容を要約する。

デノスマブの開発プログラム開始からこれまでに（20[redacted] 年[redacted] 月[redacted] 日カットオフ）累積でアムジェン社が主導する臨床試験にて 12847 名の患者（38922 患者・年）に、また、アムジェン社の提携先である第一三共株式会社及びグラクソスミスクライン社が主導する臨床試験にて 1178 名の患者及び 140 名の患者にそれぞれデノスマブが投与された。加えて、デノスマブの承認以降、331895 患者・年がデノスマブの市販製剤を投与された。

現在、注意して調査すべきデノスマブの有害事象として監視されている事象には、低カルシウム血症 hypocalcaemia、顎骨壊死 osteonecrosis of the jaw (ONJ)、入院に至った皮膚感染症 skin infections leading to hospitalization、感染症 infection、過敏症反応 hypersensitivity reaction、顎以外の骨壊死 osteonecrosis outside the jaw（無腐性壊死 avascular necrosis）、骨折の遷延治癒 fracture healing complications or delayed fracture healing、心血管障害 cardiovascular events、悪性腫瘍 malignancy、免疫原性 immunogenicity、白内障 cataracts in all indications、非定型骨折 atypical fracture、膵炎 pancreatitis、及び皮膚関連事象 dermatological events がある。

アムジェン社は市販後データを対象に以下の安全性解析、すなわちデノスマブ投与による過敏症発現に関する評価、低カルシウム血症と筋痙縮発現に関する評価、肺炎発現に関する評価、製品概要（Summary of Product Characteristics）に記載されていない重篤な感染症発現の関連に関する評価、及び四肢痛を除く筋骨格痛発現に関する評価を実施した。これら安全性解析は、

デノスマブ

前者 2 項目はデノスマブ市販後第 1 回目の定期的安全性最新報告（PSUR Number 01）、後者 3 項目は第 2 回目の定期的安全性最新報告（PSUR Number 02）に対する欧州規制当局による評価報告書中に記載された要求により実施した。また、第 3 回目の定期的安全性最新報告（PSUR Number 03）に記載された肺炎発現に関する評価、製品概要に記載されていない重篤な感染症との関連に関する評価に対し、欧州規制当局より追加の要求があったため、追加の安全性解析を実施した。

薬物過敏症に関する安全性自発報告を精査したところ、デノスマブ投与と過敏症（発疹 rash、蕁麻疹 urticaria、顔面浮腫 face oedema、及び紅斑 erythema など）との関連が示唆された。このため、過敏症反応を市販後の安全性報告報告対象に追加し、中核データシート（Core Data Sheet：CDS）と各地域のデノスマブの添付文書に追加した。

一方で低カルシウム血症はデノスマブ投与による特定されたリスクとして同定されており、本事象のリスクは CDS 中の禁忌、重要な基本的注意事項、及び副作用の項目に記載されている。低カルシウム血症と筋痙縮に関しての報告はまれであり、当該事象が発現した患者でもその患者背景が事象発現の要因になっていることが示された。なお、これまでにデノスマブ投与による低カルシウム血症が合計で 219 件（64.5/100000 患者・年）がアムジェン社に報告されている。これらの中に重篤な低カルシウム血症の報告（報告時期：20[redacted] 年[redacted] 月[redacted] 日～20[redacted] 年[redacted] 月[redacted] 日）があったため、包括的な安全評価を行った。重篤な低カルシウム血症が自発報告された 37 名のうち、デノスマブ投与と時間的関連性がある重度又は症候性の低カルシウム血症として 8 名が報告された。このうち 7 名が慢性腎疾患、腎不全、末期腎疾患による透析等の背景を有していた。安全性評価の結果、重度の症候性低カルシウム血症と本剤投与との関連性を否定するには至らなかった。そのため、本事象がデノスマブの副作用として CDS の改訂版に追加された（PSUR Number 04 第 9.1.2 項）。

肺炎の有害事象の内容を精査したところ、デノスマブ投与と肺炎の発現に関連性は示唆されなかった。そのため、デノスマブ投与時の肺炎発現に関する安全性情報の変更は不要と判断された。

また、製品概要に記載されていない重篤な感染症との関連を精査したところ、デノスマブ投与によるこれら感染症の徴候並びに関連する安全性情報は認められず、本剤のベネフィット/リスクに変更はなく、今回の解析結果からデノスマブに関連する安全性情報を変更する必要はないと考えられた。

上記 2 つの感染症に関する評価結果に対し、規制当局はそれぞれ妥当との判断を示したが、肺炎に関しては事象の叙述の追加するよう要求したためこれに対応した。また、製品概要に記載されていない重篤な感染症との関連の評価に関しては、重篤な皮膚感染症を含め事象の発現傾向と潜在性又は無症候性の感染症に対してデノスマブ投与が与える影響を評価するよう要求した。評価の結果、臨床試験データ及び市販後データのいずれからもデノスマブ投与が潜在性又は無症候性の感染症に対して悪影響を与える傾向は認められず、現時点において、デノスマブに関連する安全性情報を変更する必要はないと考えられた。また、重篤な皮膚感染症に関しても、追加情報によりこれまでのデノスマブに関連する安全性情報を変更する必要はないと

考えられた。

さらに、四肢痛を除く筋骨格痛に関する評価を実施したところ、市販後の筋骨格痛の事象の報告数は予期されていたものと比較し、高くないと考えられた。本剤が投与される患者の年齢層を考慮した場合、背部痛や変形性関節症を含む骨格筋痛がデノスマブの主要な臨床試験において比較的良く見られた有害事象として報告されたのも予期していたとおりである。したがって、現時点において、デノスマブに関連する安全性情報を変更する必要はないと考えられた。

なお、第 4 回定期安全性最新報告のデータカットオフ以降、臨床試験から報告された 2 件の大腿骨骨幹部骨折が非定型骨折として同定されたため、非定型骨折を警告及び使用上の注意の項目に追加するため CDS を改訂した。

その他に得られたデノスマブの安全性情報は、これまでの臨床試験の内容と一貫するものであった。現在のところ、本薬剤の全体的なベネフィット/リスクは現在の適応症への使用に対して有益なものである。第一三共株式会社及びアムジェン社は今後も臨床試験及び市販後から得られるデノスマブの安全性情報を定期的に監視していく。

7. 付録

付録 A. 参考文献

Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res. 2009;24:1095-102.

Alexander MY. RANKL links arterial calcification with osteolysis. Circ Res. 2009;104;1032-4.

Atkinson J, Cranmer P, Saunders T, et al. AMG 162, a fully human RANKL antibody, increases bone mass and bone strength in cynomolgus monkeys. J Bone Min Res. 2005;20(suppl 1):S294.

Bachmann MF, Wong BR, Josien R, et al. TRANCE, a tumor necrosis family member critical for CD40 ligand-independent T helper cell activation. J Exp Med. 1999;189:1025-31.

Bauer DC, Black DM, Garnero P, et al. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture interventional trial. J Bone Miner Res. 2004;19:1250-8.

Bennett BJ, Scatena M, Kirk EA, et al. Osteoprotegerin inactivation accelerates advanced atherosclerotic lesion progression and calcification in older ApoE-/- Mice. Arterioscler Thromb Vasc Biol. 2006;26:2117-24.

Choi BG, Vilahur G, Cardoso L, et al. Ovariectomy increases vascular calcification via the OPG/RANKL cytokine signalling pathway. Eur J Clin Invest. 2008:38:211-7.

Crisafulli A, Micari A, Altavilla D, et al. Serum levels of osteoprotegerin and RANKL in patients with ST elevation acute myocardial infarction. Clin Sci. 2005;109:389-95.

Delmas PD, Munoz F, Cosman F, et al. Relationship of bone turnover marker (PINP) and changes in femoral neck bone mineral density to fractyre risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg (ZOL): the horizon-pft study. OR 1027, 30th annual scientific sessions of the American Society for Bone and Mineral Research, Montreal, Canada, 2008.

The Eye Diseases Prevalence Research Group. Prevalence of Cataract and Pseudophakia/Aphakia Among Adults in the United States. Arch Ophthalmol. 2004;122:487-94.

Green EA, Choi Y, Flavell RA. Pancreatic lymph node-derived CD4(+)CD25(+) Treg cells: highly potent regulators of diabetes that require TRANCE-RANK signals. Immunity. 2002;16:183-91.

Helas S, Goettsch C, Schoppet M, et al. Inhibition of receptor activator of NF-kappaB ligand by denosumab attenuates vascular calcium deposition in mice. Am J Path. 2009;175:473-8.

Kiechl S, Schett G, Schwaiger J, et al. Soluble receptor activator of nuclear factor-kappa B ligand and risk for cardiovascular disease. Circulation. 2007;116:385-91.

Kiechl S, Werner P, Knoflach M, et al. The osteoprotegerin/RANK/RANKL system: a bone key to vascular disease. Exp Rev Cardiovasc Ther. 2006;4:801-11.

Klein BEK, Klein R, Lee KE. Incidence of age-related cataract over a 10-year interval: the Beaver Dam Eye Study. Ophthalmology. 2002;109:2052-7.

Knudsen ST, Foss CH, Poulsen PL, et al. Increased plasma concentrations of osteoprotegerin in type 2 diabetic patients with microvascular complications. Eur J Endocrinol. 2003;149:39-42.

Kwek EBK, Goh SK, Koh JSB, et al. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury. 2008;39:224-31.

Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. New Engl J Med. 2008;358:1304-5.

Loser K, Mehling A, Loeser S, et al. Epidermal RANKL controls regulatory Tcell numbers via activation of dendritic cells. Nat Med. 2006;12:1372-9.

Marie PJ, Hott M, Garba MT. Inhibition of Bone Matrix Apposition by (3-Amino-1-Hydroxypropylidene)-1,1-Bisphosphonate (AHPrBP) in the Mouse. Bone. 1985;6:193-200.

Miller RE, Branstetter D, Armstrong A, et al. Receptor activator of NF-κB ligand inhibition suppresses bone resorption and hypercalcemia but does not affect host immune response to influenza infection. J Immunol. 2007;179:266 74.

Min H, Morony S, Sarosi I, et al. Osteoprotegerin Reverses Osteoporosis by Inhibiting Endosteal Osteoclasts and Prevents Vascular Calcification by Blocking a Process Resembling Osteoclastogenesis. J Exp Med. 2000;192:463-74.

Morony S, Tintut Y, Zhang Z, et al. Osteoprotegerin inhibits vascular calcification without affecting atherosclerosis in ldlr(-/-) mice. Circulation. 2008;117:411-20.

Nakamura M, Udagawa N, Matsuura S, et al. Osteoprotegerin regulates bone formation through a coupling mechanism with bone resorption. Endocrinol. 2003;144:5441-9.

Odvina C, Levy S, Rao S, et al. Unusual mid-shaft fractures during long term bisphosphonate therapy. Clin Endocrinol. 2010;72:161-8.

Odvina CV, Zerwekh JE, Rao DS, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294-301.

Padigel UM, Kim N, Choi Y, Farrell JP. TRANCE-RANK costimulation is required for IL 12 production and the initiation of a Th1-type response to Leishmania major infection in CD40L-deficient mice. J Immunol. 2003;171:5437-41.

Panizo S, Cardus A, Encinas M, et al. RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4–dependent pathway. Circ Res. 2009;104:1041-8.

Price PA, June HH, Buckley JR, et al. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol. 2001;21:1610-6.

Ruben FL, Dearwater SR, Norden CW et al. Clinical infections in the noninstitutionalized geriatric age group: methods utilized and incidence of infections. The Pittsburgh Good Health Study. Am J Epidemiol. 1995;141:145-57.

Sandberg WJ, Yndestad A, Oie E, et al. Enhanced T-cell expression of RANK ligand in acute coronary syndrome: possible role in plaque destabilization. Arterioscler Thromb Vasc Biol. 2006;26:857-63.

Shane E, Burr D, Ebeling PR, et al. Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010;25:2267-94.

Somford MP, Draijer FW, Thomassen BJ, et al. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. J Bone Miner Res. 2009;24:1736-40.

Stolina M, Guo J, Faggioni R, et al. Regulatory effects of osteoprotegerin on cellular and humoral immune responses. Clin Immunol. 2003;109:347-54.

Tintut Y, Demer L. Role of osteoprotegerin and its ligands and competing receptors in atherosclerotic calcification. J Invest Med. 2006;54:395-401.

Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy? Ann Oncol. 2006;17:1197-204.

Whyte MP, Bergfeld MA, Murphy WA, et al. Postmenopausal osteoporosis. A heterogeneous disorder as assessed by histomorphometric analysis of Iliac crest bone from untreated patients. Am J Med. 1982;72:193-202.

Yamaguchi T, Sakaguchi S. Skin controls immune regulators. Nat Med. 2006;12:1358-9.

Yoneda T, Hagino H, Sugimoto T, et al. Bisphosphonate-Related Osteonecrosis of the Jaw: Position Paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. J Bone Miner Metab. 2010;28:365-83.

付録 B.　有害事象集計用の MedDRA 基本語

　複合事象カテゴリーを規定するために使用した有害事象集計用の MedDRA 基本語を提示する。集計は治験薬投与後に発現した有害事象について行った。

表 7-1　低カルシウム血症の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]
Blood calcium decreased
Calcium deficiency
Calcium ionised decreased
Hypocalcaemia

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[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-2　細菌性蜂巣炎定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Anorectal cellulitis	Cellulitis streptococcal	Culture wound positive	Pyoderma
Application site cellulitis	External ear cellulitis	Dermatitis infected	Pyoderma streptococcal
Breast cellulitis	Implant site cellulitis	Diabetic foot infection	Rash follicular
Catheter site cellulitis	Incision site cellulitis	Ear lobe infection	Rash pustular
Cellulitis	Infusion site cellulitis	Eczema impetiginous	Skin bacterial infection
Cellulitis enterococcal	Injection site cellulitis	Eczema infected	Skin infection
Cellulitis gangrenous	Periorbital cellulitis	Eosinophilic cellulitis	Staphylococcal impetigo
Cellulitis of male external genital organ	Post procedural cellulitis	Erysipelas	Staphylococcal skin infection
Cellulitis orbital	Vaccination site cellulitis	Erysipeloid	Streptococcal impetigo
Cellulitis pasteurella	Vaginal cellulitis	Eyelid infection	
Cellulitis staphylococcal	Bullous impetigo	Impetigo	

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[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
5q minus syndrome	Acute lymphocytic leukaemia recurrent	Adenosquamous cell carcinoma	Adult T-cell lymphoma/leukaemia stage I
Abdominal neoplasm	Acute megakaryocytic leukaemia	Adenosquamous cell lung cancer	Adult T-cell lymphoma/leukaemia stage II
Abdominal wall neoplasm	Acute megakaryocytic leukaemia (in remission)	Adenosquamous cell lung cancer recurrent	Adult T-cell lymphoma/leukaemia stage III
Abdominal wall neoplasm malignant	Acute monocytic leukaemia	Adenosquamous cell lung cancer stage 0	Adult T-cell lymphoma/leukaemia stage IV
Acral lentiginous melanoma stage I	Acute monocytic leukaemia (in remission)	Adenosquamous cell lung cancer stage I	Aesthesioneuroblastoma
Acral lentiginous melanoma stage II	Acute myeloid leukaemia	Adenosquamous cell lung cancer stage II	Aleukaemic leukaemia
Acral lentiginous melanoma stage III	Acute myeloid leukaemia (in remission)	Adenosquamous cell lung cancer stage III	Alveolar soft part sarcoma
Acral lentiginous melanoma stage IV	Acute myeloid leukaemia recurrent	Adenosquamous cell lung cancer stage IV	Alveolar soft part sarcoma metastatic
Acral lentiginous melanoma stage unspecified	Acute myelomonocytic leukaemia	Adrenal carcinoma	Alveolar soft part sarcoma non-metastatic
ACTH-producing pituitary tumour	Acute promyelocytic leukaemia	Adrenal gland cancer metastatic	Alveolar soft part sarcoma recurrent
Acute biphenotypic leukaemia	Adenocarcinoma	Adrenal neoplasm	Anal cancer
Acute leukaemia	Adenocarcinoma of the cervix	Adrenocortical carcinoma	Anal cancer metastatic
Acute leukaemia in remission	Adenocarcinoma pancreas	Adult T-cell lymphoma/leukaemia	Anal cancer recurrent
Acute lymphocytic leukaemia	Adenoid cystic carcinoma	Adult T-cell lymphoma/leukaemia recurrent	Anal cancer stage 0
Acute lymphocytic leukaemia (in remission)	Adenosquamous carcinoma of the cervix	Adult T-cell lymphoma/leukaemia refractory	Anal cancer stage I

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Anal cancer stage II	Angiocentric lymphoma stage I	APUDoma	B-cell small lymphocytic lymphoma stage I
Anal cancer stage III	Angiocentric lymphoma stage II	Astrocytoma	B-cell small lymphocytic lymphoma stage II
Anal cancer stage IV	Angiocentric lymphoma stage III	Astrocytoma malignant	B-cell small lymphocytic lymphoma stage III
Anal neoplasm	Angiocentric lymphoma stage IV	Atypical fibroxanthoma	B-cell small lymphocytic lymphoma stage IV
Anaplastic astrocytoma	Angioimmunoblastic T-cell lymphoma	B precursor type acute leukaemia	B-cell type acute leukaemia
Anaplastic large cell lymphoma T- and null-cell types	Angioimmunoblastic T-cell lymphoma recurrent	B-cell lymphoma	B-cell unclassifiable lymphoma high grade
Anaplastic large cell lymphoma T- and null-cell types recurrent	Angioimmunoblastic T-cell lymphoma refractory	B-cell lymphoma recurrent	B-cell unclassifiable lymphoma low grade
Anaplastic large cell lymphoma T- and null-cell types refractory	Angioimmunoblastic T-cell lymphoma stage I	B-cell lymphoma refractory	Basal cell carcinoma
Anaplastic large cell lymphoma T- and null-cell types stage I	Angioimmunoblastic T-cell lymphoma stage II	B-cell lymphoma stage I	Basosquamous carcinoma
Anaplastic large cell lymphoma T- and null-cell types stage II	Angioimmunoblastic T-cell lymphoma stage III	B-cell lymphoma stage II	Basosquamous carcinoma of skin
Anaplastic large cell lymphoma T- and null-cell types stage III	Angioimmunoblastic T-cell lymphoma stage IV	B-cell lymphoma stage III	Bile duct cancer
Anaplastic large cell lymphoma T- and null-cell types stage IV	Angiosarcoma	B-cell lymphoma stage IV	Bile duct cancer non-resectable
Angiocentric lymphoma	Angiosarcoma metastatic	B-cell small lymphocytic lymphoma	Bile duct cancer recurrent
Angiocentric lymphoma recurrent	Angiosarcoma non-metastatic	B-cell small lymphocytic lymphoma recurrent	Bile duct cancer resectable
Angiocentric lymphoma refractory	Angiosarcoma recurrent	B-cell small lymphocytic lymphoma refractory	Bile duct cancer stage 0

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Bile duct cancer stage I	Bladder cancer stage 0, with cancer in situ	Bladder transitional cell carcinoma	Bone sarcoma
Bile duct cancer stage II	Bladder cancer stage 0, without cancer in situ	Bladder transitional cell carcinoma recurrent	Borderline ovarian tumour
Bile duct cancer stage III	Bladder cancer stage I, with cancer in situ	Bladder transitional cell carcinoma stage 0	Bowen's disease
Bile duct cancer stage IV	Bladder cancer stage I, without cancer in situ	Bladder transitional cell carcinoma stage I	Brain cancer metastatic
Biliary cancer metastatic	Bladder cancer stage II	Bladder transitional cell carcinoma stage II	Brain neoplasm
Biliary neoplasm	Bladder cancer stage III	Bladder transitional cell carcinoma stage III	Brain neoplasm malignant
Bladder adenocarcinoma recurrent	Bladder cancer stage IV	Bladder transitional cell carcinoma stage IV	Brain stem glioma
Bladder adenocarcinoma stage 0	Bladder neoplasm	Blast cell crisis	Brain teratoma
Bladder adenocarcinoma stage I	Bladder squamous cell carcinoma recurrent	Blast crisis in myelogenous leukaemia	Breast cancer
Bladder adenocarcinoma stage II	Bladder squamous cell carcinoma stage 0	Bone cancer metastatic	Breast cancer female
Bladder adenocarcinoma stage III	Bladder squamous cell carcinoma stage I	Bone giant cell tumour	Breast cancer in situ
Bladder adenocarcinoma stage IV	Bladder squamous cell carcinoma stage II	Bone marrow leukaemic cell infiltration	Breast cancer male
Bladder adenocarcinoma stage unspecified	Bladder squamous cell carcinoma stage III	Bone marrow tumour cell infiltration	Breast cancer metastatic
Bladder cancer	Bladder squamous cell carcinoma stage IV	Bone neoplasm	Breast cancer recurrent
Bladder cancer recurrent	Bladder squamous cell carcinoma stage unspecified	Bone neoplasm malignant	Breast cancer stage I

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Breast cancer stage II	Burkitt's lymphoma stage II	Carcinoma in situ	Cervix cancer metastatic
Breast cancer stage III	Burkitt's lymphoma stage III	Carcinoma in situ of eye	Cervix carcinoma
Breast cancer stage IV	Burkitt's lymphoma stage IV	Carcinoma in situ of penis	Cervix carcinoma recurrent
Breast neoplasm	Buschke-Lowenstein's tumour	Carcinoma in situ of skin	Cervix carcinoma stage 0
Breast sarcoma	Cancer in remission	Carcinoma in situ of trachea	Cervix carcinoma stage I
Breast sarcoma metastatic	Carcinoid tumour	Cardiac neoplasm malignant	Cervix carcinoma stage II
Breast sarcoma recurrent	Carcinoid tumour of the appendix	Cardiac neoplasm unspecified	Cervix carcinoma stage III
Bronchial carcinoma	Carcinoid tumour of the caecum	Cardiac teratoma	Cervix carcinoma stage IV
Bronchial neoplasm	Carcinoid tumour of the duodenum	Carotid body tumour	Cervix neoplasm
Bronchioloalveolar carcinoma	Carcinoid tumour of the gastrointestinal tract	Cartilage neoplasm	Chloroma
Burkitt's leukaemia	Carcinoid tumour of the pancreas	Central nervous system lymphoma	Chloroma (in remission)
Burkitt's lymphoma	Carcinoid tumour of the prostate	Central nervous system neoplasm	Chondrosarcoma
Burkitt's lymphoma recurrent	Carcinoid tumour of the small bowel	Cerebellar tumour	Chondrosarcoma metastatic
Burkitt's lymphoma refractory	Carcinoid tumour of the stomach	Cerebellopontine angle tumour	Chondrosarcoma recurrent
Burkitt's lymphoma stage I	Carcinoid tumour pulmonary	Cerebral neuroblastoma	Chordoma

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Choriocarcinoma	Chronic lymphocytic leukaemia stage 4	Colon cancer stage II	Conjunctival neoplasm
Choroid melanoma	Chronic lymphocytic leukaemia transformation	Colon cancer stage III	Conjunctival primary acquired melanosis
Choroid neoplasm	Chronic myeloid leukaemia	Colon cancer stage IV	Contralateral breast cancer
Choroid plexus carcinoma	Chronic myeloid leukaemia (in remission)	Colon neoplasm	Cystosarcoma phyllodes
Chronic eosinophilic leukaemia	Chronic myeloid leukaemia transformation	Colorectal cancer	Dermatofibrosarcoma
Chronic leukaemia	Chronic myelomonocytic leukaemia	Colorectal cancer metastatic	Desmoplastic small round cell tumour
Chronic leukaemia in remission	Chronic myelomonocytic leukaemia (in remission)	Colorectal cancer recurrent	Diaphragm neoplasm
Chronic lymphocytic leukaemia	Clear cell endometrial carcinoma	Colorectal cancer stage I	Diffuse large B-cell lymphoma
Chronic lymphocytic leukaemia (in remission)	Clear cell sarcoma of the kidney	Colorectal cancer stage II	Diffuse large B-cell lymphoma recurrent
Chronic lymphocytic leukaemia recurrent	CNS germinoma	Colorectal cancer stage III	Diffuse large B-cell lymphoma refractory
Chronic lymphocytic leukaemia refractory	Colon cancer	Colorectal cancer stage IV	Diffuse large B-cell lymphoma stage I
Chronic lymphocytic leukaemia stage 0	Colon cancer metastatic	Colorectal carcinoma stage 0	Diffuse large B-cell lymphoma stage II
Chronic lymphocytic leukaemia stage 1	Colon cancer recurrent	Congenital fibrosarcoma	Diffuse large B-cell lymphoma stage III
Chronic lymphocytic leukaemia stage 2	Colon cancer stage 0	Congenital teratoma	Diffuse large B-cell lymphoma stage IV
Chronic lymphocytic leukaemia stage 3	Colon cancer stage I	Conjunctival melanoma	Disseminated large cell lymphoma

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Duodenal neoplasm	Endometrial neoplasm	Erythroleukaemia	Extragonadal primary non-seminoma stage I
Dysplastic naevus syndrome	Endometrial sarcoma	Ewing's sarcoma	Extragonadal primary non-seminoma stage II
Ear neoplasm	Endometrial sarcoma metastatic	Ewing's sarcoma metastatic	Extragonadal primary non-seminoma stage III
Ear neoplasm malignant	Endometrial sarcoma recurrent	Ewing's sarcoma recurrent	Extragonadal primary non-seminoma stage IV
Eccrine carcinoma	Eosinophilic leukaemia	Extra-osseous Ewing's sarcoma	Extragonadal primary seminoma (pure) stage I
Endocrine neoplasm	Ependymoma	Extra-osseous Ewing's sarcoma metastatic	Extragonadal primary seminoma (pure) stage II
Endocrine neoplasm malignant	Ependymoma malignant	Extra-osseous Ewing's sarcoma nonmetastatic	Extragonadal primary seminoma (pure) stage III
Endometrial cancer	Epididymal neoplasm	Extra-osseous Ewing's sarcoma recurrent	Extragonadal primary seminoma (pure) stage IV
Endometrial cancer metastatic	Epiglottic carcinoma	Extragonadal primary embryonal carcinoma	Extramammary Paget's disease
Endometrial cancer recurrent	Epithelioid sarcoma	Extragonadal primary germ cell cancer	Extranodal marginal zone B-cell lymphoma (MALT type)
Endometrial cancer stage 0	Epithelioid sarcoma metastatic	Extragonadal primary germ cell tumour mixed stage I	Extranodal marginal zone B-cell lymphoma (MALT type) recurrent
Endometrial cancer stage I	Epithelioid sarcoma non-metastatic	Extragonadal primary germ cell tumour mixed stage II	Extranodal marginal zone B-cell lymphoma (MALT type) refractory
Endometrial cancer stage II	Epithelioid sarcoma recurrent	Extragonadal primary germ cell tumour mixed stage III	Extranodal marginal zone B-cell lymphoma (MALT type) stage I
Endometrial cancer stage III	Epstein-Barr virus associated lymphoproliferative disorder	Extragonadal primary malignant teratoma	Extranodal marginal zone B-cell lymphoma (MALT type) stage II
Endometrial cancer stage IV	Erythraemic myelosis (in remission)	Extragonadal primary non-seminoma	Extranodal marginal zone B-cell lymphoma (MALT type) stage III

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Extranodal marginal zone B-cell lymphoma (MALT type) stage IV	Fallopian tube cancer stage II	Follicle centre lymphoma diffuse small cell lymphoma stage IV	Gallbladder cancer stage III
Extranodal NK/T-cell lymphoma, nasal type	Fallopian tube cancer stage III	Follicle centre lymphoma, follicular grade I, II, III	Gallbladder cancer stage IV
Extraocular retinoblastoma	Fallopian tube cancer stage IV	Follicle centre lymphoma, follicular grade I, II, III recurrent	Ganglioneuroblastoma
Extraskeletal chondrosarcoma	Fallopian tube neoplasm	Follicle centre lymphoma, follicular grade I, II, III refractory	Gastric cancer
Extraskeletal chondrosarcoma metastatic	Female reproductive neoplasm	Follicle centre lymphoma, follicular grade I, II, III stage I	Gastric cancer recurrent
Extraskeletal chondrosarcoma non-metastatic	Female reproductive tract carcinoma in situ	Follicle centre lymphoma, follicular grade I, II, III stage II	Gastric cancer stage 0
Extraskeletal chondrosarcoma recurrent	Fibrosarcoma	Follicle centre lymphoma, follicular grade I, II, III stage III	Gastric cancer stage I
Extraskeletal osteosarcoma	Fibrosarcoma metastatic	Follicle centre lymphoma, follicular grade I, II, III stage IV	Gastric cancer stage II
Extraskeletal osteosarcoma metastatic	Fibrosarcoma non-metastatic	Gallbladder cancer	Gastric cancer stage III
Extraskeletal osteosarcoma non-metastatic	Follicle centre lymphoma diffuse small cell lymphoma	Gallbladder cancer metastatic	Gastric cancer stage IV
Extraskeletal osteosarcoma recurrent	Follicle centre lymphoma diffuse small cell lymphoma recurrent	Gallbladder cancer non-resectable	Gastric neoplasm
Eyelid tumour	Follicle centre lymphoma diffuse small cell lymphoma refractory	Gallbladder cancer recurrent	Gastric sarcoma
Fallopian tube cancer	Follicle centre lymphoma diffuse small cell lymphoma stage I	Gallbladder cancer stage 0	Gastrinoma
Fallopian tube cancer metastatic	Follicle centre lymphoma diffuse small cell lymphoma stage II	Gallbladder cancer stage I	Gastrinoma malignant
Fallopian tube cancer stage I	Follicle centre lymphoma diffuse small cell lymphoma stage III	Gallbladder cancer stage II	Gastrointestinal cancer metastatic

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Gastrointestinal carcinoma	Gliomatosis cerebri	Hepatic cancer stage I	Hereditary papillary renal carcinoma
Gastrointestinal carcinoma in situ	Glioneuronal tumour	Hepatic cancer stage II	High grade B-cell lymphoma Burkitt-like lymphoma
Gastrointestinal neoplasm	Gliosarcoma	Hepatic cancer stage III	High grade B-cell lymphoma Burkitt-like lymphoma recurrent
Gastrointestinal stromal tumour	Glottis carcinoma	Hepatic cancer stage IV	High grade B-cell lymphoma Burkitt-like lymphoma refractory
Gastrooesophageal cancer	Glucagonoma	Hepatic neoplasm	High grade B-cell lymphoma Burkitt-like lymphoma stage I
Genital neoplasm malignant female	Granular cell tumour	Hepatic neoplasm malignant	High grade B-cell lymphoma Burkitt-like lymphoma stage II
Genital neoplasm malignant male	Growth hormone-producing pituitary tumour	Hepatic neoplasm malignant non-resectable	High grade B-cell lymphoma Burkitt-like lymphoma stage III
Genitourinary tract neoplasm	Haemangiopericytoma	Hepatic neoplasm malignant recurrent	High grade B-cell lymphoma Burkitt-like lymphoma stage IV
Germ cell cancer	Haemangiopericytoma of meninges	Hepatic neoplasm malignant resectable	Histiocytic medullary reticulosis
Germ cell cancer metastatic	Haematological malignancy	Hepatobiliary carcinoma in situ	Hodgkin's disease
Gestational trophoblastic tumour	Haematopoietic neoplasm	Hepatobiliary neoplasm	Hodgkin's disease lymphocyte depletion stage I site unspecified
Gingival cancer	Hairy cell leukaemia	Hepatoblastoma	Hodgkin's disease lymphocyte depletion stage I subdiaphragm
Glioblastoma	Head and neck cancer	Hepatoblastoma recurrent	Hodgkin's disease lymphocyte depletion stage I supradiaphragm
Glioblastoma multiforme	Hepatic angiosarcoma	Hepatosplenic T-cell lymphoma	Hodgkin's disease lymphocyte depletion stage II site unspecified
Glioma	Hepatic cancer metastatic	Hereditary leiomyomatosis renal cell carcinoma	Hodgkin's disease lymphocyte depletion stage II subdiaphragm

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Hodgkin's disease lymphocyte depletion stage II supradiaphragm	Hodgkin's disease lymphocyte predominance type stage IV	Hodgkin's disease nodular sclerosis stage I subdiaphragmatic	Hypopharyngeal cancer
Hodgkin's disease lymphocyte depletion type recurrent	Hodgkin's disease lymphocyte predominance type stage unspecified	Hodgkin's disease nodular sclerosis stage I supradiaphragmatic	Hypopharyngeal cancer recurrent
Hodgkin's disease lymphocyte depletion type refractory	Hodgkin's disease mixed cellularity recurrent	Hodgkin's disease nodular sclerosis stage II subdiaphragmatic	Hypopharyngeal cancer stage 0
Hodgkin's disease lymphocyte depletion type stage III	Hodgkin's disease mixed cellularity refractory	Hodgkin's disease nodular sclerosis stage II supradiaphragmatic	Hypopharyngeal cancer stage I
Hodgkin's disease lymphocyte depletion type stage IV	Hodgkin's disease mixed cellularity stage I site unspecified	Hodgkin's disease nodular sclerosis stage III	Hypopharyngeal cancer stage II
Hodgkin's disease lymphocyte depletion type stage unspecified	Hodgkin's disease mixed cellularity stage I subdiaphragmatic	Hodgkin's disease nodular sclerosis stage IV	Hypopharyngeal cancer stage III
Hodgkin's disease lymphocyte predominance stage I site unspec	Hodgkin's disease mixed cellularity stage I supradiaphragmatic	Hodgkin's disease nodular sclerosis stage unspecified	Hypopharyngeal cancer stage IV
Hodgkin's disease lymphocyte predominance stage I subdiaphragm	Hodgkin's disease mixed cellularity stage II subdiaphragmatic	Hodgkin's disease recurrent	Hypopharyngeal neoplasm
Hodgkin's disease lymphocyte predominance stage I supradiaphragm	Hodgkin's disease mixed cellularity stage II supradiaphragmatic	Hodgkin's disease refractory	Immunoblastic lymphoma
Hodgkin's disease lymphocyte predominance stage II site unspec	Hodgkin's disease mixed cellularity stage III	Hodgkin's disease stage I	Inflammatory carcinoma of breast recurrent
Hodgkin's disease lymphocyte predominance stage II subdiaphragm	Hodgkin's disease mixed cellularity stage IV	Hodgkin's disease stage II	Inflammatory carcinoma of breast stage III
Hodgkin's disease lymphocyte predominance stage II supradiaphragm	Hodgkin's disease mixed cellularity stage unspecified	Hodgkin's disease stage III	Inflammatory carcinoma of breast stage IV
Hodgkin's disease lymphocyte predominance type recurrent	Hodgkin's disease nodular sclerosis recurrent	Hodgkin's disease stage IV	Inflammatory carcinoma of the breast
Hodgkin's disease lymphocyte predominance type refractory	Hodgkin's disease nodular sclerosis refractory	Hodgkin's disease unclassifiable	Inflammatory myofibroblastic tumour
Hodgkin's disease lymphocyte predominance type stage III	Hodgkin's disease nodular sclerosis stage I site unspecified	Hormone-secreting ovarian tumour	Insulinoma

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Intestinal adenocarcinoma	Kaposi's sarcoma AIDS related	Laryngeal cancer	Lentigo maligna stage II
Intestinal T-cell lymphoma	Kaposi's sarcoma classical type	Laryngeal cancer metastatic	Lentigo maligna stage III
Intestinal T-cell lymphoma recurrent	Keratoacanthoma	Laryngeal cancer recurrent	Lentigo maligna stage IV
Intestinal T-cell lymphoma refractory	Lacrimal duct neoplasm	Laryngeal cancer stage 0	Lentigo maligna stage unspecified
Intestinal T-cell lymphoma stage I	Langerhans' cell histiocytosis	Laryngeal cancer stage I	Leukaemia
Intestinal T-cell lymphoma stage II	Large cell carcinoma of the respiratory tract stage unspecified	Laryngeal cancer stage II	Leukaemia basophilic
Intestinal T-cell lymphoma stage III	Large cell lung cancer metastatic	Laryngeal cancer stage III	Leukaemia cutis
Intestinal T-cell lymphoma stage IV	Large cell lung cancer recurrent	Laryngeal cancer stage IV	Leukaemia granulocytic
Intracranial meningioma malignant	Large cell lung cancer stage 0	Laryngeal neoplasm	Leukaemia in remission
Intraocular melanoma	Large cell lung cancer stage I	Leiomyosarcoma	Leukaemia monocytic
Intraocular retinoblastoma	Large cell lung cancer stage II	Leiomyosarcoma metastatic	Leukaemia plasmacytic
Iris neoplasm	Large cell lung cancer stage III	Leiomyosarcoma non-metastatic	Leukaemia plasmacytic (in remission)
Iritic melanoma	Large cell lung cancer stage IV	Leiomyosarcoma recurrent	Leukaemia recurrent
Juvenile chronic myelomonocytic leukaemia	Large granular lymphocytosis	Lentigo maligna recurrent	Leukaemic infiltration
Kaposi's sarcoma	Large intestine carcinoma	Lentigo maligna stage I	Leukaemic infiltration brain

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Leukaemic infiltration extramedullary	Lip neoplasm	Lung cancer metastatic	Lung squamous cell carcinoma stage IV
Leukaemic infiltration gingiva	Lip neoplasm malignant stage unspecified	Lung carcinoma cell type unspecified recurrent	Lung squamous cell carcinoma stage unspecified
Leukaemic infiltration hepatic	Liposarcoma	Lung carcinoma cell type unspecified stage 0	Lymph node cancer metastatic
Leukaemic infiltration pulmonary	Liposarcoma metastatic	Lung carcinoma cell type unspecified stage I	Lymphangiosarcoma
Leukaemic infiltration renal	Liposarcoma non-metastatic	Lung carcinoma cell type unspecified stage II	Lymphangiosis carcinomatosa
Leukaemic lymphoma	Liposarcoma recurrent	Lung carcinoma cell type unspecified stage III	Lymphatic system neoplasm
Leukaemic retinopathy	Liver carcinoma ruptured	Lung carcinoma cell type unspecified stage IV	Lymphocytic leukaemia
Linitis plastica	Lung adenocarcinoma	Lung infiltration malignant	Lymphocytic lymphoma
Lip and/or oral cavity cancer	Lung adenocarcinoma metastatic	Lung neoplasm	Lymphoid leukaemia (in remission)
Lip and/or oral cavity cancer recurrent	Lung adenocarcinoma recurrent	Lung neoplasm malignant	Lymphoma
Lip and/or oral cavity cancer stage 0	Lung adenocarcinoma stage 0	Lung squamous cell carcinoma recurrent	Lymphoma AIDS related
Lip and/or oral cavity cancer stage I	Lung adenocarcinoma stage I	Lung squamous cell carcinoma stage 0	Lymphoma cutis
Lip and/or oral cavity cancer stage II	Lung adenocarcinoma stage II	Lung squamous cell carcinoma stage I	Lymphoma transformation
Lip and/or oral cavity cancer stage III	Lung adenocarcinoma stage III	Lung squamous cell carcinoma stage II	Lymphoplasmacytoid lymphoma/immunocytoma
Lip and/or oral cavity cancer stage IV	Lung adenocarcinoma stage IV	Lung squamous cell carcinoma stage III	Lymphoplasmacytoid lymphoma/immunocytoma recurrent

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Lymphoplasmacytoid lymphoma/immunocytoma refractory	Malignant glioma	Malignant melanoma of eyelid	Malignant neoplasm of choroid
Lymphoplasmacytoid lymphoma/immunocytoma stage I	Malignant haemangiopericytoma	Malignant melanoma of sites other than skin	Malignant neoplasm of conjunctiva
Lymphoplasmacytoid lymphoma/immunocytoma stage II	Malignant haemangiopericytoma metastatic	Malignant melanoma stage I	Malignant neoplasm of cornea
Lymphoplasmacytoid lymphoma/immunocytoma stage III	Malignant haemangiopericytoma non-metastatic	Malignant melanoma stage II	Malignant neoplasm of epididymis
Lymphoplasmacytoid lymphoma/immunocytoma stage IV	Malignant haemangiopericytoma recurrent	Malignant melanoma stage III	Malignant neoplasm of eye
Lymphoproliferative disorder	Malignant hepatobiliary neoplasm	Malignant melanoma stage IV	Malignant neoplasm of eyelid
Lymphoproliferative disorder in remission	Malignant histiocytosis	Malignant mesenchymoma	Malignant neoplasm of islets of Langerhans
Male reproductive tract carcinoma in situ	Malignant hydatidiform mole	Malignant mesenchymoma metastatic	Malignant neoplasm of lacrimal duct
Male reproductive tract neoplasm	Malignant lymphoid neoplasm	Malignant mesenchymoma non-metastatic	Malignant neoplasm of lacrimal gland
Malignant anorectal neoplasm	Malignant lymphoma unclassifiable high grade	Malignant mesenchymoma recurrent	Malignant neoplasm of orbit
Malignant cranial nerve neoplasm	Malignant lymphoma unclassifiable low grade	Malignant mesenteric neoplasm	Malignant neoplasm of paraurethral glands
Malignant fibrous histiocytoma	Malignant mast cell neoplasm	Malignant middle ear neoplasm	Malignant neoplasm of placenta
Malignant fibrous histiocytoma metastatic	Malignant mediastinal neoplasm	Malignant muscle neoplasm	Malignant neoplasm of pleura
Malignant fibrous histiocytoma non-metastatic	Malignant melanoma	Malignant neoplasm of ampulla of Vater	Malignant neoplasm of renal pelvis
Malignant fibrous histiocytoma recurrent	Malignant melanoma in situ	Malignant neoplasm of auricular cartilage	Malignant neoplasm of retina

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Malignant neoplasm of seminal vesicle	Malignant respiratory tract neoplasm	Mediastinum neoplasm	Metastases to biliary tract
Malignant neoplasm of spermatic cord	Malignant soft tissue neoplasm	Medulloblastoma	Metastases to bladder
Malignant neoplasm of spinal cord	Malignant splenic neoplasm	Medulloblastoma recurrent	Metastases to bone
Malignant neoplasm of thorax	Malignant transformation	Melanoma recurrent	Metastases to bone marrow
Malignant neoplasm of uterine adnexa	Malignant urinary tract neoplasm	Melanomatous meningitis	Metastases to breast
Malignant nervous system neoplasm	Mantle cell lymphoma	Meningeal neoplasm	Metastases to central nervous system
Malignant nipple neoplasm	Mantle cell lymphoma recurrent	Meningioma malignant	Metastases to chest wall
Malignant nipple neoplasm female	Mantle cell lymphoma refractory	Mesothelioma	Metastases to diaphragm
Malignant nipple neoplasm male	Mantle cell lymphoma stage I	Mesothelioma malignancy unspecified	Metastases to eustachian tube
Malignant oligodendroglioma	Mantle cell lymphoma stage II	Mesothelioma malignant	Metastases to eye
Malignant ovarian cyst	Mantle cell lymphoma stage III	Mesothelioma malignant advanced	Metastases to fallopian tube
Malignant palate neoplasm	Mantle cell lymphoma stage IV	Mesothelioma malignant recurrent	Metastases to gallbladder
Malignant pericardial neoplasm	Mastocytic leukaemia	Metastases to abdominal cavity	Metastases to gastrointestinal tract
Malignant peritoneal neoplasm	Mature B-cell type acute leukaemia	Metastases to abdominal wall	Metastases to heart
Malignant pituitary tumour	Maxillofacial sinus neoplasm	Metastases to adrenals	Metastases to kidney

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Metastases to large intestine	Metastases to penis	Metastases to small intestine	Metastatic carcinoid tumour
Metastases to larynx	Metastases to perineum	Metastases to soft tissue	Metastatic carcinoma of the bladder
Metastases to liver	Metastases to peripheral nervous system	Metastases to spine	Metastatic gastric cancer
Metastases to lung	Metastases to peripheral vascular system	Metastases to spleen	Metastatic glioma
Metastases to lymph nodes	Metastases to peritoneum	Metastases to stomach	Metastatic malignant melanoma
Metastases to meninges	Metastases to pharynx	Metastases to testicle	Metastatic neoplasm
Metastases to mouth	Metastases to pituitary gland	Metastases to the mediastinum	Metastatic ocular melanoma
Metastases to muscle	Metastases to placenta	Metastases to the respiratory system	Metastatic renal cell carcinoma
Metastases to nasal sinuses	Metastases to pleura	Metastases to thorax	Metastatic salivary gland cancer
Metastases to neck	Metastases to prostate	Metastases to thyroid	Metastatic squamous cell carcinoma
Metastases to nervous system	Metastases to rectum	Metastases to trachea	Metastatic uterine cancer
Metastases to oesophagus	Metastases to reproductive organ	Metastases to urinary tract	Mixed astrocytoma-ependymoma
Metastases to ovary	Metastases to retroperitoneum	Metastases to uterus	Mixed hepatocellular cholangiocarcinoma
Metastases to pancreas	Metastases to salivary gland	Metastasis	Mixed oligo-astrocytoma
Metastases to pelvis	Metastases to skin	Metastatic bronchial carcinoma	Mixed salivary tumour

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Monocytic leukaemia in remission	Myeloid leukaemia in remission	Neonatal neuroblastoma	Neuroblastoma recurrent
Mucinous endometrial carcinoma	Myeloma recurrence	Neoplasm	Neuroectodermal neoplasm
Mucoepidermoid carcinoma	Nasal cavity cancer	Neoplasm malignant	Neuroendocrine carcinoma
Mueller's mixed tumour	Nasal neoplasm	Neoplasm of appendix	Neuroendocrine carcinoma of the skin
Multiple myeloma	Nasal sinus cancer	Neoplasm of cornea unspecified malignancy	Neuroendocrine tumour
Muscle neoplasm	Nasopharyngeal cancer	Neoplasm of orbit	Neurofibrosarcoma
Mycosis fungoides	Nasopharyngeal cancer recurrent	Neoplasm of thymus	Neurofibrosarcoma metastatic
Mycosis fungoides recurrent	Nasopharyngeal cancer stage 0	Neoplasm progression	Neurofibrosarcoma non-metastatic
Mycosis fungoides refractory	Nasopharyngeal cancer stage I	Neoplasm prostate	Neurofibrosarcoma recurrent
Mycosis fungoides stage I	Nasopharyngeal cancer stage II	Neoplasm recurrence	Neurotensinoma
Mycosis fungoides stage II	Nasopharyngeal cancer stage III	Neoplasm skin	Nipple neoplasm
Mycosis fungoides stage III	Nasopharyngeal cancer stage IV	Nephroblastoma	Nodal marginal zone B-cell lymphoma
Mycosis fungoides stage IV	Natural killer-cell leukaemia	Nervous system neoplasm	Nodal marginal zone B-cell lymphoma recurrent
Myeloblastoma	Natural killer-cell lymphoblastic lymphoma	Neurilemmoma malignant	Nodal marginal zone B-cell lymphoma refractory
Myeloid leukaemia	Neonatal leukaemia	Neuroblastoma	Nodal marginal zone B-cell lymphoma stage I

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Nodal marginal zone B-cell lymphoma stage II	Non-Hodgkin's lymphoma unspecified histology aggressive stage II	Non-small cell lung cancer stage II	Oesophageal adenocarcinoma stage III
Nodal marginal zone B-cell lymphoma stage III	Non-Hodgkin's lymphoma unspecified histology aggressive stage III	Non-small cell lung cancer stage III	Oesophageal adenocarcinoma stage IV
Nodal marginal zone B-cell lymphoma stage IV	Non-Hodgkin's lymphoma unspecified histology aggressive stage IV	Non-small cell lung cancer stage IIIA	Oesophageal cancer metastatic
Non-Hodgkin's lymphoma	Non-Hodgkin's lymphoma unspecified histology indolent	Non-small cell lung cancer stage IIIB	Oesophageal carcinoma
Non-Hodgkin's lymphoma recurrent	Non-Hodgkin's lymphoma unspecified histology indolent stage I	Non-small cell lung cancer stage IV	Oesophageal carcinoma recurrent
Non-Hodgkin's lymphoma refractory	Non-Hodgkin's lymphoma unspecified histology indolent stage II	Nongerminomatous germ cell tumour of the CNS	Oesophageal carcinoma stage 0
Non-Hodgkin's lymphoma stage I	Non-Hodgkin's lymphoma unspecified histology indolent stage III	Ocular cancer metastatic	Oesophageal neoplasm
Non-Hodgkin's lymphoma stage II	Non-Hodgkin's lymphoma unspecified histology indolent stage IV	Ocular haemangiopericytoma	Oesophageal squamous cell carcinoma
Non-Hodgkin's lymphoma stage III	Non-renal cell carcinoma of kidney	Ocular neoplasm	Oesophageal squamous cell carcinoma metastatic
Non-Hodgkin's lymphoma stage IV	Non-secretory adenoma of pituitary	Oesophageal adenocarcinoma	Oesophageal squamous cell carcinoma recurrent
Non-Hodgkin's lymphoma transformed recurrent	Non-small cell lung cancer	Oesophageal adenocarcinoma metastatic	Oesophageal squamous cell carcinoma stage 0
Non-Hodgkin's lymphoma unspecified histology aggressive	Non-small cell lung cancer metastatic	Oesophageal adenocarcinoma recurrent	Oesophageal squamous cell carcinoma stage I
Non-Hodgkin's lymphoma unspecified histology aggressive recurrent	Non-small cell lung cancer recurrent	Oesophageal adenocarcinoma stage 0	Oesophageal squamous cell carcinoma stage II
Non-Hodgkin's lymphoma unspecified histology aggressive refractory	Non-small cell lung cancer stage 0	Oesophageal adenocarcinoma stage I	Oesophageal squamous cell carcinoma stage III
Non-Hodgkin's lymphoma unspecified histology aggressive stage I	Non-small cell lung cancer stage I	Oesophageal adenocarcinoma stage II	Oesophageal squamous cell carcinoma stage IV

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Oligodendroglioma	Osteosarcoma localised	Ovarian dysgerminoma stage unspecified	Ovarian germ cell choriocarcinoma stage II
Omentum neoplasm	Osteosarcoma metastatic	Ovarian embryonal carcinoma	Ovarian germ cell choriocarcinoma stage III
Optic nerve glioma	Osteosarcoma recurrent	Ovarian epithelial cancer	Ovarian germ cell choriocarcinoma stage IV
Optic nerve neoplasm	Otic cancer metastatic	Ovarian epithelial cancer metastatic	Ovarian germ cell embryonal carcinoma stage I
Optic tract glioma	Ovarian cancer	Ovarian epithelial cancer recurrent	Ovarian germ cell embryonal carcinoma stage II
Oral cavity cancer metastatic	Ovarian cancer metastatic	Ovarian epithelial cancer stage I	Ovarian germ cell embryonal carcinoma stage III
Oral neoplasm	Ovarian cancer recurrent	Ovarian epithelial cancer stage II	Ovarian germ cell embryonal carcinoma stage IV
Oropharyngeal cancer recurrent	Ovarian cancer stage I	Ovarian epithelial cancer stage III	Ovarian germ cell endodermal sinus tumour stage I
Oropharyngeal cancer stage 0	Ovarian cancer stage II	Ovarian epithelial cancer stage IV	Ovarian germ cell endodermal sinus tumour stage II
Oropharyngeal cancer stage I	Ovarian cancer stage III	Ovarian germ cell cancer	Ovarian germ cell endodermal sinus tumour stage III
Oropharyngeal cancer stage II	Ovarian cancer stage IV	Ovarian germ cell cancer stage I	Ovarian germ cell endodermal sinus tumour stage IV
Oropharyngeal cancer stage III	Ovarian dysgerminoma stage I	Ovarian germ cell cancer stage II	Ovarian germ cell polyembryoma stage I
Oropharyngeal cancer stage IV	Ovarian dysgerminoma stage II	Ovarian germ cell cancer stage III	Ovarian germ cell polyembryoma stage II
Oropharyngeal cancer stage unspecified	Ovarian dysgerminoma stage III	Ovarian germ cell cancer stage IV	Ovarian germ cell polyembryoma stage III
Oropharyngeal neoplasm	Ovarian dysgerminoma stage IV	Ovarian germ cell choriocarcinoma stage I	Ovarian germ cell polyembryoma stage IV

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Ovarian germ cell teratoma stage I	Pancreatic carcinoma non-resectable	Paranasal sinus and nasal cavity malignant neoplasm	Penis carcinoma recurrent
Ovarian germ cell teratoma stage II	Pancreatic carcinoma recurrent	Paranasal sinus and nasal cavity malignant neoplasm recurrent	Penis carcinoma stage I
Ovarian germ cell teratoma stage III	Pancreatic carcinoma resectable	Paranasal sinus and nasal cavity malignant neoplasm stage 0	Penis carcinoma stage II
Ovarian germ cell teratoma stage IV	Pancreatic carcinoma stage 0	Paranasal sinus and nasal cavity malignant neoplasm stage I	Penis carcinoma stage III
Ovarian granulosa-theca cell tumour	Pancreatic carcinoma stage I	Paranasal sinus and nasal cavity malignant neoplasm stage II	Penis carcinoma stage IV
Ovarian low malignant potential tumour	Pancreatic carcinoma stage II	Paranasal sinus and nasal cavity malignant neoplasm stage III	Pericardial mesothelioma malignant advanced
Ovarian neoplasm	Pancreatic carcinoma stage III	Paranasal sinus and nasal cavity malignant neoplasm stage IV	Pericardial mesothelioma malignant localised
Ovarian stromal cancer	Pancreatic carcinoma stage IV	Paranasal sinus neoplasm	Pericardial mesothelioma malignant recurrent
Paget's disease of penis	Pancreatic neoplasm	Parathyroid tumour	Pericardial neoplasm
Paget's disease of skin	Pancreatic neuroendocrine tumour	Parathyroid tumour malignant	Peripheral nervous system neoplasm
Paget's disease of the breast	Pancreatic neuroendocrine tumour metastatic	Pelvic neoplasm	Peripheral neuroepithelioma
Paget's disease of the vulva	Pancreatic sarcoma	Penile malignant neoplasm	Peripheral neuroepithelioma of bone
Pancoast's tumour	Papillary serous endometrial carcinoma	Penile neoplasm	Peripheral neuroepithelioma of bone metastatic
Pancreatic carcinoma	Paraganglion neoplasm	Penis carcinoma	Peripheral neuroepithelioma of bone recurrent
Pancreatic carcinoma metastatic	Paraganglion neoplasm malignant	Penis carcinoma metastatic	Peripheral neuroepithelioma of soft tissue

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Peripheral T-cell lymphoma unspecified	Pharyngeal cancer metastatic	Pituitary neoplasm malignant recurrent	Precursor B-lymphoblastic lymphoma
Peripheral T-cell lymphoma unspecified recurrent	Pharyngeal cancer recurrent	Pituitary tumour	Precursor B-lymphoblastic lymphoma recurrent
Peripheral T-cell lymphoma unspecified refractory	Pharyngeal cancer stage 0	Pituitary tumour recurrent	Precursor B-lymphoblastic lymphoma refractory
Peripheral T-cell lymphoma unspecified stage I	Pharyngeal cancer stage I	Placental neoplasm	Precursor B-lymphoblastic lymphoma stage I
Peripheral T-cell lymphoma unspecified stage II	Pharyngeal cancer stage II	Plasmablastic lymphoma	Precursor B-lymphoblastic lymphoma stage II
Peripheral T-cell lymphoma unspecified stage III	Pharyngeal cancer stage III	Plasmacytoma	Precursor B-lymphoblastic lymphoma stage III
Peripheral T-cell lymphoma unspecified stage IV	Pharyngeal cancer stage IV	Pleura carcinoma	Precursor B-lymphoblastic lymphoma stage IV
Peritoneal carcinoma metastatic	Pharyngeal cancer stage unspecified	Pleural mesothelioma	Precursor T-lymphoblastic lymphoma/leukaemia
Peritoneal mesothelioma malignant	Pharyngeal neoplasm	Pleural mesothelioma malignant	Precursor T-lymphoblastic lymphoma/leukaemia recurrent
Peritoneal mesothelioma malignant advanced	Pineal germinoma	Pleural mesothelioma malignant advanced	Precursor T-lymphoblastic lymphoma/leukaemia refractory
Peritoneal mesothelioma malignant recurrent	Pineal neoplasm	Pleural mesothelioma malignant recurrent	Precursor T-lymphoblastic lymphoma/leukaemia stage I
Peritoneal neoplasm	Pineal parenchymal neoplasm malignant	Pleural neoplasm	Precursor T-lymphoblastic lymphoma/leukaemia stage II
Peritoneal sarcoma	Pinealoblastoma	Pleural sarcoma	Precursor T-lymphoblastic lymphoma/leukaemia stage III
Phaeochromocytoma	Pinealoma	Porocarcinoma	Precursor T-lymphoblastic lymphoma/leukaemia stage IV
Phaeochromocytoma malignant	Pituitary cancer metastatic	Postcricoid cancer	Primary effusion lymphoma

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Primary mediastinal large B-cell lymphoma	Prostate cancer stage I	Rectosigmoid cancer metastatic	Renal cancer stage IV
Primary mediastinal large B-cell lymphoma recurrent	Prostate cancer stage II	Rectosigmoid cancer recurrent	Renal cell carcinoma
Primary mediastinal large B-cell lymphoma refractory	Prostate cancer stage III	Rectosigmoid cancer stage 0	Renal cell carcinoma recurrent
Primary mediastinal large B-cell lymphoma stage I	Prostate cancer stage IV	Rectosigmoid cancer stage I	Renal cell carcinoma stage I
Primary mediastinal large B-cell lymphoma stage II	Pseudosarcoma	Rectosigmoid cancer stage II	Renal cell carcinoma stage II
Primary mediastinal large B-cell lymphoma stage III	Rectal cancer	Rectosigmoid cancer stage III	Renal cell carcinoma stage III
Primary mediastinal large B-cell lymphoma stage IV	Rectal cancer metastatic	Rectosigmoid cancer stage IV	Renal cell carcinoma stage IV
Primitive neuroectodermal tumour	Rectal cancer recurrent	Recurrent cancer	Renal neoplasm
Primitive neuroectodermal tumour metastatic	Rectal cancer stage 0	Refractory cancer	Respiratory tract carcinoma in situ
Prolactin-producing pituitary tumour	Rectal cancer stage I	Renal cancer	Respiratory tract neoplasm
Prolymphocytic leukaemia	Rectal cancer stage II	Renal cancer metastatic	Retinal melanoma
Prostate cancer	Rectal cancer stage III	Renal cancer recurrent	Retinal neoplasm
Prostate cancer metastatic	Rectal cancer stage IV	Renal cancer stage I	Retinoblastoma
Prostate cancer recurrent	Rectal neoplasm	Renal cancer stage II	Retinoblastoma bilateral
Prostate cancer stage 0	Rectosigmoid cancer	Renal cancer stage III	Retinoblastoma unilateral

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Retro-orbital neoplasm	Salivary gland neoplasm	Small cell carcinoma	Small intestine carcinoma stage III
Retroperitoneal cancer	Sarcoma	Small cell carcinoma of the cervix	Small intestine carcinoma stage IV
Retroperitoneal neoplasm	Sarcoma metastatic	Small cell lung cancer extensive stage	Small intestine leiomyosarcoma
Retroperitoneal neoplasm metastatic	Sarcoma of skin	Small cell lung cancer limited stage	Smooth muscle cell neoplasm
Rhabdoid tumour of the kidney	Sarcoma uterus	Small cell lung cancer metastatic	Soft tissue neoplasm
Rhabdomyosarcoma	Sarcomatosis	Small cell lung cancer recurrent	Solid pseudopapillary tumour of the pancreas
Rhabdomyosarcoma recurrent	Scrotal cancer	Small cell lung cancer stage unspecified	Somatostatinoma
Richter's syndrome	Sebaceous carcinoma	Small intestine carcinoma	Spinal cord neoplasm
Salivary gland cancer	Secretory adenoma of pituitary	Small intestine carcinoma metastatic	Spinal meningioma malignant
Salivary gland cancer recurrent	Seminoma	Small intestine carcinoma non-resectable	Spindle cell sarcoma
Salivary gland cancer stage 0	Signet-ring cell carcinoma	Small intestine carcinoma recurrent	Splenic marginal zone lymphoma
Salivary gland cancer stage I	Sinus cancer metastatic	Small intestine carcinoma resectable	Splenic marginal zone lymphoma recurrent
Salivary gland cancer stage II	Skin cancer	Small intestine carcinoma stage 0	Splenic marginal zone lymphoma refractory
Salivary gland cancer stage III	Skin cancer metastatic	Small intestine carcinoma stage I	Splenic marginal zone lymphoma stage I
Salivary gland cancer stage IV	Skin neoplasm bleeding	Small intestine carcinoma stage II	Splenic marginal zone lymphoma stage II

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Splenic marginal zone lymphoma stage III	Synovial sarcoma non-metastatic	Teratoma	Testicular germ cell tumour mixed stage II
Splenic marginal zone lymphoma stage IV	Synovial sarcoma recurrent	Teratoma of testis	Testicular germ cell tumour mixed stage III
Splenic neoplasm malignancy unspecified	T-cell chronic lymphocytic leukaemia	Testicular cancer metastatic	Testicular leiomyosarcoma
Squamous cell carcinoma	T-cell lymphoma	Testicular choriocarcinoma	Testicular malignant teratoma stage I
Squamous cell carcinoma of skin	T-cell lymphoma recurrent	Testicular choriocarcinoma recurrent	Testicular malignant teratoma stage II
Squamous cell carcinoma of the cervix	T-cell lymphoma refractory	Testicular choriocarcinoma stage I	Testicular malignant teratoma stage III
Squamous endometrial carcinoma	T-cell lymphoma stage I	Testicular choriocarcinoma stage II	Testicular neoplasm
Stewart-Treves syndrome	T-cell lymphoma stage II	Testicular choriocarcinoma stage III	Testicular seminoma (pure)
Superficial spreading melanoma stage I	T-cell lymphoma stage III	Testicular embryonal carcinoma	Testicular seminoma (pure) stage I
Superficial spreading melanoma stage II	T-cell lymphoma stage IV	Testicular embryonal carcinoma stage I	Testicular seminoma (pure) stage II
Superficial spreading melanoma stage III	T-cell prolymphocytic leukaemia	Testicular embryonal carcinoma stage II	Testicular seminoma (pure) stage III
Superficial spreading melanoma stage IV	T-cell type acute leukaemia	Testicular embryonal carcinoma stage III	Testicular yolk sac tumour stage I
Superficial spreading melanoma stage unspecified	T-cell unclassifiable lymphoma high grade	Testicular germ cell cancer	Testicular yolk sac tumour stage II
Synovial sarcoma	T-cell unclassifiable lymphoma low grade	Testicular germ cell cancer metastatic	Testicular yolk sac tumour stage III
Synovial sarcoma metastatic	Tendon neoplasm	Testicular germ cell tumour mixed stage I	Testis cancer

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Testis cancer recurrent	Tongue cancer metastatic	Transitional cell cancer of the renal pelvis and ureter recurrent	Urethral cancer regional
Throat cancer	Tongue carcinoma stage 0	Transitional cell cancer of the renal pelvis and ureter regional	Urethral neoplasm
Thymic cancer metastatic	Tongue carcinoma stage I	Transitional cell carcinoma	Urinary bladder sarcoma
Thymoma	Tongue carcinoma stage II	Transitional cell carcinoma metastatic	Urinary tract carcinoma in situ
Thymoma malignant	Tongue carcinoma stage III	Undifferentiated sarcoma	Urinary tract neoplasm
Thymoma malignant recurrent	Tongue carcinoma stage IV	Ureteral neoplasm	Uterine cancer
Thyroid cancer	Tongue neoplasm	Ureteric cancer	Uterine carcinoma in situ
Thyroid cancer metastatic	Tongue neoplasm malignant stage unspecified	Ureteric cancer local	Uterine leiomyosarcoma
Thyroid cancer stage 0	Tonsil cancer	Ureteric cancer metastatic	Uterine neoplasm
Thyroid cancer stage I	Tonsillar neoplasm	Ureteric cancer recurrent	Vaginal cancer
Thyroid cancer stage II	Tracheal cancer	Ureteric cancer regional	Vaginal cancer metastatic
Thyroid cancer stage III	Tracheal neoplasm	Urethral cancer	Vaginal cancer recurrent
Thyroid cancer stage IV	Transitional cell cancer of renal pelvis and ureter metastatic	Urethral cancer local	Vaginal cancer stage 0
Thyroid neoplasm	Transitional cell cancer of the renal pelvis and ureter	Urethral cancer metastatic	Vaginal cancer stage I
Thyroid stimulating hormone-producing pituitary tumour	Transitional cell cancer of the renal pelvis and ureter localised	Urethral cancer recurrent	Vaginal cancer stage II

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-3　悪性腫瘍及び詳細不明の腫瘍の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Vaginal cancer stage III	Vulval neoplasm		
Vaginal cancer stage IVA	Waldenstrom's macroglobulinaemia		
Vaginal cancer stage IVB	Waldenstrom's macroglobulinaemia recurrent		
Vaginal neoplasm	Waldenstrom's macroglobulinaemia refractory		
Vascular neoplasm	Waldenstrom's macroglobulinaemia stage I		
Vipoma	Waldenstrom's macroglobulinaemia stage II		
Vocal cord neoplasm	Waldenstrom's macroglobulinaemia stage III		
Vulval cancer	Waldenstrom's macroglobulinaemia stage IV		
Vulval cancer metastatic	Yolk sac tumour site unspecified		
Vulval cancer recurrent			
Vulval cancer stage 0			
Vulval cancer stage I			
Vulval cancer stage II			
Vulval cancer stage III			
Vulval cancer stage IV			

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-4　過敏症と関連する可能性のある有害事象の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Acute generalised exanthematous pustulosis	Analgesic asthma syndrome	Bromoderma	Dermatitis exfoliative
Administration site rash	Anaphylactic reaction	Bronchospasm	Dermatitis exfoliative generalised
Allergic bronchitis	Anaphylactic shock	Catheter site rash	Dermatitis herpetiformis
Allergic colitis	Anaphylactic transfusion reaction	Catheter site urticaria	Dermatitis infected
Allergic cough	Anaphylactoid reaction	Circumoral oedema	Dermatitis psoriasiform
Allergic cystitis	Anaphylactoid shock	Conjunctival oedema	Documented hypersensitivity to administered drug
Allergic granulomatous angiitis	Anaphylaxis treatment	Conjunctivitis allergic	Drug eruption
Allergic hepatitis	Angioedema	Contact stomatitis	Drug hypersensitivity
Allergic keratitis	Anti-neutrophil cytoplasmic antibody positive vasculitis	Contrast media allergy	Drug rash with eosinophilia and systemic symptoms
Allergic myocarditis	Antiallergic therapy	Contrast media reaction	Eczema
Allergic oedema	Antiendomysial antibody positive	Corneal oedema	Eczema infantile
Allergic otitis media	Application site dermatitis	Cutaneous vasculitis	Eczema nummular
Allergic pharyngitis	Application site hypersensitivity	Dapsone syndrome	Eczema vaccinatum
Allergic respiratory disease	Application site rash	Dennie-Morgan fold	Eczema vesicular
Allergic respiratory symptom	Application site urticaria	Dermatitis	Eczema weeping
Allergic sinusitis	Arthritis allergic	Dermatitis acneiform	Encephalitis allergic
Allergic transfusion reaction	Atopy	Dermatitis allergic	Encephalopathy allergic
Allergy test positive	Blepharitis allergic	Dermatitis atopic	Epidermal necrosis
Allergy to vaccine	Blood immunoglobulin E abnormal	Dermatitis bullous	Epidermolysis
Alveolitis allergic	Blood immunoglobulin E increased	Dermatitis contact	Epidermolysis bullosa

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-4　過敏症と関連する可能性のある有害事象の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Epiglottic oedema	Implant site rash	Limbal swelling	Radioallergosorbent test positive
Erythema multiforme	Implant site urticaria	Lip oedema	Rash
Erythema nodosum	Infusion site dermatitis	Lip swelling	Rash erythematous
Exfoliative rash	Infusion site hypersensitivity	Mucocutaneous rash	Rash follicular
Eye allergy	Infusion site rash	Multiple allergies	Rash generalised
Eye oedema	Infusion site urticaria	Nephritis allergic	Rash macular
Eyelid oedema	Injection site dermatitis	Nikolsky's sign	Rash maculo-papular
Face oedema	Injection site hypersensitivity	Oculomucocutaneous syndrome	Rash maculovesicular
First use syndrome	Injection site rash	Oculorespiratory syndrome	Rash morbilliform
Fixed eruption	Injection site urticaria	Oedema mouth	Rash neonatal
Giant papillary conjunctivitis	Injection site vasculitis	Oral allergy syndrome	Rash papulosquamous
Haemorrhagic urticaria	Interstitial granulomatous dermatitis	Oropharyngeal blistering	Rash pruritic
Henoch-Schonlein purpura	Iodine allergy	Oropharyngeal spasm	Rash pustular
Henoch-Schonlein purpura nephritis	Kaposi's varicelliform eruption	Oropharyngeal swelling	Rash rubelliform
Heparin-induced thrombocytopenia	Kounis syndrome	Palatal oedema	Rash scarlatiniform
Hypersensitivity	Laryngeal oedema	Palpable purpura	Rash vesicular
Immediate post-injection reaction	Laryngitis allergic	Periorbital oedema	Reaction to azo-dyes
Immune tolerance induction	Laryngospasm	Pharyngeal oedema	Reaction to colouring
Implant site dermatitis	Laryngotracheal oedema	Photosensitivity allergic reaction	Reaction to drug excipients
Implant site hypersensitivity	Leukocytoclastic vasculitis	Pruritus allergic	Reaction to preservatives

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-4　過敏症と関連する可能性のある有害事象の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Red man syndrome	Type I hypersensitivity	Vasculitic rash	
Rhinitis allergic	Type II hypersensitivity	Vulval ulceration	
Scleral oedema	Type III immune complex mediated reaction	Vulvovaginal ulceration	
Scleritis allergic	Type IV hypersensitivity reaction		
Scrotal oedema	Urticaria		
Serum sickness	Urticaria cholinergic		
Serum sickness-like reaction	Urticaria chronic		
Skin necrosis	Urticaria contact		
Skin reaction	Urticaria papular		
Skin test positive	Urticaria physical		
Small bowel angioedema	Urticaria pigmentosa		
Solar urticaria	Urticaria vesiculosa		
Solvent sensitivity	Vaccination site dermatitis		
Stevens-Johnson syndrome	Vaccination site exfoliation		
Swelling face	Vaccination site hypersensitivity		
Swollen tongue	Vaccination site rash		
Tongue oedema	Vaccination site urticaria		
Toxic epidermal necrolysis	Vaccination site vesicles		
Toxic skin eruption	Vaginal exfoliation		
Tracheal oedema	Vaginal ulceration		

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-5　湿疹の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Application site dermatitis	Eczema eyelids	Injection site eczema	
Application site eczema	Eczema herpeticum	Perivascular dermatitis	
Dermatitis	Eczema impetiginous		
Dermatitis allergic	Eczema infantile		
Dermatitis atopic	Eczema infected		
Dermatitis contact	Eczema nummular		
Dermatitis infected	Eczema vaccinatum		
Dyshidrosis	Eczema vesicular		
Eczema	Eczema weeping		
Eczema asteatotic	Injection site dermatitis		

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[a] Adverse events used in search strategy based on MedDRA Version 14.0.

表 7-6　急性膵炎の定義に使用した MedDRA 基本語

MedDRA Preferred Term[a]			
Cullen’s sign	Pancreatitis necrotising	Blood amylase abnormal	Jaundice
Hereditary pancreatitis	Pancreatitis relapsing	Blood amylase increased	Lipase abnormal
Ischaemic pancreatitis	Pancreatorenal syndrome	Blood bilirubin increased	Lipase increased
Oedematous pancreatitis	Abdominal compartment syndrome	Blood trypsin increased	Lipase urine increased
Pancreatic abscess	Abdominal distension	Fat necrosis	Nausea
Pancreatic haemorrhage	Abdominal pain	Gastrointestinal pain	Pancreatic enzyme abnormality
Pancreatic necrosis	Abdominal pain upper	Gastrointestinal sounds abnormal	Pancreatic enzymes abnormal
Pancreatic phlegmon	Abdominal rebound tenderness	Haemorrhagic ascites	Pancreatic enzymes increased
Pancreatic pseudocyst	Abdominal rigidity	Hyperamylasaemia	Peripancreatic fluid collection
Pancreatic pseudocyst drainage	Abdominal tenderness	Hyperbilirubinaemia	Urine amylase abnormal
Pancreatitis	Acute abdomen	Hyperlipasaemia	Urine amylase increased
Pancreatitis acute	Ascites	Ileus paralytic	Vomiting
Pancreatitis haemorrhagic	Bilirubin conjugated abnormal	Intra-abdominal pressure increased	Vomiting projectile

Page 1 of 1

[a] Adverse events used in search strategy based on MedDRA Version 14.0.

付録 C. 米国国立がん研究所 CTCAE – JCOG 版による臨床検査結果の重症度等級基準

表 7-7 米国国立がん研究所 有害事象共通用語規準（Version 4.0）JCOG 版

Category	Grade				
Adverse Event	0	1	2	3	4
Blood and lymphatic system disorders					
Anemia	WNL	Hemoglobin <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80 g/L	Hemoglobin <8.0 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L	Hemoglobin <6.5 g/dL; <4.0 mmol/L; <65 g/L
Leukocytosis	WNL	-	-	>100000 /mm^3	-
Investigations					
Alanine aminotransferase increased	WNL	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Alkaline phosphatase increased	WNL	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Aspartate aminotransferase increased	WNL	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Blood bilirubin increased	WNL	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Creatinine increased	WNL	>1 - 1.5 × baseline; >ULN - 1.5 × ULN	>1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	>3.0 baseline; >3.0 - 6.0 × ULN	>6.0 × ULN
GGT increased	WNL	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Hemoglobin increased	WNL	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN	-
Lymphocyte count decreased	WNL	<LLN - 800/mm^3; <LLN - 0.8 × 10e9 /L	<800 - 500/mm^3; <0.8 - 0.5 × 10e9 /L	<500 - 200/mm^3; <0.5 - 0.2 × 10e9 /L	<200/mm^3; <0.2 × 10e9 /L
Lymphocyte count increased	WNL	-	>4000/mm^3 - 20000/mm^3	>20000/mm^3	-
Neutrophil count decreased	WNL	<LLN - 1500/mm^3; <LLN - 1.5 × 10e9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 × 10e9 /L	<1000 - 500/mm^3; <1.0 - 0.5 × 10e9 /L	<500/mm^3; <0.5 × 10e9 /L
Platelet count decreased	WNL	<LLN - 75000/mm^3; <LLN - 75.0 × 10e9 /L	<75000 - 50000/mm^3; <75.0 - 50.0 × 10e9 /L	<50000 - 25000/mm^3; <50.0 - 25.0 × 10e9 /L	<25000/mm^3; <25.0 × 10e9 /L
White blood cell decreased	WNL	<LLN - 3000/mm^3; <LLN - 3.0 × 10e9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 × 10e9 /L	<2000 - 1000/mm^3; <2.0 - 1.0 × 10e9 /L	<1000/mm^3; <1.0 × 10e9 /L

Source: National Cancer Institute Common Toxicity Criteria, Version 4.0 - Japan Clinical Oncology Group
Note: WNL = within normal limits, LLN = lower limit of normal, ULN = upper limit of normal.

表 7-7　米国国立がん研究所 有害事象共通用語規準（Version 4.0）JCOG 版

Category / Adverse Event	Grade 0	1	2	3	4
Metabolism and nutrition disorders					
Hypercalcemia	WNL	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L
Hyperglycemia	WNL	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L	>500 mg/dL; >27.8 mmol/L
Hyperkalemia	WNL	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypermagnesemia	WNL	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
Hypernatremia	WNL	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypoalbuminemia	WNL	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	-
Hypocalcemia	WNL	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L
Renal and urinary disorders					
Proteinuria	WNL	1+ proteinuria; urinary protein <1.0 g/24 hrs	2+ proteinuria; urinary protein 1.0 - 3.5 g/24 hrs	urinary protein ≥3.5 g/24 hrs;	-

Source:　National Cancer Institute Common Toxicity Criteria, Version 4.0 - Japan Clinical Oncology Group
Note: WNL = within normal limits, LLN = lower limit of normal, ULN = upper limit of normal.

付録 D.　付表

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab							
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	Denosumab 60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting adverse events	49 (90.7)	50 (94.3)	47 (87.0)	48 (94.1)	446 (92.7)	448 (94.3)	229 (94.6)	495 (92.5)	593 (93.7)
INFECTIONS AND INFESTATIONS	28 (51.9)	30 (56.6)	27 (50.0)	29 (56.9)	269 (55.9)	286 (60.2)	131 (54.1)	297 (55.5)	372 (58.8)
Nasopharyngitis	21 (38.9)	18 (34.0)	22 (40.7)	22 (43.1)	203 (42.2)	211 (44.4)	93 (38.4)	224 (41.9)	273 (43.1)
Cystitis	3 (5.6)	2 (3.8)	2 (3.7)	0 (0.0)	29 (6.0)	28 (5.9)	9 (3.7)	32 (6.0)	32 (5.1)
Gastroenteritis	0 (0.0)	3 (5.7)	1 (1.9)	2 (3.9)	17 (3.5)	23 (4.8)	10 (4.1)	17 (3.2)	29 (4.6)
Pharyngitis	1 (1.9)	3 (5.7)	1 (1.9)	1 (2.0)	19 (4.0)	23 (4.8)	12 (5.0)	20 (3.7)	28 (4.4)
Oral herpes	0 (0.0)	3 (5.7)	1 (1.9)	0 (0.0)	7 (1.5)	17 (3.6)	5 (2.1)	7 (1.3)	21 (3.3)
Bronchitis	0 (0.0)	0 (0.0)	3 (5.6)	0 (0.0)	23 (4.8)	15 (3.2)	5 (2.1)	23 (4.3)	18 (2.8)
Herpes zoster	1 (1.9)	4 (7.5)	0 (0.0)	0 (0.0)	11 (2.3)	11 (2.3)	4 (1.7)	12 (2.2)	15 (2.4)
Tinea pedis	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	7 (1.5)	9 (1.9)	3 (1.2)	8 (1.5)	10 (1.6)
Rhinitis	0 (0.0)	1 (1.9)	0 (0.0)	1 (2.0)	3 (0.6)	7 (1.5)	2 (0.8)	3 (0.6)	9 (1.4)
Paronychia	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	4 (0.8)	7 (1.5)	1 (0.4)	5 (0.9)	8 (1.3)
Influenza	0 (0.0)	1 (1.9)	0 (0.0)	1 (2.0)	5 (1.0)	4 (0.8)	3 (1.2)	5 (0.9)	6 (0.9)
Onychomycosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	6 (1.3)	2 (0.8)	4 (0.7)	6 (0.9)
Tinea infection	0 (0.0)	2 (3.8)	1 (1.9)	1 (2.0)	1 (0.2)	2 (0.4)	1 (0.4)	1 (0.2)	6 (0.9)
Otitis media	2 (3.7)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.4)	4 (0.8)	3 (1.2)	4 (0.7)	5 (0.8)
Hordeolum	1 (1.9)	0 (0.0)	0 (0.0)	3 (5.9)	2 (0.4)	2 (0.4)	1 (0.4)	3 (0.6)	5 (0.8)
Otitis externa	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	5 (1.1)	2 (0.8)	3 (0.6)	5 (0.8)
Pneumonia	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.4)	4 (0.8)	4 (1.7)	3 (0.6)	5 (0.8)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab							
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	Denosumab 60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS (Cont'd)									
Gastroenteritis viral	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	6 (1.2)	3 (0.6)	2 (0.8)	7 (1.3)	4 (0.6)
Sinusitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	4 (0.8)	4 (1.7)	4 (0.7)	4 (0.6)
Pulpitis dental	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.8)	1 (0.4)	1 (0.2)	4 (0.6)
Tonsillitis	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	3 (0.5)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.4)	2 (0.4)	3 (1.2)	2 (0.4)	3 (0.5)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	3 (0.5)
Enteritis infectious	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	2 (0.4)	3 (1.2)	1 (0.2)	3 (0.5)
Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	1 (0.4)	1 (0.2)	3 (0.5)
Helicobacter infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Acute sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Herpes virus infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Atypical mycobacterial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Arthritis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Chronic sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Enterocolitis viral	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Gastroenteritis norovirus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Laryngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Parotitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab							
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	Denosumab 60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS (Cont'd)									
Pyelonephritis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Subcutaneous abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Vaginal infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Acute tonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bronchopneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Chronic tonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dacryocystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dermatitis infected	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Eczema infected	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Fungal skin infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastroenteritis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Impetigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Nail candida	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Omphalitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Osteomyelitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory moniliasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Skin infection	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab							
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	Denosumab 60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS (Cont'd)									
Urethritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Vulvitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Wound infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Adenoviral conjunctivitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Furuncle	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Herpes simplex	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)
Abscess oral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Body tinea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Eczema impetiginous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Genital herpes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Gingival abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hepatitis C	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Mumps	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Oral candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Otitis media chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Pyoderma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)

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n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab							
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	Denosumab 60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS (Cont'd)									
Sialoadenitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tooth infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Upper respiratory tract infection	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vaginitis bacterial	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Anal abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Bacterial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Eyelid folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Fungal infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Groin abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Tooth abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Vulvovaginal candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	20 (37.0)	18 (34.0)	17 (31.5)	15 (29.4)	225 (46.8)	252 (53.1)	133 (55.0)	245 (45.8)	302 (47.7)
Back pain	4 (7.4)	3 (5.7)	8 (14.8)	9 (17.6)	60 (12.5)	69 (14.5)	28 (11.6)	64 (12.0)	89 (14.1)
Osteoarthritis	3 (5.6)	0 (0.0)	2 (3.7)	2 (3.9)	43 (8.9)	77 (16.2)	37 (15.3)	46 (8.6)	81 (12.8)
Arthralgia	0 (0.0)	4 (7.5)	3 (5.6)	0 (0.0)	30 (6.2)	38 (8.0)	17 (7.0)	30 (5.6)	45 (7.1)
Spinal osteoarthritis	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	24 (5.0)	27 (5.7)	14 (5.8)	24 (4.5)	29 (4.6)
Periarthritis	6 (11.1)	1 (1.9)	1 (1.9)	1 (2.0)	26 (5.4)	23 (4.8)	17 (7.0)	32 (6.0)	26 (4.1)
Pain in extremity	4 (7.4)	2 (3.8)	1 (1.9)	2 (3.9)	25 (5.2)	21 (4.4)	12 (5.0)	29 (5.4)	26 (4.1)
Musculoskeletal pain	1 (1.9)	3 (5.7)	2 (3.7)	1 (2.0)	12 (2.5)	18 (3.8)	9 (3.7)	13 (2.4)	24 (3.8)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (3.5)	20 (4.2)	9 (3.7)	17 (3.2)	20 (3.2)
Musculoskeletal stiffness	2 (3.7)	4 (7.5)	1 (1.9)	1 (2.0)	11 (2.3)	14 (2.9)	8 (3.3)	13 (2.4)	20 (3.2)
Myalgia	2 (3.7)	1 (1.9)	1 (1.9)	0 (0.0)	22 (4.6)	17 (3.6)	9 (3.7)	24 (4.5)	19 (3.0)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)	17 (3.6)	10 (4.1)	7 (1.3)	17 (2.7)
Intervertebral disc protrusion	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.3)	2 (0.8)	1 (0.2)	11 (1.7)
Arthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.9)	9 (1.9)	6 (2.5)	9 (1.7)	9 (1.4)
Trigger finger	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	4 (0.8)	8 (1.7)	1 (0.4)	4 (0.7)	9 (1.4)
Tenosynovitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.3)	8 (1.7)	9 (3.7)	11 (2.1)	8 (1.3)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	7 (1.5)	3 (1.2)	0 (0.0)	8 (1.3)
Neck pain	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	11 (2.3)	6 (1.3)	7 (2.9)	11 (2.1)	7 (1.1)
Synovial cyst	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	7 (1.5)	3 (1.2)	6 (1.1)	7 (1.1)
Musculoskeletal chest pain	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	1 (0.4)	1 (0.2)	4 (0.6)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (Cont'd)									
Tendonitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)	2 (0.8)	3 (0.6)	3 (0.5)
Rotator cuff syndrome	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.4)	1 (0.2)	3 (0.5)
Spondylolisthesis	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	6 (1.2)	1 (0.2)	1 (0.4)	6 (1.1)	2 (0.3)
Fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	2 (0.4)	1 (0.4)	5 (0.9)	2 (0.3)
Nodal osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	2 (0.4)	2 (0.8)	4 (0.7)	2 (0.3)
Facet joint syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Myofascitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	3 (1.2)	2 (0.4)	2 (0.3)
Bursitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	2 (0.8)	1 (0.2)	2 (0.3)
Coccydynia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Temporomandibular joint syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Foot deformity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Joint swelling	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Upper extremity mass	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Intervertebral disc disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Myositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Spinal column stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Tenosynovitis stenosans	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Chondrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Ligamentitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (Cont'd)									
Limb discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Muscle atrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Muscle tightness	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Muscular weakness	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Osteonecrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Rheumatoid arthritis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
SAPHO syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Synovitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bone pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
Arthropathy	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Chondrocalcinosis pyrophosphate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Haemarthrosis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Chondropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Groin pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Myalgia intercostal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Pain in jaw	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Plantar fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Sinus tarsi syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Muscle fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (Cont'd)									
Muscle twitching	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Osteochondrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS	15 (27.8)	16 (30.2)	15 (27.8)	18 (35.3)	231 (48.0)	240 (50.5)	137 (56.6)	246 (46.0)	289 (45.7)
Dental caries	4 (7.4)	1 (1.9)	0 (0.0)	1 (2.0)	64 (13.3)	73 (15.4)	29 (12.0)	68 (12.7)	75 (11.8)
Constipation	1 (1.9)	5 (9.4)	5 (9.3)	2 (3.9)	37 (7.7)	49 (10.3)	21 (8.7)	38 (7.1)	61 (9.6)
Periodontitis	1 (1.9)	0 (0.0)	2 (3.7)	3 (5.9)	27 (5.6)	41 (8.6)	16 (6.6)	28 (5.2)	46 (7.3)
Stomatitis	1 (1.9)	1 (1.9)	2 (3.7)	1 (2.0)	24 (5.0)	35 (7.4)	7 (2.9)	25 (4.7)	39 (6.2)
Diarrhoea	4 (7.4)	3 (5.7)	2 (3.7)	3 (5.9)	15 (3.1)	23 (4.8)	16 (6.6)	19 (3.6)	31 (4.9)
Gastritis	0 (0.0)	1 (1.9)	3 (5.6)	0 (0.0)	26 (5.4)	20 (4.2)	13 (5.4)	26 (4.9)	24 (3.8)
Abdominal discomfort	3 (5.6)	3 (5.7)	0 (0.0)	1 (2.0)	15 (3.1)	20 (4.2)	10 (4.1)	18 (3.4)	24 (3.8)
Reflux oesophagitis	1 (1.9)	0 (0.0)	0 (0.0)	2 (3.9)	11 (2.3)	17 (3.6)	7 (2.9)	12 (2.2)	19 (3.0)
Abdominal pain upper	0 (0.0)	2 (3.8)	2 (3.7)	1 (2.0)	7 (1.5)	12 (2.5)	8 (3.3)	7 (1.3)	17 (2.7)
Gingivitis	1 (1.9)	1 (1.9)	3 (5.6)	1 (2.0)	11 (2.3)	11 (2.3)	7 (2.9)	12 (2.2)	16 (2.5)
Periodontal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	18 (3.7)	9 (1.9)	7 (2.9)	18 (3.4)	9 (1.4)
Haemorrhoids	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	13 (2.7)	8 (1.7)	1 (0.4)	14 (2.6)	9 (1.4)
Vomiting	1 (1.9)	3 (5.7)	0 (0.0)	0 (0.0)	9 (1.9)	6 (1.3)	7 (2.9)	10 (1.9)	9 (1.4)
Enterocolitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	9 (1.9)	4 (1.7)	5 (0.9)	9 (1.4)
Colonic polyp	0 (0.0)	2 (3.8)	1 (1.9)	0 (0.0)	14 (2.9)	5 (1.1)	2 (0.8)	14 (2.6)	8 (1.3)
Cheilitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.7)	8 (1.7)	6 (2.5)	8 (1.5)	8 (1.3)
Nausea	0 (0.0)	1 (1.9)	1 (1.9)	2 (3.9)	7 (1.5)	3 (0.6)	5 (2.1)	7 (1.3)	7 (1.1)
Toothache	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	5 (1.0)	6 (1.3)	2 (0.8)	5 (0.9)	7 (1.1)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	5 (1.1)	2 (0.8)	4 (0.7)	5 (0.8)

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Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS (Cont'd)									
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	3 (0.6)	4 (0.8)	1 (0.4)	3 (0.6)	5 (0.8)
Gastric polyps	2 (3.7)	0 (0.0)	1 (1.9)	0 (0.0)	3 (0.6)	3 (0.6)	0 (0.0)	5 (0.9)	4 (0.6)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	4 (0.8)	2 (0.8)	2 (0.4)	4 (0.6)
Glossitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	3 (0.6)	2 (0.4)	1 (0.4)	3 (0.6)	3 (0.5)
Gastritis erosive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	1 (0.4)	1 (0.2)	3 (0.5)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	1 (0.4)	2 (0.4)	2 (0.3)
Duodenal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.4)	1 (0.2)	2 (0.3)
Hiatus hernia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)
Tooth loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	2 (0.8)	1 (0.2)	2 (0.3)
Colitis ischaemic	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Anal fissure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.2)	1 (0.4)	4 (0.7)	1 (0.2)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Aphthous stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.8)	1 (0.2)	1 (0.2)
Colitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Diverticulum intestinal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.8)	1 (0.2)	1 (0.2)
Dry mouth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Gingival atrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Gingival bleeding	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Gingival swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)

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n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS (Cont'd)									
Radicular cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Abdominal hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Anal polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Chapped lips	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Dental necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Duodenitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dyschezia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Femoral hernia, obstructive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Food poisoning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal mucosal exfoliation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Glossodynia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hypoaesthesia oral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Large intestine perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Malocclusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Oesophageal polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Oral disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Oral lichen planus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172 Placebo (N=54) n (%)	Study 20050172 Denosumab 14 mg Q6M (N=53) n (%)	Study 20050172 Denosumab 60 mg Q6M (N=54) n (%)	Study 20050172 Denosumab 100 mg Q6M (N=51) n (%)	Study AMG162-A-J301 Placebo (N=481) n (%)	Study AMG162-A-J301 Denosumab 60 mg Q6M (N=475) n (%)	Study AMG162-A-J301 Alendronate [a] (N=242) n (%)	Overall Placebo (N=535) n (%)	Overall Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS (Cont'd)									
Pancreatic cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Paraesthesia oral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Salivary gland calculus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Traumatic occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	4 (1.7)	4 (0.7)	0 (0.0)
Loose tooth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	3 (1.2)	4 (0.7)	0 (0.0)
Sensitivity of teeth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Rectal prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Enamel anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Epigastric discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	3 (1.2)	1 (0.2)	0 (0.0)
Gastritis atrophic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Gingival pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Haematochezia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Hyperchlorhydria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lip swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Parotid gland enlargement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS (Cont'd)									
Proctalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Duodenal polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis haemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gingival recession	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Oedema mouth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Oesophageal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Periproctitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Swollen tongue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	15 (27.8)	8 (15.1)	9 (16.7)	11 (21.6)	166 (34.5)	156 (32.8)	92 (38.0)	181 (33.8)	184 (29.1)
Contusion	8 (14.8)	1 (1.9)	4 (7.4)	1 (2.0)	74 (15.4)	80 (16.8)	54 (22.3)	82 (15.3)	86 (13.6)
Joint sprain	2 (3.7)	1 (1.9)	1 (1.9)	5 (9.8)	18 (3.7)	17 (3.6)	9 (3.7)	20 (3.7)	24 (3.8)
Arthropod sting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (3.5)	19 (4.0)	4 (1.7)	17 (3.2)	19 (3.0)
Tooth fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	13 (2.7)	12 (2.5)	8 (3.3)	13 (2.4)	13 (2.1)
Thermal burn	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	3 (0.6)	11 (2.3)	2 (0.8)	3 (0.6)	13 (2.1)
Epicondylitis	1 (1.9)	0 (0.0)	0 (0.0)	2 (3.9)	9 (1.9)	6 (1.3)	2 (0.8)	10 (1.9)	8 (1.3)
Foot fracture	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	7 (1.5)	6 (1.3)	2 (0.8)	7 (1.3)	7 (1.1)
Chillblains	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	6 (1.3)	1 (0.4)	1 (0.2)	6 (0.9)
Spinal fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (4.6)	5 (1.1)	6 (2.5)	22 (4.1)	5 (0.8)
Wound	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	7 (1.5)	4 (0.8)	5 (2.1)	7 (1.3)	5 (0.8)
Muscle strain	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	6 (1.2)	4 (0.8)	1 (0.4)	6 (1.1)	5 (0.8)
Radius fracture	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	5 (1.1)	3 (1.2)	6 (1.1)	5 (0.8)
Patella fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)	1 (0.4)	0 (0.0)	5 (0.8)
Rib fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.7)	4 (0.8)	1 (0.4)	8 (1.5)	4 (0.6)
Excoriation	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)	4 (0.8)	3 (0.6)	1 (0.4)	5 (0.9)	4 (0.6)
Ulna fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	3 (0.6)	0 (0.0)	4 (0.7)	3 (0.5)
Arthropod bite	2 (3.7)	1 (1.9)	1 (1.9)	1 (2.0)	1 (0.2)	0 (0.0)	1 (0.4)	3 (0.6)	3 (0.5)
Muscle injury	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	3 (0.6)	1 (0.2)	2 (0.8)	3 (0.6)	3 (0.5)
Head injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)	1 (0.4)	2 (0.4)	3 (0.5)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (Cont'd)									
Meniscus lesion	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (0.4)	2 (0.4)	1 (0.4)	2 (0.4)	3 (0.5)
Ankle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.5)
Procedural pain	0 (0.0)	2 (3.8)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
Animal bite	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)	4 (0.7)	2 (0.3)
Skeletal injury	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	4 (0.7)	2 (0.3)
Foreign body in eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Joint dislocation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Hand fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Stab wound	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.4)	1 (0.2)	2 (0.3)
Frostbite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Heat illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Traumatic haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Laceration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	2 (0.8)	3 (0.6)	1 (0.2)
Cartilage injury	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Crush injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Fibula fracture	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Humerus fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.8)	1 (0.2)	1 (0.2)
Subcutaneous haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172 Placebo (N=54) n (%)	Study 20050172 Denosumab 14 mg Q6M (N=53) n (%)	Study 20050172 Denosumab 60 mg Q6M (N=54) n (%)	Study 20050172 Denosumab 100 mg Q6M (N=51) n (%)	Study AMG162-A-J301 Placebo (N=481) n (%)	Study AMG162-A-J301 Denosumab 60 mg Q6M (N=475) n (%)	Study AMG162-A-J301 Alendronate [a] (N=242) n (%)	Overall Placebo (N=535) n (%)	Overall Denosumab (N=633) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (Cont'd)									
Subdural haematoma	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Tooth injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Burns second degree	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Fractured coccyx	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Nail avulsion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Femoral neck fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Fractured sacrum	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Cerebral haemorrhage traumatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Corneal abrasion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Foreign body	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Fractured ischium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Heat exhaustion	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ligament injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ligament sprain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Nail injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Periorbital haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pubis fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (Cont'd)									
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Scapula fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tendon rupture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Wound complication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Eye injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Face injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Muscle rupture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Peripheral nerve injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11 (20.4)	12 (22.6)	11 (20.4)	14 (27.5)	122 (25.4)	129 (27.2)	60 (24.8)	133 (24.9)	166 (26.2)
Eczema	5 (9.3)	6 (11.3)	4 (7.4)	6 (11.8)	41 (8.5)	39 (8.2)	16 (6.6)	46 (8.6)	55 (8.7)
Dermatitis contact	1 (1.9)	1 (1.9)	0 (0.0)	1 (2.0)	28 (5.8)	21 (4.4)	14 (5.8)	29 (5.4)	23 (3.6)
Pruritus	0 (0.0)	0 (0.0)	1 (1.9)	3 (5.9)	8 (1.7)	10 (2.1)	4 (1.7)	8 (1.5)	14 (2.2)
Dermatitis	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	8 (1.7)	10 (2.1)	3 (1.2)	9 (1.7)	11 (1.7)
Haemorrhage subcutaneous	2 (3.7)	1 (1.9)	0 (0.0)	1 (2.0)	3 (0.6)	9 (1.9)	1 (0.4)	5 (0.9)	11 (1.7)
Rash	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.9)	9 (1.9)	2 (0.8)	10 (1.9)	9 (1.4)
Heat rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	8 (1.7)	1 (0.4)	2 (0.4)	8 (1.3)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.2)	7 (1.5)	3 (1.2)	6 (1.1)	7 (1.1)
Erythema	1 (1.9)	1 (1.9)	1 (1.9)	1 (2.0)	4 (0.8)	4 (0.8)	2 (0.8)	5 (0.9)	7 (1.1)
Eczema asteatotic	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	4 (0.8)	5 (1.1)	0 (0.0)	4 (0.7)	7 (1.1)
Xeroderma	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	6 (1.3)	5 (2.1)	1 (0.2)	7 (1.1)
Hyperkeratosis	0 (0.0)	1 (1.9)	1 (1.9)	0 (0.0)	9 (1.9)	4 (0.8)	8 (3.3)	9 (1.7)	6 (0.9)
Seborrhoeic dermatitis	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	4 (0.8)	1 (0.4)	1 (0.2)	5 (0.8)
Dry skin	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	4 (0.6)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)	2 (0.8)	2 (0.4)	3 (0.5)
Ingrowing nail	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	3 (0.5)
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	2 (0.8)	1 (0.2)	3 (0.5)
Asteatosis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	3 (1.2)	2 (0.4)	2 (0.3)
Blister	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	1 (0.4)	2 (0.4)	2 (0.3)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172 Placebo (N=54) n (%)	Study 20050172 Denosumab 14 mg Q6M (N=53) n (%)	Study 20050172 Denosumab 60 mg Q6M (N=54) n (%)	Study 20050172 Denosumab 100 mg Q6M (N=51) n (%)	Study AMG162-A-J301 Placebo (N=481) n (%)	Study AMG162-A-J301 Denosumab 60 mg Q6M (N=475) n (%)	Study AMG162-A-J301 Alendronate [a] (N=242) n (%)	Overall Placebo (N=535) n (%)	Overall Denosumab (N=633) n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS (Cont'd)									
Dyshidrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Polymorphic light eruption	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Pruritus generalised	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Skin exfoliation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Decubitus ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Dermal cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Lentigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Alopecia areata	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Eczema nummular	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Keloid scar	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Milia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Papule	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Petechiae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Prurigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Purpura	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Pustular psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Skin haemorrhage	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Skin tightness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Stasis dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS (Cont'd)									
Acne	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Hyperkeratosis palmaris and plantaris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Senile pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Hypoaesthesia facial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Nail disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pemphigoid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Photosensitivity reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin chapped	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Urticaria chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Dandruff	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Nail discolouration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Onychoclasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pigmentation disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NERVOUS SYSTEM DISORDERS	11 (20.4)	12 (22.6)	11 (20.4)	10 (19.6)	72 (15.0)	101 (21.3)	35 (14.5)	83 (15.5)	134 (21.2)
Headache	5 (9.3)	7 (13.2)	6 (11.1)	3 (5.9)	19 (4.0)	23 (4.8)	6 (2.5)	24 (4.5)	39 (6.2)
Hypoaesthesia	3 (5.6)	1 (1.9)	2 (3.7)	5 (9.8)	10 (2.1)	10 (2.1)	3 (1.2)	13 (2.4)	18 (2.8)
Dizziness	2 (3.7)	1 (1.9)	1 (1.9)	1 (2.0)	6 (1.2)	15 (3.2)	5 (2.1)	8 (1.5)	18 (2.8)
Sciatica	1 (1.9)	0 (0.0)	0 (0.0)	2 (3.9)	9 (1.9)	13 (2.7)	6 (2.5)	10 (1.9)	15 (2.4)
Carpal tunnel syndrome	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	3 (0.6)	6 (1.3)	0 (0.0)	3 (0.6)	7 (1.1)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	6 (1.3)	0 (0.0)	1 (0.2)	7 (1.1)
Cervicobrachial syndrome	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	2 (0.4)	4 (0.8)	2 (0.8)	2 (0.4)	6 (0.9)
Tension headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	5 (1.1)	1 (0.4)	2 (0.4)	5 (0.8)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	4 (0.8)	0 (0.0)	2 (0.4)	4 (0.6)
Neuropathy peripheral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	1 (0.4)	3 (0.6)	3 (0.5)
Somnolence	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.4)	2 (0.4)	3 (0.5)
Cervical neuritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	2 (0.8)	1 (0.2)	3 (0.5)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	3 (0.5)
Neuralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.5)
Occipital neuralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.5)
Intercostal neuralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.4)	1 (0.4)	3 (0.6)	2 (0.3)
Autonomic nervous system imbalance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Dizziness postural	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	2 (0.3)
Tremor	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NERVOUS SYSTEM DISORDERS (Cont'd)									
Intracranial aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Lacunar infarction	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Loss of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	3 (0.6)	1 (0.2)
Nystagmus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Post herpetic neuralgia	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Sensory disturbance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Cerebellar haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cerebral artery embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cerebral ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cubital tunnel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dementia Alzheimer's type	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Dyslalia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Morton's neuralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Nervous system disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Tarsal tunnel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
VIIth nerve paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	1 (0.4)	3 (0.6)	0 (0.0)
Trigeminal neuralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Altered state of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NERVOUS SYSTEM DISORDERS (Cont'd)									
Amnesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Diabetic neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dysaesthesia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Essential tremor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Facial spasm	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Intention tremor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Central pain syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Migraine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Parkinson's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Parkinsonism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Thoracic outlet syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	10 (18.5)	11 (20.8)	7 (13.0)	9 (17.6)	69 (14.3)	83 (17.5)	36 (14.9)	79 (14.8)	110 (17.4)
Upper respiratory tract inflammation	8 (14.8)	4 (7.5)	3 (5.6)	6 (11.8)	35 (7.3)	31 (6.5)	19 (7.9)	43 (8.0)	44 (7.0)
Oropharyngeal pain	1 (1.9)	3 (5.7)	1 (1.9)	1 (2.0)	7 (1.5)	6 (1.3)	1 (0.4)	8 (1.5)	11 (1.7)
Cough	0 (0.0)	2 (3.8)	0 (0.0)	2 (3.9)	3 (0.6)	7 (1.5)	2 (0.8)	3 (0.6)	11 (1.7)
Rhinitis allergic	0 (0.0)	1 (1.9)	1 (1.9)	0 (0.0)	7 (1.5)	8 (1.7)	3 (1.2)	7 (1.3)	10 (1.6)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.2)	10 (2.1)	0 (0.0)	6 (1.1)	10 (1.6)
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.4)	4 (0.8)	2 (0.8)	2 (0.4)	5 (0.8)
Oropharyngeal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)	1 (0.4)	2 (0.4)	3 (0.5)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	3 (0.5)
Productive cough	0 (0.0)	1 (1.9)	1 (1.9)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.5)
Epistaxis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.8)	0 (0.0)	3 (0.5)
Interstitial lung disease	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Bronchitis chronic	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.4)	3 (0.6)	1 (0.2)
Allergic bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Haemoptysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Pleurisy	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Pharyngeal oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Bronchiectasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dysaesthesia pharynx	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Dysphonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	4 (1.7)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (Cont'd)									
Emphysema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Foreign body aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Nasal congestion	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pharyngeal polyp	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pneumonia aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Sleep apnoea syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Paranasal cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sputum retention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vocal cord inflammation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Yawning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Vasomotor rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INVESTIGATIONS	1 (1.9)	4 (7.5)	4 (7.4)	7 (13.7)	86 (17.9)	89 (18.7)	46 (19.0)	87 (16.3)	104 (16.4)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	22 (4.6)	28 (5.9)	15 (6.2)	22 (4.1)	29 (4.6)
Blood pressure increased	0 (0.0)	2 (3.8)	0 (0.0)	1 (2.0)	14 (2.9)	13 (2.7)	6 (2.5)	14 (2.6)	16 (2.5)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	2 (3.7)	3 (5.9)	11 (2.3)	11 (2.3)	4 (1.7)	11 (2.1)	16 (2.5)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	0 (0.0)	6 (1.3)	2 (0.8)	0 (0.0)	8 (1.3)
Protein urine present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.7)	1 (0.4)	0 (0.0)	8 (1.3)
Aspartate aminotransferase increased	0 (0.0)	1 (1.9)	1 (1.9)	1 (2.0)	1 (0.2)	4 (0.8)	3 (1.2)	1 (0.2)	7 (1.1)
Blood creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	6 (1.3)	0 (0.0)	1 (0.2)	6 (0.9)
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)	4 (0.8)	0 (0.0)	7 (1.3)	4 (0.6)
Blood potassium increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	4 (0.8)	3 (1.2)	2 (0.4)	4 (0.6)
Blood glucose increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.2)	3 (0.6)	2 (0.8)	6 (1.1)	3 (0.5)
Weight increased	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	3 (0.5)
White blood cell count decreased	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	1 (0.2)	1 (0.2)	3 (1.2)	1 (0.2)	3 (0.5)
Blood bilirubin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.4)	2 (0.8)	3 (0.6)	2 (0.3)
White blood cell count increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	2 (0.3)
Liver function test abnormal	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.8)	1 (0.2)	2 (0.3)
Blood alkaline phosphatase decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Blood urea increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	9 (1.9)	0 (0.0)	2 (0.8)	9 (1.7)	1 (0.2)

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a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INVESTIGATIONS (Cont'd)									
Eosinophil count increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.2)	0 (0.0)	4 (0.7)	1 (0.2)
Blood urine present	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)
Blood pressure decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Glucose urine present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Heart rate increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Helicobacter test positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Blood 25-hydroxycholecalciferol increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood calcium decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.8)	0 (0.0)	1 (0.2)
Blood pressure diastolic increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood sodium decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood thyroid stimulating hormone increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Blood triglycerides increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
C-reactive protein increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac murmur	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Heart rate decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatitis C antibody positive	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Immunoglobulins increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Protein urine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood insulin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INVESTIGATIONS (Cont'd)									
Blood pressure systolic increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Body temperature decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Foetal haemoglobin increased	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Glycosylated haemoglobin increased	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Low density lipoprotein increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.8)	1 (0.2)	0 (0.0)
Renal function test abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Thyroxine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tri-iodothyronine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Urine output decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Brain natriuretic peptide increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Fibrin D dimer increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Neutrophil count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Occult blood positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Protein total increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
EYE DISORDERS	9 (16.7)	6 (11.3)	4 (7.4)	7 (13.7)	68 (14.1)	82 (17.3)	42 (17.4)	77 (14.4)	99 (15.6)
Cataract	1 (1.9)	3 (5.7)	0 (0.0)	1 (2.0)	27 (5.6)	25 (5.3)	14 (5.8)	28 (5.2)	29 (4.6)
Conjunctivitis	1 (1.9)	0 (0.0)	1 (1.9)	2 (3.9)	13 (2.7)	17 (3.6)	7 (2.9)	14 (2.6)	20 (3.2)
Dry eye	2 (3.7)	0 (0.0)	0 (0.0)	2 (3.9)	7 (1.5)	9 (1.9)	1 (0.4)	9 (1.7)	11 (1.7)
Asthenopia	2 (3.7)	1 (1.9)	0 (0.0)	1 (2.0)	4 (0.8)	7 (1.5)	2 (0.8)	6 (1.1)	9 (1.4)
Conjunctivitis allergic	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	11 (2.3)	5 (1.1)	6 (2.5)	12 (2.2)	6 (0.9)
Conjunctival haemorrhage	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	4 (0.8)	5 (1.1)	2 (0.8)	4 (0.7)	6 (0.9)
Vitreous floaters	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	4 (0.8)	0 (0.0)	2 (0.4)	5 (0.8)
Posterior capsule opacification	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.4)	0 (0.0)	4 (0.6)
Pterygium	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	4 (0.6)
Glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	1 (0.4)	3 (0.6)	3 (0.5)
Ocular hyperaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	0 (0.0)	3 (0.6)	3 (0.5)
Corneal erosion	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	3 (0.5)
Keratitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.5)
Blepharitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	2 (0.8)	2 (0.4)	2 (0.3)
Eye pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)
Trichiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Vitreous detachment	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	1 (0.2)	2 (0.3)
Angle closure glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Corneal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
EYE DISORDERS (Cont'd)									
Punctate keratitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Lacrimation increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Maculopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Eyelid oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Normal tension glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Xerophthalmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Arteriosclerotic retinopathy	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Blepharal pigmentation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blepharitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Conjunctival deposit	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Dacryostenosis acquired	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Eye pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Keratoconjunctivitis sicca	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Narrow anterior chamber angle	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pingueculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Scleral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Retinal tear	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Conjunctival hyperaemia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Eczema eyelids	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
EYE DISORDERS (Cont'd)									
Episcleritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Eye discharge	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Eye inflammation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lacrimation decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Macular degeneration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Retinal aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Retinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Scleritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Uveitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Vision blurred	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Conjunctivochalasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Eyelid ptosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Optic nerve disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Retinal detachment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Retinal vein occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (18.5)	5 (9.4)	6 (11.1)	7 (13.7)	56 (11.6)	47 (9.9)	28 (11.6)	66 (12.3)	65 (10.3)
Device breakage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.9)	13 (2.7)	9 (3.7)	9 (1.7)	13 (2.1)
Oedema peripheral	1 (1.9)	0 (0.0)	2 (3.7)	2 (3.9)	2 (0.4)	9 (1.9)	3 (1.2)	3 (0.6)	13 (2.1)
Malaise	5 (9.3)	2 (3.8)	1 (1.9)	2 (3.9)	5 (1.0)	6 (1.3)	1 (0.4)	10 (1.9)	11 (1.7)
Chest pain	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	11 (2.3)	5 (1.1)	6 (2.5)	12 (2.2)	6 (0.9)
Pyrexia	1 (1.9)	0 (0.0)	1 (1.9)	1 (2.0)	4 (0.8)	3 (0.6)	1 (0.4)	5 (0.9)	5 (0.8)
Fatigue	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	7 (1.5)	3 (0.6)	0 (0.0)	8 (1.5)	4 (0.6)
Feeling abnormal	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	3 (1.2)	4 (0.7)	3 (0.5)
Oedema	0 (0.0)	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.5)
Face oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	4 (0.8)	1 (0.2)	0 (0.0)	4 (0.7)	2 (0.3)
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Thirst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	2 (0.8)	3 (0.6)	1 (0.2)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Injection site pain	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.2)
Device dislocation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Device failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site haemorrhage	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Patient-device incompatibility	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Sensation of foreign body	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (Cont'd)									
Application site eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Generalised oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Inflammation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Injection site erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Injection site haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Local swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gait disturbance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
VASCULAR DISORDERS	2 (3.7)	5 (9.4)	4 (7.4)	1 (2.0)	49 (10.2)	51 (10.7)	14 (5.8)	51 (9.5)	61 (9.6)
Hypertension	1 (1.9)	2 (3.8)	3 (5.6)	1 (2.0)	36 (7.5)	39 (8.2)	11 (4.5)	37 (6.9)	45 (7.1)
Varicose vein	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	2 (0.8)	1 (0.2)	4 (0.6)
Peripheral coldness	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	4 (0.6)
Haematoma	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	3 (0.5)
Hot flush	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.2)	0 (0.0)	5 (0.9)	1 (0.2)
Hypotension	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Aortic aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Arteriosclerosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Peripheral circulatory failure	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Phlebitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Renovascular hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Vascular stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.8)	2 (0.4)	0 (0.0)
Peripheral vascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Arteriosclerosis obliterans	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Circulatory collapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Peripheral arterial occlusive disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
VASCULAR DISORDERS (Cont'd)									
Varicophlebitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Venous thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	2 (3.7)	1 (1.9)	2 (3.7)	2 (3.9)	35 (7.3)	49 (10.3)	17 (7.0)	37 (6.9)	54 (8.5)
Hyperlipidaemia	2 (3.7)	0 (0.0)	1 (1.9)	1 (2.0)	15 (3.1)	18 (3.8)	5 (2.1)	17 (3.2)	20 (3.2)
Decreased appetite	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	3 (0.6)	10 (2.1)	1 (0.4)	3 (0.6)	11 (1.7)
Hypercholesterolaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	4 (0.8)	5 (1.1)	1 (0.4)	4 (0.7)	6 (0.9)
Dyslipidaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	6 (1.3)	1 (0.4)	2 (0.4)	6 (0.9)
Diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	5 (1.1)	5 (2.1)	4 (0.7)	5 (0.8)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	3 (0.6)	1 (0.4)	5 (0.9)	3 (0.5)
Hypocalcaemia	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Glucose tolerance impaired	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Gout	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Periarthritis calcarea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Type 2 diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hyperuricaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Hypertriglyceridaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
PSYCHIATRIC DISORDERS	2 (3.7)	3 (5.7)	2 (3.7)	0 (0.0)	29 (6.0)	37 (7.8)	21 (8.7)	31 (5.8)	42 (6.6)
Insomnia	2 (3.7)	2 (3.8)	2 (3.7)	0 (0.0)	21 (4.4)	26 (5.5)	18 (7.4)	23 (4.3)	30 (4.7)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	3 (0.6)	0 (0.0)	4 (0.7)	3 (0.5)
Anxiety disorder	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	3 (0.6)	2 (0.3)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Delirium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Depressed mood	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Restlessness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Sleep disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Adjustment disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bruxism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dysthymic disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Initial insomnia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dissociative disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Neurosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hallucination, auditory	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
EAR AND LABYRINTH DISORDERS	1 (1.9)	3 (5.7)	1 (1.9)	1 (2.0)	30 (6.2)	35 (7.4)	17 (7.0)	31 (5.8)	40 (6.3)
Vertigo	1 (1.9)	1 (1.9)	1 (1.9)	1 (2.0)	16 (3.3)	12 (2.5)	9 (3.7)	17 (3.2)	15 (2.4)
Tinnitus	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.4)	10 (2.1)	1 (0.4)	2 (0.4)	11 (1.7)
Vertigo positional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.2)	5 (1.1)	4 (1.7)	6 (1.1)	5 (0.8)
Sudden hearing loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)	0 (0.0)	2 (0.4)	3 (0.5)
Deafness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Eustachian tube patulous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Meniere's disease	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	2 (0.3)
Deafness neurosensory	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Ear pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Eustachian tube stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Deafness unilateral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Inner ear disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Auricular swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vestibular disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
CARDIAC DISORDERS	1 (1.9)	1 (1.9)	3 (5.6)	3 (5.9)	16 (3.3)	20 (4.2)	7 (2.9)	17 (3.2)	27 (4.3)
Palpitations	0 (0.0)	0 (0.0)	3 (5.6)	1 (2.0)	4 (0.8)	6 (1.3)	1 (0.4)	4 (0.7)	10 (1.6)
Arrhythmia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.8)	0 (0.0)	2 (0.4)	4 (0.6)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	2 (0.8)	2 (0.4)	2 (0.3)
Supraventricular extrasystoles	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Aortic valve incompetence	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Atrioventricular block complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Mitral valve incompetence	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.8)	1 (0.2)	1 (0.2)
Arrhythmia supraventricular	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Atrioventricular block	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hypertensive heart disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Prinzmetal angina	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Tricuspid valve incompetence	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Sick sinus syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
CARDIAC DISORDERS (Cont'd)									
Atrioventricular block second degree	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypertensive cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Left ventricular hypertrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
RENAL AND URINARY DISORDERS	2 (3.7)	1 (1.9)	1 (1.9)	1 (2.0)	22 (4.6)	23 (4.8)	7 (2.9)	24 (4.5)	26 (4.1)
Hypertonic bladder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (2.1)	6 (1.3)	1 (0.4)	10 (1.9)	6 (0.9)
Pollakiuria	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.4)	4 (0.8)	0 (0.0)	2 (0.4)	5 (0.8)
Cystitis noninfective	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Haematuria	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Neurogenic bladder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Nephrolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Renal cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Dysuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Mixed incontinence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Urethral disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Urinary retention	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Nocturia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.8)	3 (0.6)	0 (0.0)
Calculus ureteric	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cystitis haemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hydronephrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Proteinuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Renal failure chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
RENAL AND URINARY DISORDERS (Cont'd)									
Cystitis-like symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Stress urinary incontinence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (1.9)	0 (0.0)	2 (3.7)	0 (0.0)	26 (5.4)	14 (2.9)	3 (1.2)	27 (5.0)	16 (2.5)
Breast cancer	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)	3 (0.6)	3 (0.5)
Seborrhoeic keratosis	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	3 (0.5)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Metastases to lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Ovarian neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Gastric cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Skin papilloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Benign gastric neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Colon adenoma	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Acrochordon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bile duct cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to liver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Lipoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	4 (0.7)	0 (0.0)
Metastases to lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Insulinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Large intestine carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Meningioma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) (Cont'd)									
Neurilemmoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Neurofibroma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Oral fibroma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Paget's disease of the breast	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pseudolymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tongue neoplasm benign	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Haemangioblastoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
HEPATOBILIARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (4.0)	12 (2.5)	3 (1.2)	19 (3.6)	12 (1.9)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	8 (1.7)	2 (0.8)	5 (0.9)	8 (1.3)
Hepatic cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Gallbladder polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Liver disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Alcoholic liver disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Cholangitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Hepatic steatosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)
Jaundice	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Cholestasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chronic hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Biliary cirrhosis primary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (3.7)	1 (1.9)	0 (0.0)	1 (2.0)	10 (2.1)	9 (1.9)	3 (1.2)	12 (2.2)	11 (1.7)
Anaemia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	4 (0.8)	1 (0.4)	6 (1.1)	4 (0.6)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	2 (0.8)	2 (0.4)	1 (0.2)
Haemorrhagic anaemia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Lymphadenopathy	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Thrombocytopenia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Anaemia vitamin B12 deficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bone marrow failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pancytopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Lymphadenitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Leukopenia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
IMMUNE SYSTEM DISORDERS	3 (5.6)	0 (0.0)	0 (0.0)	3 (5.9)	7 (1.5)	4 (0.8)	3 (1.2)	10 (1.9)	7 (1.1)
Seasonal allergy	3 (5.6)	0 (0.0)	0 (0.0)	1 (2.0)	5 (1.0)	4 (0.8)	2 (0.8)	8 (1.5)	5 (0.8)
Food allergy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Drug hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sarcoidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	9 (1.9)	5 (1.1)	6 (2.5)	9 (1.7)	7 (1.1)
Benign prostatic hyperplasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Atrophic vulvovaginitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	3 (0.6)	1 (0.2)
Breast mass	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Genital haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Uterine polyp	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)
Cystocele	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Genital discharge	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gynaecomastia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pelvic prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vulvovaginal pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Breast disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pelvic pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Vaginal relaxation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-8　有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
ENDOCRINE DISORDERS	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	5 (1.0)	5 (1.1)	1 (0.4)	5 (0.9)	6 (0.9)
Goitre	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Hyperthyroidism	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)
Basedow's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Autoimmune thyroiditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Thyroid mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Thyroiditis chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
SURGICAL AND MEDICAL PROCEDURES	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	4 (0.6)
Cataract operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Varicose vein operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Tooth extraction	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Porokeratosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Accessory spleen	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.1

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting investigational product-related adverse events	9 (16.7)	7 (13.2)	5 (9.3)	9 (17.6)	81 (16.8)	97 (20.4)	55 (22.7)	90 (16.8)	118 (18.6)
INVESTIGATIONS	0 (0.0)	0 (0.0)	1 (1.9)	3 (5.9)	14 (2.9)	27 (5.7)	8 (3.3)	14 (2.6)	31 (4.9)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	1 (1.9)	2 (3.9)	2 (0.4)	6 (1.3)	1 (0.4)	2 (0.4)	9 (1.4)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	4 (0.6)
Protein urine present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	4 (0.6)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.5)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	2 (0.8)	1 (0.2)	2 (0.3)
Blood potassium increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Blood bilirubin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Blood creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
White blood cell count decreased	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Blood glucose increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Blood pressure increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Blood alkaline phosphatase decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood calcium decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INVESTIGATIONS (Cont'd)									
Blood sodium decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood urea increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Cardiac murmur	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Eosinophil count increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Immunoglobulins increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Protein urine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood insulin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Blood urine present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Helicobacter test positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Renal function test abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
White blood cell count increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Liver function test abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS	1 (1.9)	2 (3.8)	0 (0.0)	0 (0.0)	16 (3.3)	20 (4.2)	26 (10.7)	17 (3.2)	22 (3.5)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	4 (0.8)	3 (1.2)	4 (0.7)	4 (0.6)
Colonic polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)	3 (0.6)	2 (0.3)
Dental caries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)	3 (0.6)	2 (0.3)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	2 (0.8)	1 (0.2)	2 (0.3)
Colitis ischaemic	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Periodontitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.8)	1 (0.2)	1 (0.2)
Glossitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (1.2)	0 (0.0)	1 (0.2)
Dental necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Duodenitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastric polyps	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Reflux oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.8)	0 (0.0)	1 (0.2)
Periodontal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS (Cont'd)									
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Haemorrhoids	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Parotid gland enlargement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sensitivity of teeth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Abdominal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Cheilitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Duodenal polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Duodenal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Enterocolitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Epigastric discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis erosive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis haemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Loose tooth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS (Cont'd)									
Oedema mouth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Oesophageal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS	1 (1.9)	1 (1.9)	0 (0.0)	1 (2.0)	14 (2.9)	13 (2.7)	4 (1.7)	15 (2.8)	15 (2.4)
Oral herpes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.4)	1 (0.2)
Parotitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Sinusitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Acute sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Atypical mycobacterial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastroenteritis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Osteomyelitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Otitis media	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Tinea infection	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)
Body tinea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS (Cont'd)									
Chronic sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Eczema impetiginous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Furuncle	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gingival abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Herpes simplex	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tinea pedis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tooth abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.7)	15 (3.2)	10 (4.1)	14 (2.6)	15 (2.4)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	4 (0.8)	1 (0.4)	3 (0.6)	4 (0.6)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	4 (1.7)	1 (0.2)	3 (0.5)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.4)	0 (0.0)	3 (0.5)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Pain in extremity	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Musculoskeletal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Osteonecrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Rotator cuff syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
SAPHO syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Spinal osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Neck pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Arthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chondrocalcinosis pyrophosphate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Periarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (Cont'd)									
Plantar fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tendonitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Trigger finger	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Osteochondrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Spondylolisthesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Synovial cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (1.9)	0 (0.0)	1 (1.9)	2 (3.9)	9 (1.9)	9 (1.9)	4 (1.7)	10 (1.9)	12 (1.9)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.2)	3 (0.6)	0 (0.0)	6 (1.1)	3 (0.5)
Pruritus	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.5)
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Eczema asteatotic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Eczema nummular	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Papule	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Stasis dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blister	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Dermatitis contact	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Haemorrhage subcutaneous	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hyperkeratosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Urticaria chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dermal cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NERVOUS SYSTEM DISORDERS	1 (1.9)	1 (1.9)	2 (3.7)	1 (2.0)	6 (1.2)	7 (1.5)	4 (1.7)	7 (1.3)	11 (1.7)
Headache	0 (0.0)	1 (1.9)	2 (3.7)	1 (2.0)	4 (0.8)	0 (0.0)	1 (0.4)	4 (0.7)	4 (0.6)
Dizziness	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	1 (0.2)	2 (0.3)
Hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Cerebral infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Sciatica	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Altered state of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cervicobrachial syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Parkinsonism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
VIIth nerve paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	1 (1.9)	0 (0.0)	1 (2.0)	3 (0.6)	8 (1.7)	1 (0.4)	3 (0.6)	10 (1.6)
Dyslipidaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.4)	0 (0.0)	3 (0.5)
Hypercholesterolaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Hypocalcaemia	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Hyperlipidaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Periarthritis calcarea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hyperuricaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (7.4)	2 (3.8)	2 (3.7)	3 (5.9)	4 (0.8)	2 (0.4)	3 (1.2)	8 (1.5)	9 (1.4)
Malaise	1 (1.9)	1 (1.9)	1 (1.9)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.5)
Oedema peripheral	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Injection site pain	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Pyrexia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Face oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Oedema	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.8)	1 (0.2)	0 (0.0)
Feeling abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
VASCULAR DISORDERS	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	9 (1.9)	7 (1.5)	0 (0.0)	9 (1.7)	8 (1.3)
Hypertension	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	6 (1.2)	7 (1.5)	0 (0.0)	6 (1.1)	8 (1.3)
Hot flush	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Peripheral vascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	5 (1.0)	5 (1.1)	3 (1.2)	5 (0.9)	6 (0.9)
Upper respiratory tract inflammation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.4)	1 (0.2)	2 (0.3)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Productive cough	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Rhinitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Sputum retention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Yawning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dysphonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
HEPATOBILIARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	6 (1.3)	0 (0.0)	1 (0.2)	6 (0.9)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	3 (0.5)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gallbladder polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Liver disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)	5 (1.1)	0 (0.0)	7 (1.3)	5 (0.8)
Benign gastric neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Seborrhoeic keratosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lipoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin papilloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tongue neoplasm benign	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
CARDIAC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	5 (1.1)	0 (0.0)	5 (0.9)	5 (0.8)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Aortic valve incompetence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sick sinus syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
EAR AND LABYRINTH DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	5 (1.1)	1 (0.4)	2 (0.4)	5 (0.8)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Vertigo positional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Inner ear disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Tinnitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Eustachian tube stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
EYE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	5 (1.1)	4 (1.7)	2 (0.4)	5 (0.8)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Blepharitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Conjunctivitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dry eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Normal tension glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Uveitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Episcleritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Vitreous detachment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	4 (0.8)	0 (0.0)	1 (0.2)	5 (0.8)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Bone marrow failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pancytopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Lymphadenopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
ENDOCRINE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	3 (0.5)
Goitre	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
IMMUNE SYSTEM DISORDERS	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.4)	1 (0.2)	0 (0.0)	3 (0.6)	2 (0.3)
Seasonal allergy	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Drug hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
RENAL AND URINARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	1 (0.4)	3 (0.6)	1 (0.2)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hydronephrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypertonic bladder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Proteinuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cystitis-like symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Tooth fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-9　治験薬との関連性があると判定された有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Accessory spleen	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
PSYCHIATRIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-2.8

表 7-10　死に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects with fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	5 (1.1)	0 (0.0)	5 (0.9)	5 (0.8)
NERVOUS SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
CARDIAC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
GASTROINTESTINAL DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Large intestine perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Cerebral haemorrhage traumatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects with ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-3.1

表 7-11　治験薬との関連性があると判定された死に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects with investigational product-related fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
CARDIAC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
NERVOUS SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects with ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)

Source: IAS 表-4-3.3

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting serious adverse events	4 (7.4)	6 (11.3)	4 (7.4)	2 (3.9)	68 (14.1)	66 (13.9)	30 (12.4)	72 (13.5)	78 (12.3)
GASTROINTESTINAL DISORDERS	1 (1.9)	3 (5.7)	0 (0.0)	1 (2.0)	12 (2.5)	7 (1.5)	4 (1.7)	13 (2.4)	11 (1.7)
Colonic polyp	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	5 (1.0)	1 (0.2)	1 (0.4)	5 (0.9)	2 (0.3)
Haemorrhoids	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)
Colitis ischaemic	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Abdominal hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Enterocolitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Femoral hernia, obstructive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal mucosal exfoliation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Large intestine perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Rectal prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Colitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Duodenal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gastric polyps	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Proctalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172 Placebo (N=54) n (%)	Study 20050172 Denosumab 14 mg Q6M (N=53) n (%)	Study 20050172 Denosumab 60 mg Q6M (N=54) n (%)	Study 20050172 Denosumab 100 mg Q6M (N=51) n (%)	Study AMG162-A-J301 Placebo (N=481) n (%)	Study AMG162-A-J301 Denosumab 60 mg Q6M (N=475) n (%)	Study AMG162-A-J301 Alendronate [a] (N=242) n (%)	Overall Placebo (N=535) n (%)	Overall Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS (Cont'd)									
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Oesophageal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (3.7)	0 (0.0)	1 (1.9)	0 (0.0)	3 (0.6)	10 (2.1)	6 (2.5)	5 (0.9)	11 (1.7)
Intervertebral disc protrusion	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.4)	1 (0.2)	4 (0.6)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	1 (0.4)	1 (0.2)	3 (0.5)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	3 (1.2)	1 (0.2)	3 (0.5)
Muscle atrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Rotator cuff syndrome	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Haemarthrosis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tenosynovitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Spondylolisthesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	14 (2.9)	9 (1.9)	3 (1.2)	14 (2.6)	10 (1.6)
Head injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Rib fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Contusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	3 (0.6)	1 (0.2)
Spinal fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	3 (0.6)	1 (0.2)
Radius fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Subdural haematoma	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Ulna fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Ankle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Foot fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Fractured coccyx	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Heat illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Patella fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Cerebral haemorrhage traumatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Femoral neck fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Fractured ischium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Fractured sacrum	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Humerus fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pubis fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (Cont'd)									
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Scapula fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tendon rupture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM DISORDERS	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	8 (1.7)	8 (1.7)	1 (0.4)	8 (1.5)	10 (1.6)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	4 (0.6)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	3 (0.5)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Cerebellar haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cerebral artery embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Loss of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)
Altered state of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Autonomic nervous system imbalance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Intracranial aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	10 (2.1)	8 (1.7)	3 (1.2)	10 (1.9)	9 (1.4)
Breast cancer	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)	3 (0.6)	3 (0.5)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Metastases to lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Gastric cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Bile duct cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Colon adenoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to liver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Large intestine carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Paget's disease of the breast	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Haemangioblastoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
CARDIAC DISORDERS	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	5 (1.0)	5 (1.1)	1 (0.4)	5 (0.9)	6 (0.9)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Atrioventricular block complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Palpitations	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Mitral valve incompetence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)	5 (1.1)	3 (1.2)	8 (1.5)	5 (0.8)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Enteritis infectious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory moniliasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Arthritis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hepatitis C	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.8)	1 (0.2)	0 (0.0)
Pyelonephritis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
VASCULAR DISORDERS	0 (0.0)	1 (1.9)	1 (1.9)	0 (0.0)	2 (0.4)	2 (0.4)	1 (0.4)	2 (0.4)	4 (0.6)
Varicose vein	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	2 (0.3)
Aortic aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hypotension	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Circulatory collapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
HEPATOBILIARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	0 (0.0)	3 (0.6)	3 (0.5)
Hepatic cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cholangitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	1 (0.4)	3 (0.6)	3 (0.5)
Haemoptysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Foreign body aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pneumonia aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Paranasal cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pleurisy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
EAR AND LABYRINTH DISORDERS	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	2 (0.8)	1 (0.2)	3 (0.5)
Meniere's disease	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.8)	0 (0.0)	1 (0.2)
Vertigo positional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Sudden hearing loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
EYE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)	2 (0.4)	5 (2.1)	7 (1.3)	2 (0.3)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)	2 (0.4)	5 (2.1)	7 (1.3)	2 (0.3)
Maculopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Macular degeneration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.4)	1 (0.2)	2 (0.3)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Device dislocation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Device breakage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
PSYCHIATRIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dysthymic disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Neurosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
SURGICAL AND MEDICAL PROCEDURES	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Cataract operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Varicose vein operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
RENAL AND URINARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Mixed incontinence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Nephrolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-12　重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	2 (0.8)	3 (0.6)	0 (0.0)
Uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)
Cystocele	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pelvic prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vaginal relaxation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ENDOCRINE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Thyroid mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.1

表 7-13　治験薬との関連性があると判定された重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting investigational product-related serious adverse events	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	8 (1.7)	12 (2.5)	4 (1.7)	8 (1.5)	14 (2.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	0 (0.0)	3 (0.6)	3 (0.5)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
GASTROINTESTINAL DISORDERS	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	3 (0.5)
Colitis ischaemic	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Colonic polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Enterocolitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.8

表 7-13　治験薬との関連性があると判定された重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NERVOUS SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.2)	3 (0.5)
Cerebral infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Altered state of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
HEPATOBILIARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
CARDIAC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
INFECTIONS AND INFESTATIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.8

表 7-13　治験薬との関連性があると判定された重篤な有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Spondylolisthesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
EYE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
VASCULAR DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-4.8

表 7-14　治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting adverse events leading to investigational product discontinuation	2 (3.7)	3 (5.7)	2 (3.7)	2 (3.9)	31 (6.4)	23 (4.8)	18 (7.4)	33 (6.2)	30 (4.7)
GASTROINTESTINAL DISORDERS	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)	7 (2.9)	2 (0.4)	5 (0.8)
Periodontitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Abdominal pain upper	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Colitis ischaemic	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Femoral hernia, obstructive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Duodenal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis erosive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Oedema mouth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Oesophageal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Reflux oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.7

表 7-14　治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	4 (0.8)	3 (0.6)	1 (0.4)	5 (0.9)	4 (0.6)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Muscle atrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Rheumatoid arthritis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Intervertebral disc disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Osteoarthritis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.7

表 7-14　治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NERVOUS SYSTEM DISORDERS	1 (1.9)	0 (0.0)	1 (1.9)	1 (2.0)	1 (0.2)	2 (0.4)	3 (1.2)	2 (0.4)	4 (0.6)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Carpal tunnel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cerebral artery embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Altered state of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dizziness	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypoaesthesia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tremor	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Sciatica	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
VIIth nerve paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.7

表 7-14　治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.5)	3 (0.6)	3 (1.2)	7 (1.3)	3 (0.5)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Metastases to lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastric cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Large intestine carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Metastases to lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Paget's disease of the breast	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Haemangioblastoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
CARDIAC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Atrioventricular block	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Atrioventricular block complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.7

表 7-14　治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
ENDOCRINE DISORDERS	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	2 (0.3)
Basedow's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Hyperthyroidism	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
EAR AND LABYRINTH DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Sudden hearing loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Vertigo positional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
INVESTIGATIONS	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Blood creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood potassium increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood thyroid stimulating hormone increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
VASCULAR DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Aortic aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.7

表 7-14　治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	1 (0.2)	2 (0.8)	4 (0.7)	1 (0.2)
Prurigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Pemphigoid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	3 (0.6)	1 (0.2)
Tooth fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Spinal fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.2)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sensation of foreign body	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bone marrow failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.7

表 7-14　治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
INFECTIONS AND INFESTATIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Atypical mycobacterial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
PSYCHIATRIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Neurosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
EYE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Uveitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
IMMUNE SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Drug hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.7

表 7-15　治験薬との関連性があると判定された治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting investigational product-related adverse events leading to investigational product discontinuation	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	8 (1.7)	4 (0.8)	9 (3.7)	8 (1.5)	5 (0.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bone marrow failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.10

表 7-15　治験薬との関連性があると判定された治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.1)	0 (0.0)	1 (0.2)
Colitis ischaemic	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Duodenal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis erosive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Oedema mouth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Oesophageal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Reflux oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
INFECTIONS AND INFESTATIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Atypical mycobacterial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
CARDIAC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
ENDOCRINE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.10

表 7-15　治験薬との関連性があると判定された治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
EYE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Uveitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
IMMUNE SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Drug hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Altered state of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
VIIth nerve paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.10

表 7-15　治験薬との関連性があると判定された治験薬の投与中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.10

表 7-16　試験の中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting adverse events leading to study discontinuation	2 (3.7)	3 (5.7)	3 (5.6)	2 (3.9)	2 (0.4)	5 (1.1)	2 (0.8)	4 (0.7)	13 (2.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (0.4)	3 (0.6)	0 (0.0)	2 (0.4)	4 (0.6)
Breast cancer	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)
Bile duct cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Gastric cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to liver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Metastases to lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
NERVOUS SYSTEM DISORDERS	1 (1.9)	0 (0.0)	1 (1.9)	1 (2.0)	0 (0.0)	2 (0.4)	1 (0.4)	1 (0.2)	4 (0.6)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Cerebral artery embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Dizziness	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypoaesthesia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tremor	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.1

表 7-16　試験の中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Study 20050172 Placebo (N=54) n (%)	Study 20050172 Denosumab 14 mg Q6M (N=53) n (%)	Study 20050172 Denosumab 60 mg Q6M (N=54) n (%)	Study 20050172 Denosumab 100 mg Q6M (N=51) n (%)	Study AMG162-A-J301 Placebo (N=481) n (%)	Study AMG162-A-J301 Denosumab 60 mg Q6M (N=475) n (%)	Study AMG162-A-J301 Alendronate [a] (N=242) n (%)	Overall Placebo (N=535) n (%)	Overall Denosumab (N=633) n (%)
GASTROINTESTINAL DISORDERS	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Abdominal pain upper	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Colitis ischaemic	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.2)
Rheumatoid arthritis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Osteoarthritis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
ENDOCRINE DISORDERS	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hyperthyroidism	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
INVESTIGATIONS	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Blood thyroid stimulating hormone increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.1

表 7-17　治験薬との関連性があると判定された試験の中止に至った有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

	Study 20050172				Study AMG162-A-J301			Overall	
		Denosumab				Denosumab			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=54) n (%)	14 mg Q6M (N=53) n (%)	60 mg Q6M (N=54) n (%)	100 mg Q6M (N=51) n (%)	Placebo (N=481) n (%)	60 mg Q6M (N=475) n (%)	Alendronate [a] (N=242) n (%)	Placebo (N=535) n (%)	Denosumab (N=633) n (%)
Number of subjects reporting investigational product-related adverse events leading to study discontinuation	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
GASTROINTESTINAL DISORDERS	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Colitis ischaemic	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
a: Reference control (non-blinded)
Source: IAS 表-4-5.4

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
Number of subjects on study at the beginning of the time period of interest	535	535	515	453	196	633	633	608	495	191
Number of subjects reporting adverse events	495 (92.5)	347	96	52	0	593 (93.7)	461	93	38	1
Number of subjects with fatal adverse events	5 (0.9)	1	0	4	0	5 (0.8)	0	3	2	0
Number of subjects reporting serious adverse events	72 (13.5)	21	21	30	0	78 (12.3)	27	19	32	0
Number of subjects discontinued study	68 (12.7)	20	21	27	0	75 (11.8)	25	23	25	2
INFECTIONS AND INFESTATIONS	297 (55.5)	112	94	89	2	372 (58.8)	180	110	79	3
Nasopharyngitis	224 (41.9)	71	75	76	2	273 (43.1)	122	81	68	2
Cystitis	32 (6.0)	9	11	12	0	32 (5.1)	13	8	11	0
Gastroenteritis	17 (3.2)	0	6	11	0	29 (4.6)	5	8	15	1
Pharyngitis	20 (3.7)	4	8	7	1	28 (4.4)	9	10	9	0
Oral herpes	7 (1.3)	0	4	3	0	21 (3.3)	8	5	8	0
Bronchitis	23 (4.3)	5	7	11	0	18 (2.8)	7	3	8	0
Herpes zoster	12 (2.2)	3	3	6	0	15 (2.4)	6	4	5	0
Tinea pedis	8 (1.5)	1	3	4	0	10 (1.6)	4	2	3	1
Rhinitis	3 (0.6)	1	0	2	0	9 (1.4)	4	5	0	0
Paronychia	5 (0.9)	4	0	1	0	8 (1.3)	1	3	4	0
Influenza	5 (0.9)	0	3	2	0	6 (0.9)	3	2	1	0
Onychomycosis	4 (0.7)	3	1	0	0	6 (0.9)	2	2	2	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INFECTIONS AND INFESTATIONS (Cont'd)										
Tinea infection	1 (0.2)	0	0	1	0	6 (0.9)	3	1	2	0
Otitis media	4 (0.7)	1	2	1	0	5 (0.8)	3	1	1	0
Hordeolum	3 (0.6)	0	1	2	0	5 (0.8)	1	2	2	0
Otitis externa	3 (0.6)	1	2	0	0	5 (0.8)	2	1	2	0
Pneumonia	3 (0.6)	1	1	1	0	5 (0.8)	2	1	2	0
Gastroenteritis viral	7 (1.3)	3	3	1	0	4 (0.6)	2	2	0	0
Sinusitis	4 (0.7)	2	0	2	0	4 (0.6)	2	0	2	0
Pulpitis dental	1 (0.2)	1	0	0	0	4 (0.6)	1	1	2	0
Tonsillitis	2 (0.4)	0	0	2	0	3 (0.5)	0	1	2	0
Urinary tract infection	2 (0.4)	2	0	0	0	3 (0.5)	1	1	1	0
Cellulitis	1 (0.2)	0	1	0	0	3 (0.5)	0	1	2	0
Enteritis infectious	1 (0.2)	0	0	1	0	3 (0.5)	1	1	1	0
Folliculitis	1 (0.2)	1	0	0	0	3 (0.5)	0	3	0	0
Helicobacter infection	1 (0.2)	0	0	1	0	2 (0.3)	0	0	2	0
Acute sinusitis	0 (0.0)	0	0	0	0	2 (0.3)	0	1	1	0
Appendicitis	0 (0.0)	0	0	0	0	2 (0.3)	0	0	2	0
Herpes virus infection	0 (0.0)	0	0	0	0	2 (0.3)	1	1	0	0
Atypical mycobacterial infection	2 (0.4)	2	0	0	0	1 (0.2)	1	0	0	0
Arthritis bacterial	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INFECTIONS AND INFESTATIONS (Cont'd)										
Chronic sinusitis	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Enterocolitis viral	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Gastroenteritis norovirus	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Laryngitis	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Parotitis	1 (0.2)	0	1	0	0	1 (0.2)	0	1	0	0
Pyelonephritis acute	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Subcutaneous abscess	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Vaginal infection	1 (0.2)	0	1	0	0	1 (0.2)	1	0	0	0
Abscess	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Acute tonsillitis	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Bronchopneumonia	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Candidiasis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Chronic tonsillitis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dacryocystitis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dermatitis infected	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Eczema infected	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Fungal skin infection	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Gastroenteritis bacterial	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Impetigo	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INFECTIONS AND INFESTATIONS (Cont'd)										
Nail candida	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Omphalitis	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Osteomyelitis	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Respiratory moniliasis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Skin infection	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Urethritis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Vulvitis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Wound infection	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Adenoviral conjunctivitis	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Furuncle	2 (0.4)	0	0	2	0	0 (0.0)	0	0	0	0
Herpes simplex	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Abscess oral	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Body tinea	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Diverticulitis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Eczema impetiginous	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Genital herpes	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Gingival abscess	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Hepatitis C	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Mumps	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INFECTIONS AND INFESTATIONS (Cont'd)										
Oral candidiasis	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Otitis media chronic	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Pyelonephritis	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Pyoderma	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Sepsis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Sialoadenitis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Tooth infection	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Upper respiratory tract infection	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Vaginitis bacterial	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535)					Denosumab (N=633)				
	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	245 (45.8)	100	75	70	0	302 (47.7)	139	79	84	0
Back pain	64 (12.0)	18	23	23	0	89 (14.1)	33	25	31	0
Osteoarthritis	46 (8.6)	17	15	14	0	81 (12.8)	30	19	31	1
Arthralgia	30 (5.6)	7	13	10	0	45 (7.1)	16	9	20	0
Spinal osteoarthritis	24 (4.5)	6	7	10	1	29 (4.6)	13	8	8	0
Periarthritis	32 (6.0)	13	9	10	0	26 (4.1)	5	10	11	0
Pain in extremity	29 (5.4)	11	9	9	0	26 (4.1)	8	4	13	1
Musculoskeletal pain	13 (2.4)	3	6	3	1	24 (3.8)	6	8	10	0
Muscle spasms	17 (3.2)	5	4	8	0	20 (3.2)	5	4	11	0
Musculoskeletal stiffness	13 (2.4)	4	4	5	0	20 (3.2)	8	5	7	0
Myalgia	24 (4.5)	6	7	9	2	19 (3.0)	10	1	8	0
Lumbar spinal stenosis	7 (1.3)	2	1	4	0	17 (2.7)	6	4	7	0
Intervertebral disc protrusion	1 (0.2)	1	0	0	0	11 (1.7)	4	2	5	0
Arthritis	9 (1.7)	1	2	6	0	9 (1.4)	2	3	4	0
Trigger finger	4 (0.7)	1	1	2	0	9 (1.4)	1	3	5	0
Tenosynovitis	11 (2.1)	4	2	5	0	8 (1.3)	4	1	3	0
Flank pain	0 (0.0)	0	0	0	0	8 (1.3)	3	4	1	0
Neck pain	11 (2.1)	4	3	4	0	7 (1.1)	2	3	2	0
Synovial cyst	6 (1.1)	2	1	3	0	7 (1.1)	3	1	3	0
Musculoskeletal chest pain	1 (0.2)	1	0	0	0	4 (0.6)	0	2	2	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (Cont'd)										
Tendonitis	3 (0.6)	1	0	2	0	3 (0.5)	2	0	1	0
Rotator cuff syndrome	1 (0.2)	1	0	0	0	3 (0.5)	0	2	1	0
Spondylolisthesis	6 (1.1)	0	2	4	0	2 (0.3)	1	1	0	0
Fasciitis	5 (0.9)	1	3	1	0	2 (0.3)	2	0	0	0
Nodal osteoarthritis	4 (0.7)	2	0	2	0	2 (0.3)	0	0	2	0
Facet joint syndrome	2 (0.4)	1	0	1	0	2 (0.3)	0	0	2	0
Myofascitis	2 (0.4)	1	0	1	0	2 (0.3)	1	1	0	0
Bursitis	1 (0.2)	1	0	0	0	2 (0.3)	1	0	1	0
Coccydynia	1 (0.2)	1	0	0	0	2 (0.3)	2	0	0	0
Temporomandibular joint syndrome	1 (0.2)	1	0	0	0	2 (0.3)	1	1	0	0
Foot deformity	0 (0.0)	0	0	0	0	2 (0.3)	0	2	0	0
Joint swelling	0 (0.0)	0	0	0	0	2 (0.3)	1	1	0	0
Upper extremity mass	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Intervertebral disc disorder	2 (0.4)	1	0	1	0	1 (0.2)	0	1	0	0
Myositis	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Spinal column stenosis	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Tenosynovitis stenosans	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Chondrosis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Ligamentitis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (Cont'd)										
Limb discomfort	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Muscle atrophy	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Muscle tightness	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Muscular weakness	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Osteonecrosis	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Rheumatoid arthritis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
SAPHO syndrome	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Synovitis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Bone pain	3 (0.6)	1	0	2	0	0 (0.0)	0	0	0	0
Arthropathy	2 (0.4)	1	1	0	0	0 (0.0)	0	0	0	0
Chondrocalcinosis pyrophosphate	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Haemarthrosis	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Chondropathy	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Groin pain	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Myalgia intercostal	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Pain in jaw	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Plantar fasciitis	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Sinus tarsi syndrome	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
GASTROINTESTINAL DISORDERS	246 (46.0)	86	71	89	0	289 (45.7)	141	72	75	1
Dental caries	68 (12.7)	18	25	25	0	75 (11.8)	23	20	32	0
Constipation	38 (7.1)	14	9	15	0	61 (9.6)	30	13	18	0
Periodontitis	28 (5.2)	11	4	13	0	46 (7.3)	16	11	19	0
Stomatitis	25 (4.7)	6	10	9	0	39 (6.2)	16	6	17	0
Diarrhoea	19 (3.6)	9	6	4	0	31 (4.9)	11	11	8	1
Gastritis	26 (4.9)	7	5	14	0	24 (3.8)	11	6	7	0
Abdominal discomfort	18 (3.4)	4	8	6	0	24 (3.8)	8	4	12	0
Reflux oesophagitis	12 (2.2)	4	2	6	0	19 (3.0)	6	4	9	0
Abdominal pain upper	7 (1.3)	2	2	3	0	17 (2.7)	9	1	7	0
Gingivitis	12 (2.2)	3	3	6	0	16 (2.5)	3	5	8	0
Periodontal disease	18 (3.4)	3	4	10	1	9 (1.4)	2	4	3	0
Haemorrhoids	14 (2.6)	6	4	4	0	9 (1.4)	3	3	3	0
Vomiting	10 (1.9)	3	2	5	0	9 (1.4)	3	3	3	0
Enterocolitis	5 (0.9)	1	2	2	0	9 (1.4)	4	2	3	0
Colonic polyp	14 (2.6)	3	4	7	0	8 (1.3)	3	4	1	0
Cheilitis	8 (1.5)	3	4	1	0	8 (1.3)	2	2	4	0
Nausea	7 (1.3)	1	2	4	0	7 (1.1)	3	3	1	0
Toothache	5 (0.9)	1	2	2	0	7 (1.1)	3	0	4	0
Gastric ulcer	4 (0.7)	0	1	3	0	5 (0.8)	2	2	1	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
GASTROINTESTINAL DISORDERS (Cont'd)										
Abdominal distension	3 (0.6)	0	1	2	0	5 (0.8)	2	1	2	0
Gastric polyps	5 (0.9)	1	2	2	0	4 (0.6)	0	2	2	0
Abdominal pain	2 (0.4)	0	1	1	0	4 (0.6)	1	1	2	0
Glossitis	3 (0.6)	0	2	1	0	3 (0.5)	1	1	1	0
Gastritis erosive	1 (0.2)	0	0	1	0	3 (0.5)	1	1	1	0
Gastrointestinal disorder	2 (0.4)	0	1	1	0	2 (0.3)	1	0	1	0
Duodenal ulcer	1 (0.2)	1	0	0	0	2 (0.3)	0	1	1	0
Hiatus hernia	1 (0.2)	1	0	0	0	2 (0.3)	1	0	1	0
Tooth loss	1 (0.2)	0	1	0	0	2 (0.3)	0	1	1	0
Colitis ischaemic	0 (0.0)	0	0	0	0	2 (0.3)	1	1	0	0
Anal fissure	4 (0.7)	0	1	3	0	1 (0.2)	0	1	0	0
Abdominal pain lower	2 (0.4)	1	1	0	0	1 (0.2)	0	1	0	0
Aphthous stomatitis	1 (0.2)	1	0	0	0	1 (0.2)	1	0	0	0
Colitis	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Diverticulum intestinal	1 (0.2)	0	1	0	0	1 (0.2)	0	1	0	0
Dry mouth	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Gingival atrophy	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Gingival bleeding	1 (0.2)	0	1	0	0	1 (0.2)	1	0	0	0
Gingival swelling	1 (0.2)	0	1	0	0	1 (0.2)	1	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
GASTROINTESTINAL DISORDERS (Cont'd)										
Radicular cyst	1 (0.2)	0	1	0	0	1 (0.2)	0	1	0	0
Abdominal hernia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Anal polyp	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Chapped lips	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Dental necrosis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Duodenitis	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Dyschezia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dysphagia	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Femoral hernia, obstructive	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Food poisoning	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Gastrointestinal haemorrhage	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Gastrointestinal mucosal exfoliation	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Glossodynia	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Hypoaesthesia oral	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Large intestine perforation	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Malocclusion	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Oesophageal polyp	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Oral disorder	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Oral lichen planus	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
GASTROINTESTINAL DISORDERS (Cont'd)										
Pancreatic cyst	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Paraesthesia oral	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Salivary gland calculus	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Traumatic occlusion	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dyspepsia	4 (0.7)	1	0	3	0	0 (0.0)	0	0	0	0
Loose tooth	4 (0.7)	2	1	1	0	0 (0.0)	0	0	0	0
Sensitivity of teeth	3 (0.6)	0	2	1	0	0 (0.0)	0	0	0	0
Flatulence	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Rectal prolapse	2 (0.4)	1	1	0	0	0 (0.0)	0	0	0	0
Enamel anomaly	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Epigastric discomfort	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Gastritis atrophic	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Gingival pain	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Haematochezia	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Hyperchlorhydria	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Lip swelling	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Pancreatitis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Pancreatitis acute	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Parotid gland enlargement	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
GASTROINTESTINAL DISORDERS (Cont'd)										
Proctalgia	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535)					Denosumab (N=633)				
	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	181 (33.8)	69	56	55	1	184 (29.1)	67	48	69	0
Contusion	82 (15.3)	36	22	23	1	86 (13.6)	25	27	34	0
Joint sprain	20 (3.7)	6	6	8	0	24 (3.8)	12	5	7	0
Arthropod sting	17 (3.2)	3	2	12	0	19 (3.0)	5	4	10	0
Tooth fracture	13 (2.4)	2	7	4	0	13 (2.1)	4	2	7	0
Thermal burn	3 (0.6)	2	1	0	0	13 (2.1)	4	3	6	0
Epicondylitis	10 (1.9)	2	4	4	0	8 (1.3)	2	2	4	0
Foot fracture	7 (1.3)	1	3	3	0	7 (1.1)	1	3	3	0
Chillblains	1 (0.2)	0	1	0	0	6 (0.9)	1	3	2	0
Spinal fracture	22 (4.1)	3	2	15	2	5 (0.8)	3	0	2	0
Wound	7 (1.3)	1	1	5	0	5 (0.8)	3	0	2	0
Muscle strain	6 (1.1)	5	0	1	0	5 (0.8)	2	2	1	0
Radius fracture	6 (1.1)	1	0	5	0	5 (0.8)	1	0	4	0
Patella fracture	0 (0.0)	0	0	0	0	5 (0.8)	1	2	2	0
Rib fracture	8 (1.5)	1	4	3	0	4 (0.6)	1	2	1	0
Excoriation	5 (0.9)	2	2	1	0	4 (0.6)	1	1	2	0
Ulna fracture	4 (0.7)	0	0	4	0	3 (0.5)	1	0	2	0
Arthropod bite	3 (0.6)	2	0	1	0	3 (0.5)	1	2	0	0
Muscle injury	3 (0.6)	1	0	2	0	3 (0.5)	2	0	1	0
Head injury	2 (0.4)	1	0	1	0	3 (0.5)	0	1	2	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (Cont'd)										
Meniscus lesion	2 (0.4)	2	0	0	0	3 (0.5)	1	1	1	0
Ankle fracture	0 (0.0)	0	0	0	0	3 (0.5)	1	0	2	0
Procedural pain	0 (0.0)	0	0	0	0	3 (0.5)	2	1	0	0
Animal bite	4 (0.7)	2	1	1	0	2 (0.3)	0	1	1	0
Skeletal injury	4 (0.7)	0	3	1	0	2 (0.3)	1	1	0	0
Foreign body in eye	2 (0.4)	0	1	1	0	2 (0.3)	0	0	2	0
Joint dislocation	2 (0.4)	1	0	1	0	2 (0.3)	0	2	0	0
Hand fracture	1 (0.2)	0	0	1	0	2 (0.3)	2	0	0	0
Stab wound	1 (0.2)	1	0	0	0	2 (0.3)	0	0	2	0
Frostbite	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Heat illness	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Traumatic haematoma	0 (0.0)	0	0	0	0	2 (0.3)	0	1	1	0
Laceration	3 (0.6)	0	2	1	0	1 (0.2)	0	1	0	0
Cartilage injury	2 (0.4)	1	1	0	0	1 (0.2)	0	0	1	0
Clavicle fracture	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Crush injury	1 (0.2)	0	1	0	0	1 (0.2)	0	0	1	0
Fibula fracture	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Humerus fracture	1 (0.2)	0	1	0	0	1 (0.2)	0	0	1	0
Subcutaneous haematoma	1 (0.2)	0	1	0	0	1 (0.2)	1	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (Cont'd)										
Subdural haematoma	1 (0.2)	0	1	0	0	1 (0.2)	0	1	0	0
Tooth injury	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Burns second degree	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Fractured coccyx	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Nail avulsion	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Femoral neck fracture	2 (0.4)	0	1	1	0	0 (0.0)	0	0	0	0
Fractured sacrum	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Cerebral haemorrhage traumatic	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Corneal abrasion	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Femur fracture	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Foreign body	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Fractured ischium	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Heat exhaustion	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Ligament injury	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Ligament sprain	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Lumbar vertebral fracture	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Nail injury	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Periorbital haematoma	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Pubis fracture	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (Cont'd)										
Road traffic accident	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Scapula fracture	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Tendon rupture	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Wound complication	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	133 (24.9)	51	34	48	0	166 (26.2)	77	38	51	0
Eczema	46 (8.6)	18	13	15	0	55 (8.7)	25	13	17	0
Dermatitis contact	29 (5.4)	9	5	15	0	23 (3.6)	7	7	9	0
Pruritus	8 (1.5)	2	1	5	0	14 (2.2)	7	4	3	0
Dermatitis	9 (1.7)	1	4	4	0	11 (1.7)	5	3	3	0
Haemorrhage subcutaneous	5 (0.9)	3	2	0	0	11 (1.7)	4	0	7	0
Rash	10 (1.9)	2	3	4	1	9 (1.4)	4	2	3	0
Heat rash	2 (0.4)	0	0	2	0	8 (1.3)	3	2	3	0
Urticaria	6 (1.1)	1	3	2	0	7 (1.1)	3	1	3	0
Erythema	5 (0.9)	4	0	1	0	7 (1.1)	2	2	3	0
Eczema asteatotic	4 (0.7)	2	0	2	0	7 (1.1)	2	5	0	0
Xeroderma	1 (0.2)	0	0	1	0	7 (1.1)	1	3	3	0
Hyperkeratosis	9 (1.7)	2	3	4	0	6 (0.9)	3	1	2	0
Seborrhoeic dermatitis	1 (0.2)	0	0	1	0	5 (0.8)	3	1	1	0
Dry skin	0 (0.0)	0	0	0	0	4 (0.6)	0	2	2	0
Dermatitis allergic	2 (0.4)	1	0	1	0	3 (0.5)	1	1	1	0
Ingrowing nail	2 (0.4)	0	2	0	0	3 (0.5)	1	1	1	0
Drug eruption	1 (0.2)	1	0	0	0	3 (0.5)	1	0	2	0
Asteatosis	2 (0.4)	1	0	1	0	2 (0.3)	1	1	0	0
Blister	2 (0.4)	2	0	0	0	2 (0.3)	0	1	1	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
SKIN AND SUBCUTANEOUS TISSUE DISORDERS (Cont'd)										
Dyshidrosis	2 (0.4)	0	0	2	0	2 (0.3)	2	0	0	0
Polymorphic light eruption	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Pruritus generalised	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Skin exfoliation	0 (0.0)	0	0	0	0	2 (0.3)	0	0	2	0
Decubitus ulcer	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Dermal cyst	1 (0.2)	0	1	0	0	1 (0.2)	0	1	0	0
Lentigo	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Alopecia areata	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Eczema nummular	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Keloid scar	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Milia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Papule	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Petechiae	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Prurigo	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Purpura	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Pustular psoriasis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Skin haemorrhage	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Skin tightness	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Stasis dermatitis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
SKIN AND SUBCUTANEOUS TISSUE DISORDERS (Cont'd)										
Acne	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Hyperkeratosis palmaris and plantaris	2 (0.4)	1	1	0	0	0 (0.0)	0	0	0	0
Senile pruritus	2 (0.4)	0	1	1	0	0 (0.0)	0	0	0	0
Hypoaesthesia facial	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Nail disorder	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Pemphigoid	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Photosensitivity reaction	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Psoriasis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Skin chapped	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Urticaria chronic	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
NERVOUS SYSTEM DISORDERS	83 (15.5)	25	22	36	0	134 (21.2)	51	27	56	0
Headache	24 (4.5)	7	7	10	0	39 (6.2)	16	12	11	0
Hypoaesthesia	13 (2.4)	4	4	5	0	18 (2.8)	9	4	5	0
Dizziness	8 (1.5)	2	3	3	0	18 (2.8)	7	3	8	0
Sciatica	10 (1.9)	2	2	6	0	15 (2.4)	5	2	8	0
Carpal tunnel syndrome	3 (0.6)	0	0	3	0	7 (1.1)	2	1	4	0
Cerebral infarction	1 (0.2)	1	0	0	0	7 (1.1)	3	1	3	0
Cervicobrachial syndrome	2 (0.4)	1	1	0	0	6 (0.9)	2	2	2	0
Tension headache	2 (0.4)	1	0	1	0	5 (0.8)	2	1	2	0
Dysgeusia	2 (0.4)	0	1	1	0	4 (0.6)	0	0	4	0
Neuropathy peripheral	3 (0.6)	1	0	2	0	3 (0.5)	0	0	3	0
Somnolence	2 (0.4)	2	0	0	0	3 (0.5)	1	1	1	0
Cervical neuritis	1 (0.2)	0	0	1	0	3 (0.5)	1	0	2	0
Subarachnoid haemorrhage	1 (0.2)	0	0	1	0	3 (0.5)	1	1	1	0
Neuralgia	0 (0.0)	0	0	0	0	3 (0.5)	0	0	3	0
Occipital neuralgia	0 (0.0)	0	0	0	0	3 (0.5)	1	1	1	0
Intercostal neuralgia	3 (0.6)	1	2	0	0	2 (0.3)	0	1	1	0
Autonomic nervous system imbalance	2 (0.4)	0	0	2	0	2 (0.3)	0	0	2	0
Dizziness postural	2 (0.4)	0	0	2	0	2 (0.3)	0	1	1	0
Tremor	2 (0.4)	2	0	0	0	2 (0.3)	1	0	1	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
NERVOUS SYSTEM DISORDERS (Cont'd)										
Intracranial aneurysm	1 (0.2)	0	1	0	0	2 (0.3)	0	0	2	0
Lacunar infarction	0 (0.0)	0	0	0	0	2 (0.3)	0	1	1	0
Loss of consciousness	3 (0.6)	0	0	3	0	1 (0.2)	1	0	0	0
Nystagmus	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Post herpetic neuralgia	1 (0.2)	0	1	0	0	1 (0.2)	1	0	0	0
Sensory disturbance	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Cerebellar haemorrhage	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Cerebral artery embolism	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Cerebral ischaemia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Cubital tunnel syndrome	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dementia Alzheimer's type	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dyslalia	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Morton's neuralgia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Nervous system disorder	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Tarsal tunnel syndrome	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
VIIth nerve paralysis	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Cerebral haemorrhage	3 (0.6)	2	1	0	0	0 (0.0)	0	0	0	0
Trigeminal neuralgia	2 (0.4)	0	1	1	0	0 (0.0)	0	0	0	0
Altered state of consciousness	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
NERVOUS SYSTEM DISORDERS (Cont'd)										
Amnesia	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Convulsion	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Diabetic neuropathy	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Dysaesthesia	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Essential tremor	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Facial spasm	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Intention tremor	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Transient ischaemic attack	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535)					Denosumab (N=633)				
	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	79 (14.8)	29	17	33	0	110 (17.4)	40	33	37	0
Upper respiratory tract inflammation	43 (8.0)	18	11	14	0	44 (7.0)	17	15	12	0
Oropharyngeal pain	8 (1.5)	3	2	3	0	11 (1.7)	3	3	5	0
Cough	3 (0.6)	0	0	3	0	11 (1.7)	6	2	3	0
Rhinitis allergic	7 (1.3)	2	2	3	0	10 (1.6)	2	4	4	0
Asthma	6 (1.1)	1	0	5	0	10 (1.6)	2	5	3	0
Rhinorrhoea	2 (0.4)	0	0	2	0	5 (0.8)	2	3	0	0
Oropharyngeal discomfort	2 (0.4)	0	1	1	0	3 (0.5)	0	1	2	0
Dyspnoea	1 (0.2)	1	0	0	0	3 (0.5)	1	0	2	0
Productive cough	1 (0.2)	0	0	1	0	3 (0.5)	1	1	1	0
Epistaxis	0 (0.0)	0	0	0	0	3 (0.5)	2	1	0	0
Interstitial lung disease	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Bronchitis chronic	3 (0.6)	2	0	1	0	1 (0.2)	0	1	0	0
Allergic bronchitis	2 (0.4)	0	0	2	0	1 (0.2)	1	0	0	0
Haemoptysis	2 (0.4)	1	0	1	0	1 (0.2)	0	0	1	0
Pleurisy	2 (0.4)	0	1	1	0	1 (0.2)	1	0	0	0
Pharyngeal oedema	1 (0.2)	1	0	0	0	1 (0.2)	1	0	0	0
Bronchiectasis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dysaesthesia pharynx	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Dysphonia	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (Cont'd)										
Emphysema	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Foreign body aspiration	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Nasal congestion	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Pharyngeal polyp	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Pneumonia aspiration	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Sleep apnoea syndrome	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Paranasal cyst	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Sputum retention	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Vocal cord inflammation	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Yawning	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	Placebo (N=535) ≤6M n	Placebo (N=535) >6M, ≤12M n	Placebo (N=535) >12M, ≤24M n	Placebo (N=535) >24M n	Denosumab (N=633) Total n (%)	Denosumab (N=633) ≤6M n	Denosumab (N=633) >6M, ≤12M n	Denosumab (N=633) >12M, ≤24M n	Denosumab (N=633) >24M n
INVESTIGATIONS	87 (16.3)	22	26	34	5	104 (16.4)	34	35	29	6
Blood creatine phosphokinase increased	22 (4.1)	7	6	6	3	29 (4.6)	9	9	9	2
Blood pressure increased	14 (2.6)	4	3	7	0	16 (2.5)	3	6	7	0
Gamma-glutamyltransferase increased	11 (2.1)	0	6	4	1	16 (2.5)	3	11	0	2
Alanine aminotransferase increased	0 (0.0)	0	0	0	0	8 (1.3)	2	3	3	0
Protein urine present	0 (0.0)	0	0	0	0	8 (1.3)	5	3	0	0
Aspartate aminotransferase increased	1 (0.2)	1	0	0	0	7 (1.1)	2	3	2	0
Blood creatinine increased	1 (0.2)	0	0	1	0	6 (0.9)	1	0	4	1
Weight decreased	7 (1.3)	2	1	4	0	4 (0.6)	0	1	2	1
Blood potassium increased	2 (0.4)	2	0	0	0	4 (0.6)	1	0	3	0
Blood glucose increased	6 (1.1)	3	0	3	0	3 (0.5)	0	0	3	0
Weight increased	1 (0.2)	0	1	0	0	3 (0.5)	1	1	0	1
White blood cell count decreased	1 (0.2)	0	1	0	0	3 (0.5)	2	1	0	0
Blood bilirubin increased	3 (0.6)	0	2	1	0	2 (0.3)	0	1	1	0
White blood cell count increased	2 (0.4)	0	1	1	0	2 (0.3)	2	0	0	0
Blood lactate dehydrogenase increased	1 (0.2)	0	0	0	1	2 (0.3)	0	1	1	0
Liver function test abnormal	1 (0.2)	0	0	1	0	2 (0.3)	1	1	0	0
Blood alkaline phosphatase decreased	0 (0.0)	0	0	0	0	2 (0.3)	0	2	0	0
Blood urea increased	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Blood alkaline phosphatase increased	9 (1.7)	0	1	6	2	1 (0.2)	0	1	0	0

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M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INVESTIGATIONS (Cont'd)										
Eosinophil count increased	4 (0.7)	0	2	2	0	1 (0.2)	1	0	0	0
Blood urine present	3 (0.6)	0	2	1	0	1 (0.2)	1	0	0	0
Blood pressure decreased	2 (0.4)	0	1	1	0	1 (0.2)	0	0	1	0
Glucose urine present	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Heart rate increased	1 (0.2)	0	1	0	0	1 (0.2)	0	0	1	0
Helicobacter test positive	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Blood 25-hydroxycholecalciferol increased	0 (0.0)	0	0	0	0	1 (0.2)	0	0	0	1
Blood calcium decreased	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Blood pressure diastolic increased	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Blood sodium decreased	0 (0.0)	0	0	0	0	1 (0.2)	0	0	0	1
Blood thyroid stimulating hormone increased	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Blood triglycerides increased	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
C-reactive protein increased	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Cardiac murmur	0 (0.0)	0	0	0	0	1 (0.2)	0	0	0	1
Heart rate decreased	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Hepatitis C antibody positive	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Immunoglobulins increased	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Protein urine	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Blood insulin increased	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

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M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
INVESTIGATIONS (Cont'd)										
Blood pressure systolic increased	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Body temperature decreased	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Foetal haemoglobin increased	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Glycosylated haemoglobin increased	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Low density lipoprotein increased	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Platelet count decreased	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Renal function test abnormal	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Thyroxine increased	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Tri-iodothyronine increased	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Urine output decreased	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

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Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
EYE DISORDERS	77 (14.4)	27	21	29	0	99 (15.6)	37	23	39	0
Cataract	28 (5.2)	3	9	16	0	29 (4.6)	6	7	16	0
Conjunctivitis	14 (2.6)	2	7	5	0	20 (3.2)	10	4	6	0
Dry eye	9 (1.7)	3	0	6	0	11 (1.7)	4	4	3	0
Asthenopia	6 (1.1)	3	0	3	0	9 (1.4)	3	2	4	0
Conjunctivitis allergic	12 (2.2)	6	1	5	0	6 (0.9)	1	2	3	0
Conjunctival haemorrhage	4 (0.7)	0	1	3	0	6 (0.9)	3	2	1	0
Vitreous floaters	2 (0.4)	1	0	1	0	5 (0.8)	2	1	2	0
Posterior capsule opacification	0 (0.0)	0	0	0	0	4 (0.6)	1	2	1	0
Pterygium	0 (0.0)	0	0	0	0	4 (0.6)	1	2	1	0
Glaucoma	3 (0.6)	0	1	2	0	3 (0.5)	1	0	2	0
Ocular hyperaemia	3 (0.6)	1	2	0	0	3 (0.5)	0	1	2	0
Corneal erosion	1 (0.2)	0	0	1	0	3 (0.5)	2	0	1	0
Keratitis	0 (0.0)	0	0	0	0	3 (0.5)	1	1	1	0
Blepharitis	2 (0.4)	1	0	1	0	2 (0.3)	1	1	0	0
Eye pruritus	1 (0.2)	1	0	0	0	2 (0.3)	2	0	0	0
Trichiasis	1 (0.2)	1	0	0	0	2 (0.3)	0	1	1	0
Vitreous detachment	1 (0.2)	1	0	0	0	2 (0.3)	1	0	1	0
Angle closure glaucoma	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Corneal disorder	0 (0.0)	0	0	0	0	2 (0.3)	0	0	2	0

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M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
EYE DISORDERS (Cont'd)										
Punctate keratitis	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Lacrimation increased	2 (0.4)	0	1	1	0	1 (0.2)	0	0	1	0
Maculopathy	2 (0.4)	1	1	0	0	1 (0.2)	0	0	1	0
Eyelid oedema	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Normal tension glaucoma	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Xerophthalmia	1 (0.2)	0	1	0	0	1 (0.2)	0	0	1	0
Arteriosclerotic retinopathy	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Blepharal pigmentation	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Blepharitis allergic	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Conjunctival deposit	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Dacryostenosis acquired	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Eye pain	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Keratoconjunctivitis sicca	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Narrow anterior chamber angle	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Pingueculitis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Scleral haemorrhage	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Retinal tear	2 (0.4)	1	1	0	0	0 (0.0)	0	0	0	0
Conjunctival hyperaemia	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Eczema eyelids	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
EYE DISORDERS (Cont'd)										
Episcleritis	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Eye discharge	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Eye inflammation	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Lacrimation decreased	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Macular degeneration	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Retinal aneurysm	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Retinal haemorrhage	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Scleritis	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Uveitis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Vision blurred	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535)					Denosumab (N=633)				
	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	66 (12.3)	30	14	21	1	65 (10.3)	26	18	21	0
Device breakage	9 (1.7)	1	2	6	0	13 (2.1)	4	5	4	0
Oedema peripheral	3 (0.6)	2	1	0	0	13 (2.1)	7	2	4	0
Malaise	10 (1.9)	6	3	1	0	11 (1.7)	3	4	4	0
Chest pain	12 (2.2)	5	2	4	1	6 (0.9)	2	1	3	0
Pyrexia	5 (0.9)	4	1	0	0	5 (0.8)	2	2	1	0
Fatigue	8 (1.5)	4	0	4	0	4 (0.6)	2	0	2	0
Feeling abnormal	4 (0.7)	2	2	0	0	3 (0.5)	1	1	1	0
Oedema	0 (0.0)	0	0	0	0	3 (0.5)	2	1	0	0
Face oedema	4 (0.7)	2	0	2	0	2 (0.3)	1	1	0	0
Chest discomfort	2 (0.4)	1	0	1	0	2 (0.3)	0	1	1	0
Thirst	3 (0.6)	1	0	2	0	1 (0.2)	0	0	1	0
Asthenia	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Injection site pain	1 (0.2)	0	1	0	0	1 (0.2)	1	0	0	0
Device dislocation	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Device failure	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Injection site haemorrhage	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Injection site reaction	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Patient-device incompatibility	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Sensation of foreign body	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (Cont'd)										
Application site eczema	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Generalised oedema	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Inflammation	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Injection site erythema	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Injection site haematoma	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Local swelling	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Mass	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
VASCULAR DISORDERS	51 (9.5)	17	17	16	1	61 (9.6)	26	17	18	0
Hypertension	37 (6.9)	15	10	10	2	45 (7.1)	17	14	14	0
Varicose vein	1 (0.2)	1	0	0	0	4 (0.6)	1	1	2	0
Peripheral coldness	0 (0.0)	0	0	0	0	4 (0.6)	2	0	2	0
Haematoma	1 (0.2)	0	0	1	0	3 (0.5)	3	0	0	0
Hot flush	5 (0.9)	0	3	2	0	1 (0.2)	1	0	0	0
Hypotension	2 (0.4)	0	1	1	0	1 (0.2)	0	1	0	0
Aortic aneurysm	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Arteriosclerosis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Flushing	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Peripheral circulatory failure	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Phlebitis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Renovascular hypertension	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Vascular stenosis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Orthostatic hypotension	2 (0.4)	0	2	0	0	0 (0.0)	0	0	0	0
Peripheral vascular disorder	2 (0.4)	1	0	1	0	0 (0.0)	0	0	0	0
Arteriosclerosis obliterans	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Circulatory collapse	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Deep vein thrombosis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Peripheral arterial occlusive disease	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
VASCULAR DISORDERS (Cont'd)										
Varicophlebitis	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	37 (6.9)	12	10	15	0	54 (8.5)	14	13	27	0
Hyperlipidaemia	17 (3.2)	6	5	6	0	20 (3.2)	5	7	8	0
Decreased appetite	3 (0.6)	0	1	2	0	11 (1.7)	1	1	9	0
Hypercholesterolaemia	4 (0.7)	1	1	2	0	6 (0.9)	2	1	3	0
Dyslipidaemia	2 (0.4)	0	0	2	0	6 (0.9)	1	0	5	0
Diabetes mellitus	4 (0.7)	1	1	1	1	5 (0.8)	1	2	2	0
Dehydration	5 (0.9)	3	0	2	0	3 (0.5)	2	0	1	0
Hypocalcaemia	0 (0.0)	0	0	0	0	2 (0.3)	2	0	0	0
Glucose tolerance impaired	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Gout	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Hypoglycaemia	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Periarthritis calcarea	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Type 2 diabetes mellitus	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Hyperuricaemia	2 (0.4)	0	1	1	0	0 (0.0)	0	0	0	0
Hypertriglyceridaemia	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535)					Denosumab (N=633)				
	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
PSYCHIATRIC DISORDERS	31 (5.8)	12	4	15	0	42 (6.6)	14	8	20	0
Insomnia	23 (4.3)	9	4	10	0	30 (4.7)	8	6	16	0
Anxiety	4 (0.7)	2	0	2	0	3 (0.5)	1	1	1	0
Anxiety disorder	3 (0.6)	0	1	2	0	2 (0.3)	0	1	1	0
Depression	2 (0.4)	1	0	1	0	2 (0.3)	2	0	0	0
Delirium	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Depressed mood	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Restlessness	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Sleep disorder	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Adjustment disorder	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Bruxism	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Dysthymic disorder	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Initial insomnia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Dissociative disorder	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Neurosis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
EAR AND LABYRINTH DISORDERS	31 (5.8)	11	8	11	1	40 (6.3)	11	7	22	0
Vertigo	17 (3.2)	5	4	7	1	15 (2.4)	4	3	8	0
Tinnitus	2 (0.4)	0	0	2	0	11 (1.7)	5	2	4	0
Vertigo positional	6 (1.1)	3	3	0	0	5 (0.8)	0	1	4	0
Sudden hearing loss	2 (0.4)	0	0	2	0	3 (0.5)	1	0	2	0
Deafness	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Eustachian tube patulous	0 (0.0)	0	0	0	0	2 (0.3)	0	0	2	0
Meniere's disease	0 (0.0)	0	0	0	0	2 (0.3)	1	0	1	0
Deafness neurosensory	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Ear pain	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Eustachian tube stenosis	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Deafness unilateral	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Inner ear disorder	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Auricular swelling	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Vestibular disorder	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
CARDIAC DISORDERS	17 (3.2)	2	6	9	0	27 (4.3)	8	9	10	0
Palpitations	4 (0.7)	1	1	2	0	10 (1.6)	3	4	3	0
Arrhythmia	2 (0.4)	0	2	0	0	4 (0.6)	1	1	2	0
Angina pectoris	2 (0.4)	1	0	1	0	2 (0.3)	0	1	1	0
Supraventricular extrasystoles	0 (0.0)	0	0	0	0	2 (0.3)	2	0	0	0
Acute myocardial infarction	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Aortic valve incompetence	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Atrioventricular block complete	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Mitral valve incompetence	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Arrhythmia supraventricular	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Atrial fibrillation	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Atrioventricular block	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Cardiac failure	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Hypertensive heart disease	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Myocardial ischaemia	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Prinzmetal angina	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Tachycardia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Tricuspid valve incompetence	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Ventricular extrasystoles	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Sick sinus syndrome	2 (0.4)	0	1	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
CARDIAC DISORDERS (Cont'd)										
Atrioventricular block second degree	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Bradycardia	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Cardiac failure acute	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Hypertensive cardiomyopathy	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
RENAL AND URINARY DISORDERS	24 (4.5)	4	7	12	1	26 (4.1)	10	5	10	1
Hypertonic bladder	10 (1.9)	3	2	5	0	6 (0.9)	3	1	2	0
Pollakiuria	2 (0.4)	0	1	1	0	5 (0.8)	3	2	0	0
Cystitis noninfective	1 (0.2)	0	0	1	0	2 (0.3)	1	1	0	0
Haematuria	1 (0.2)	0	1	0	0	2 (0.3)	0	0	2	0
Neurogenic bladder	1 (0.2)	0	1	0	0	2 (0.3)	1	0	1	0
Nephrolithiasis	0 (0.0)	0	0	0	0	2 (0.3)	0	0	2	0
Renal cyst	2 (0.4)	0	1	1	0	1 (0.2)	0	0	1	0
Dysuria	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Calculus urinary	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Mixed incontinence	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Renal impairment	0 (0.0)	0	0	0	0	1 (0.2)	0	0	0	1
Urethral disorder	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Urinary retention	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Nocturia	3 (0.6)	1	1	1	0	0 (0.0)	0	0	0	0
Calculus ureteric	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Cystitis haemorrhagic	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Hydronephrosis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Proteinuria	1 (0.2)	0	0	0	1	0 (0.0)	0	0	0	0
Renal failure chronic	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

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n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535)					Denosumab (N=633)				
	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	27 (5.0)	6	9	12	0	17 (2.7)	8	5	4	0
Breast cancer	3 (0.6)	3	0	0	0	3 (0.5)	1	1	1	0
Seborrhoeic keratosis	2 (0.4)	0	0	2	0	3 (0.5)	1	2	0	0
Ovarian cancer	1 (0.2)	0	0	1	0	2 (0.3)	1	1	0	0
Metastases to lung	0 (0.0)	0	0	0	0	2 (0.3)	2	0	0	0
Ovarian neoplasm	0 (0.0)	0	0	0	0	2 (0.3)	1	1	0	0
Gastric cancer	2 (0.4)	0	1	1	0	1 (0.2)	1	0	0	0
Skin papilloma	2 (0.4)	0	0	2	0	1 (0.2)	1	0	0	0
Benign gastric neoplasm	1 (0.2)	0	1	0	0	1 (0.2)	0	0	1	0
Colon adenoma	1 (0.2)	0	1	0	0	1 (0.2)	0	0	1	0
Acrochordon	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Bile duct cancer	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Metastases to liver	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Pancreatic carcinoma	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Lipoma	4 (0.7)	1	1	2	0	0 (0.0)	0	0	0	0
Metastases to lymph nodes	2 (0.4)	0	2	0	0	0 (0.0)	0	0	0	0
Colon cancer	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Insulinoma	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Large intestine carcinoma	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Lymphoma	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Meningioma	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
Uses exact time period for each time frame
Source: IAS 表-4-2.6

表 7-18　期間別の有害事象（器官別大分類及び基本語）（Japan Safety Analysis Set）

SYSTEM ORGAN CLASS Preferred Term	Placebo (N=535) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n	Denosumab (N=633) Total n (%)	≤6M n	>6M, ≤12M n	>12M, ≤24M n	>24M n
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) (Cont'd)										
Neurilemmoma	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Neurofibroma	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Oral fibroma	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Paget's disease of the breast	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Pseudolymphoma	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Tongue neoplasm benign	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
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System organ classes and preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 14.0.
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HEPATOBILIARY DISORDERS	19 (3.6)	5	4	10	0	12 (1.9)	2	4	6	0
Hepatic function abnormal	5 (0.9)	1	2	2	0	8 (1.3)	2	3	3	0
Hepatic cyst	2 (0.4)	0	0	2	0	1 (0.2)	0	0	1	0
Cholelithiasis	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Gallbladder polyp	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Liver disorder	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Alcoholic liver disease	2 (0.4)	1	1	0	0	0 (0.0)	0	0	0	0
Cholangitis	2 (0.4)	0	0	2	0	0 (0.0)	0	0	0	0
Hepatic steatosis	2 (0.4)	2	0	0	0	0 (0.0)	0	0	0	0
Jaundice	2 (0.4)	0	1	1	0	0 (0.0)	0	0	0	0
Cholestasis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Chronic hepatitis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Hepatitis	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0

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BLOOD AND LYMPHATIC SYSTEM DISORDERS	12 (2.2)	4	5	3	0	11 (1.7)	2	5	4	0
Anaemia	6 (1.1)	2	2	2	0	4 (0.6)	0	2	2	0
Iron deficiency anaemia	2 (0.4)	1	1	0	0	1 (0.2)	1	0	0	0
Haemorrhagic anaemia	1 (0.2)	1	0	0	0	1 (0.2)	0	0	1	0
Lymphadenopathy	1 (0.2)	0	0	1	0	1 (0.2)	1	0	0	0
Thrombocytopenia	1 (0.2)	1	0	0	0	1 (0.2)	0	1	0	0
Anaemia vitamin B12 deficiency	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Bone marrow failure	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Pancytopenia	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
Lymphadenitis	2 (0.4)	0	2	0	0	0 (0.0)	0	0	0	0
Leukopenia	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
IMMUNE SYSTEM DISORDERS	10 (1.9)	1	3	6	0	7 (1.1)	3	2	2	0
Seasonal allergy	8 (1.5)	0	3	5	0	5 (0.8)	2	1	2	0
Food allergy	1 (0.2)	0	0	1	0	1 (0.2)	0	1	0	0
Hypersensitivity	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Drug hypersensitivity	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

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REPRODUCTIVE SYSTEM AND BREAST DISORDERS	9 (1.7)	3	3	3	0	7 (1.1)	2	1	4	0
Benign prostatic hyperplasia	0 (0.0)	0	0	0	0	2 (0.3)	0	1	1	0
Atrophic vulvovaginitis	3 (0.6)	1	1	1	0	1 (0.2)	0	0	1	0
Breast mass	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Genital haemorrhage	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Metrorrhagia	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Uterine polyp	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Uterine prolapse	2 (0.4)	0	1	1	0	0 (0.0)	0	0	0	0
Cystocele	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Genital discharge	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
Gynaecomastia	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0
Pelvic prolapse	1 (0.2)	0	1	0	0	0 (0.0)	0	0	0	0
Vulvovaginal pruritus	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

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ENDOCRINE DISORDERS	5 (0.9)	0	1	3	1	6 (0.9)	3	0	3	0
Goitre	1 (0.2)	0	0	0	1	2 (0.3)	1	0	1	0
Hyperthyroidism	1 (0.2)	0	0	1	0	2 (0.3)	2	0	0	0
Basedow's disease	1 (0.2)	0	1	0	0	1 (0.2)	0	0	1	0
Hypothyroidism	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Autoimmune thyroiditis	0 (0.0)	0	0	0	0	1 (0.2)	0	0	1	0
Thyroid mass	1 (0.2)	0	0	1	0	0 (0.0)	0	0	0	0
SURGICAL AND MEDICAL PROCEDURES	1 (0.2)	0	0	1	0	4 (0.6)	0	1	3	0
Cataract operation	0 (0.0)	0	0	0	0	2 (0.3)	0	0	2	0
Varicose vein operation	1 (0.2)	0	0	1	0	1 (0.2)	0	0	1	0
Tooth extraction	0 (0.0)	0	0	0	0	1 (0.2)	0	1	0	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.2)	1	0	0	0	1 (0.2)	1	0	0	0
Porokeratosis	0 (0.0)	0	0	0	0	1 (0.2)	1	0	0	0
Accessory spleen	1 (0.2)	1	0	0	0	0 (0.0)	0	0	0	0

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
M = months
Includes only treatment-emergent adverse events
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Uses exact time period for each time frame
Source: IAS 表-4-2.6

付録 E.　症例一覧

症例一覧表をモジュール 5.3.7 に添付した。

デノスマブ

目次

2.7.1 で引用した文献

International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guidance for Industry: Q5E

United States Food & Drug Administration (FDA). Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001

2.7.2 で引用した文献

Camacho P, Kleerekoper M. Biochemical Markers of Bone Turnover. In: Favus MJ, ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th ed. Washington, DC: American Society for Bone and Mineral Research. 2006:127-33.

den Broeder A, van de Putte L, Rau R, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol. 2002;29:2288-98.

European Medicines Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP). Guidelines for the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis, CHMP/EWP/552/95 rev 2, November 2006.

Faulkner KG. Bone matters: are density increases necessary to reduce fracture risk? J Bone Miner Res. 2000;15:183-7.

Gertz BJ, Holland SD, Kline WF, et al. Clinical pharmacology of alendronate sodium. Osteoporosis Int. 1993;3(suppl 3):S13-6.

Hayashi N, Tsukamoto Y, Sallas WM, et al. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. Br J Clin Pharmacol. 2006;63:548-61.

Johansson AG, Lovdal T. Liver cell uptake and degradation of soluble immunoglobulin G Immune Complexes in vivo and in vitro in rats. Hepatology. 1996;24:169-75.

Ng CM, Stefanich E, Anand BS, et al. Pharmacokinetics/pharmacodynamics of nondepleting anti-CD4 monoclonal antibody (TRX1) in healthy human volunteers. Pharm Res. 2006;23:95-103.

Ng CM, Joshi A, Dedrick RL, et al. Pharmacokinetic-pharmacodynamic-efficacy analysis of efalizumab in patients with moderate to severe psoriasis. Pharm Res. 2005;22:1088-100.

Pagani F, Bonetti G, Stefini F, et al. Evaluation of a fully automated assay to measure C-telopeptide of type I collagen in serum. Clin Chem Lab Med. 2000;38:1111-3.

Rowinsky EK, Schwartz GH, Gollob JA, et al. Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. J Clin Oncol. 2004;22:3003-15.

Souberbielle J-C, Cormier C, Kindermans C. Bone markers in clinical practice. Curr Opin Rheumatol. 1999;11:312-9.

Stolina M, Schett G, Dwyer D, et al. RANKL inhibition by osteoprotegerin prevents bone loss without affecting local or systemic inflammation parameters in two rat arthritis models: comparison with anti-TNF-alpha or anti-IL-1 therapies. Arthritis Res Ther. 2009;11:R187.

Stolina M, Dwyer D, Ominsky MS, et al. Continuous RANKL inhibition in osteoprotegerin transgenic mice and rats suppresses bone resorption without impairing lymphorganogenesis or functional immune responses. J Immunol. 2007;179:7497-505.

デノスマブ

Su AI, Wiltshire T, Batalov S, et al. A gene atlas of the mouse and human protein-encoding transcriptomes. Proc Natl Acad Sci U S A. 2004;101:6062-7.

Thürmann PA, Sonnenburg C, Valentová K, et al. Pharmacokinetics of viral antibodies after administration of intravenous immunoglobulin in patients with chronic lymphocytic leukaemia or multiple myeloma. Eur J Clin Pharmacol. 2001;57:235-41.

Waldmann TA, Strober W. Metabolism of immunoglobulins. In: P Kallos P, Waksman BH, eds. Progress in Allergy, vol 13 , Basel, Switzerland: S Karger; 1969:1-110.

Xolair® (Omalizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2010.

2.7.3 で引用した文献

骨粗鬆症の予防と治療ガイドライン作成委員会．骨粗鬆症の予防と治療ガイドライン 2011 年版. 2011.

折茂肇，他．原発性骨粗鬆症の診断基準（2000 年度改訂版）．日本骨代謝学会誌. 2001;18:76-82.

日本骨代謝学会骨粗鬆症診断基準検討委員会．原発性骨粗鬆症の診断基準(1996 年度改訂版). 日骨代謝誌. 1997;14:219-33.

Cooper C, Atkinson EJ, Jacobsen SJ, et al. Population-based study of survival after osteoporotic fractures. Am J Epidemiol. 1993;137:1001-5.

Cree M, Soskolne CL, Belseck E, et al. Mortality and institutionalization following hip fracture. J Am Geriatr Soc. 2000;48:283-8.

Cummings SR and Melton LJ III. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002;359:1761-7.

Delmas PD, Seeman P. Changes in Bone Mineral Density Explain Little of the Reduction in Vertebral or Nonvertebral Fracture Risk with Anti-Resorptive Therapy. Bone. 2004;34:599-604.

EMEA. CHMP Guideline on the Evaluation of New Medicinal Products in the Treatment of Primary Osteoporosis, (May 2007).

FDA. Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention and Treatment of Postmenopausal Osteoporosis, (April 1994).

Genant HK, Wu CY, et al. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8:1137-48.

Jalava T, Sarna S, Pylkkanen L, et al. Association between vertebral fracture and increased mortality in osteoporotic patients. JBMR. 2003;18:1254-60.

Johnell O, Kanis J, Odén A, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15:38-42.

Johnell O and Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17:1726-33.

Kado DM, Browner WS, Palermo L, et al. Vertebral fractures and mortality in older women; a prospective study. Arch Intern Med. 1999;159:1215-20.

Kulak CA and Bilezikian JP. Bone mass measurement in identification of women at risk for osteoporosis. Int J Fertil Women's Med. 1999;44:269-78.

Lau E, Ong K, Kurtz S, et al. Mortality following the diagnosis of a vertebral compression fracture in the Medicare population. J Bone Joint Surg Am. 2008;90:1749-86.

Leibson CL, Tosteson AN, Gabriel SE, et al. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. J Am Geriatr Soc. 2002;50:1644-50.

Li Z, Meredith MP, Hoseyni MS. A method to assess the proportion of treatment effect explained by a surrogate endpoint. Statist Med. 2001;20:3175-88.

Magaziner J, Lydick E, Hawkes W, et al. Excess mortality attributable to hip fracture in white women aged 70 years and older. Am J Publ Health. 1997;87:1630-6.

Nevitt MC, Thompson DE, Black DM, et al. Effect of alendronate on limited-activity days and bed-disability days caused by back pain in postmenopausal women with existing vertebral fractures. Arch Int Med. 2000;160:77-85.

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285:785-95.

Papaioannou A, Watts NB, Kendler DL, et al. Diagnosis and management of vertebral fractures in elderly adults. Am J Med. 2002;113:220-8.

Sakamoto K, Nakamura T, Hagino H, et al. Report on the Japanese Orthopaedic Association's 3-year project observing hip fractures at fixed-point hospitals. J Orthop Sci 2006;11:127-34.

Sarkar S, Mitlak BH, Wong M, et al. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res. 2002;17:1-10.

Tosteson AN, Gabriel SE, Grove MR, et al. Impact of hip and vertebral fractures on quality-adjusted life years. Osteoporos Int. 2001;12:1042-9.

Watts NB, Lindsay R, Li Z, et al. Use of matched historical controls to evaluate the anti-fracture efficacy of once-a-week risedronate. Osteoporos Int. 2003;14:437-41.

2.7.4 で引用した文献

Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res. 2009;24:1095-102.

Alexander MY. RANKL links arterial calcification with osteolysis. Circ Res. 2009;104;1032-4.

Atkinson J, Cranmer P, Saunders T, et al. AMG 162, a fully human RANKL antibody, increases bone mass and bone strength in cynomolgus monkeys. J Bone Min Res. 2005;20(suppl 1):S294.

Bachmann MF, Wong BR, Josien R, et al. TRANCE, a tumor necrosis family member critical for CD40 ligand-independent T helper cell activation. J Exp Med. 1999;189:1025-31.

Bauer DC, Black DM, Garnero P, et al. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture interventional trial. J Bone Miner Res. 2004;19:1250-8.

Bennett BJ, Scatena M, Kirk EA, et al. Osteoprotegerin inactivation accelerates advanced atherosclerotic lesion progression and calcification in older ApoE-/- Mice. Arterioscler Thromb Vasc Biol. 2006;26:2117-24.

Choi BG, Vilahur G, Cardoso L, et al. Ovariectomy increases vascular calcification via the OPG/RANKL cytokine signalling pathway. Eur J Clin Invest. 2008:38:211-7.

Crisafulli A, Micari A, Altavilla D, et al. Serum levels of osteoprotegerin and RANKL in patients with ST elevation acute myocardial infarction. Clin Sci. 2005;109:389-95.

Delmas PD, Munoz F, Cosman F, et al. Relationship of bone turnover marker (PINP) and changes in femoral neck bone mineral density to fractyre risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg (ZOL): the horizon-pft study. OR 1027, 30th annual scientific sessions of the American Society for Bone and Mineral Research, Montreal, Canada, 2008.

The Eye Diseases Prevalence Research Group. Prevalence of Cataract and Pseudophakia/Aphakia Among Adults in the United States. Arch Ophthalmol. 2004;122:487-94.

Green EA, Choi Y, Flavell RA. Pancreatic lymph node-derived CD4(+)CD25(+) Treg cells: highly potent regulators of diabetes that require TRANCE-RANK signals. Immunity. 2002;16:183-91.

Helas S, Goettsch C, Schoppet M, et al. Inhibition of receptor activator of NF-kappaB ligand by denosumab attenuates vascular calcium deposition in mice. Am J Path. 2009;175:473-8.

Kiechl S, Schett G, Schwaiger J, et al. Soluble receptor activator of nuclear factor-kappa B ligand and risk for cardiovascular disease. Circulation. 2007;116:385-91.

Kiechl S, Werner P, Knoflach M, et al. The osteoprotegerin/RANK/RANKL system: a bone key to vascular disease. Exp Rev Cardiovasc Ther. 2006;4:801-11.

Klein BEK, Klein R, Lee KE. Incidence of age-related cataract over a 10-year interval: the Beaver Dam Eye Study. Ophthalmology. 2002;109:2052-7.

Knudsen ST, Foss CH, Poulsen PL, et al. Increased plasma concentrations of osteoprotegerin in type 2 diabetic patients with microvascular complications. Eur J Endocrinol. 2003;149:39-42.

Kwek EBK, Goh SK, Koh JSB, et al. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury. 2008;39:224-31.

Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. New Engl J Med. 2008;358:1304-5.

Loser K, Mehling A, Loeser S, et al. Epidermal RANKL controls regulatory Tcell numbers via activation of dendritic cells. Nat Med. 2006;12:1372-9.

Marie PJ, Hott M, Garba MT. Inhibition of Bone Matrix Apposition by (3-Amino-1-Hydroxypropylidene)-1,1-Bisphosphonate (AHPrBP) in the Mouse. Bone. 1985;6:193-200.

Miller RE, Branstetter D, Armstrong A, et al. Receptor activator of NF-κB ligand inhibition suppresses bone resorption and hypercalcemia but does not affect host immune response to influenza infection. J Immunol. 2007;179:266 74.

Min H, Morony S, Sarosi I, et al. Osteoprotegerin Reverses Osteoporosis by Inhibiting Endosteal Osteoclasts and Prevents Vascular Calcification by Blocking a Process Resembling Osteoclastogenesis. J Exp Med. 2000;192:463-74.

Morony S, Tintut Y, Zhang Z, et al. Osteoprotegerin inhibits vascular calcification without affecting atherosclerosis in ldlr(-/-) mice. Circulation. 2008;117:411-20.

Nakamura M, Udagawa N, Matsuura S, et al. Osteoprotegerin regulates bone formation through a coupling mechanism with bone resorption. Endocrinol. 2003;144:5441-9.

Odvina C, Levy S, Rao S, et al. Unusual mid-shaft fractures during long term bisphosphonate therapy. Clin Endocrinol. 2010;72:161-8.

Odvina CV, Zerwekh JE, Rao DS, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294-301.

Padigel UM, Kim N, Choi Y, Farrell JP. TRANCE-RANK costimulation is required for IL 12 production and the initiation of a Th1-type response to Leishmania major infection in CD40L-deficient mice. J Immunol. 2003;171:5437-41.

Panizo S, Cardus A, Encinas M, et al. RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4–dependent pathway. Circ Res. 2009;104:1041-8.

Price PA, June HH, Buckley JR, et al. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol. 2001;21:1610-6.

Ruben FL, Dearwater SR, Norden CW et al. Clinical infections in the noninstitutionalized geriatric age group: methods utilized and incidence of infections. The Pittsburgh Good Health Study. Am J Epidemiol. 1995;141:145-57.

Sandberg WJ, Yndestad A, Oie E, et al. Enhanced T-cell expression of RANK ligand in acute coronary syndrome: possible role in plaque destabilization. Arterioscler Thromb Vasc Biol. 2006;26:857-63.

Shane E, Burr D, Ebeling PR, et al. Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010;25:2267-94.

Somford MP, Draijer FW, Thomassen BJ, et al. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. J Bone Miner Res. 2009;24:1736-40.

Stolina M, Guo J, Faggioni R, et al. Regulatory effects of osteoprotegerin on cellular and humoral immune responses. Clin Immunol. 2003;109:347-54.

Tintut Y, Demer L. Role of osteoprotegerin and its ligands and competing receptors in atherosclerotic calcification. J Invest Med. 2006;54:395-401.

Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy? Ann Oncol. 2006;17:1197-204.

Whyte MP, Bergfeld MA, Murphy WA, et al. Postmenopausal osteoporosis. A heterogeneous disorder as assessed by histomorphometric analysis of Iliac crest bone from untreated patients. Am J Med. 1982;72:193-202.

Yamaguchi T, Sakaguchi S. Skin controls immune regulators. Nat Med. 2006;12:1358-9.

Yoneda T, Hagino H, Sugimoto T, et al. Bisphosphonate-Related Osteonecrosis of the Jaw: Position Paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. J Bone Miner Metab. 2010;28:365-83.